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RNA-binding proteins as regulators of transcription and axial patterning during *Xenopus* embryogenesis

By

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By Caitlin Suzanne DeJong

Abstract

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The over-arching goal of this thesis is to expand our knowledge of the mechanisms by which one cell, a fertilized egg, develops into an organism composed of multiple cell types, each with different functions and behaviors. RNA-binding proteins have been identified as potent regulators of development and embryogenesis. The studies presented in this thesis illustrate the pleiotropic effects of RNA-binding proteins in *Xenopus* development and will focus specifically on two RNA-binding proteins that are maternally deposited and zygotically transcribed: TAF15 and DGCR8.

TATA-binding protein-associated factor 15 (TAF15) belongs to the FET family of atypical RNA-binding proteins, which also includes Fused in sarcoma (Fus) and Ewing's sarcoma (EWS). FET proteins were originally discovered as components of fusion oncogenes and are most noted for their implication in various cancers and neuromuscular degenerative diseases. However, little is known of the endogenous function of FET proteins. The diverse biological activities of the FET family proteins can be likened to a biological Swiss army knife; as these proteins contain domains for transcriptional activation, RNA-binding, DNA-binding, and function in both RNA Polymerase II-mediated transcription and pre-mRNA splicing. An exciting possibility is that the FET proteins may function to connect transcription and splicing. By employing the bioinformatics approach of RNA-sequencing, I generated a list of significant genes that are differentially expressed between uninjected and *taf15* depleted embryos. From this analysis I found that TAF15 regulates target genes at both the transcriptional and post-transcriptional level. The studies that focus on the role of TAF15 in *Xenopus* development are described in chapters two and three of this thesis.

In the second chapter of this thesis I describe studies that illustrate the novel concept that a protein can regulate the same set of target genes but through different molecular mechanisms. Both maternal and zygotic TAF15 regulate the expression of the transcripts *fgfr4*, *isl1*, and *pax8*. Interestingly, maternal TAF15 is required for the post-transcriptional regulation of *fgfr4*, *isl1*, and *pax8*, regulating the splicing of single introns within these transcripts, whereas zygotic TAF15 is required for the transcriptional regulation of these genes. Therefore, the studies described in chapter two demonstrate, for the first time, that a single protein can utilize a different molecular mechanism to control the same target genes and the use of these different

mechanisms of action appears to be dependent on whether the protein is maternally deposited or zygotically transcribed. Single intron retention is a known mechanism to retain transcripts in the nucleus, preventing their translation. In chapter two of this thesis I provide evidence for the following model: in the absence of genome activation, before the zygotic genome is transcribed, maternal TAF15 cooperates with a splicing factor, the RNA-binding protein SRSF4, to regulate the splicing of single introns from transcripts. As a result, TAF15 and SRSF4 control the splicing of target genes and thus control the timing of transcript maturation and subsequent translation. This mechanism is logical as it provides a mechanism by which to spatially and temporally regulate gene expression in the absence of the ability to transcriptionally regulate genes. I further show evidence that following zygotic genome is activation, zygotic TAF15 activates target gene transcription, regulating genes at the transcriptional level, likely associating with the core promoter. The findings described in chapter two of this thesis are the first to show that a single protein can regulate the same gene targets but depending on the milieu of maternal of zygotic cofactors, regulates these targets via different underlying mechanisms. The variety of functional domains intrinsic to TAF15 supports the hypothesis that this atypical RNA-binding protein could operate as part of both a splicing and transcriptional complex.

In the third chapter of this thesis I describe studies that illustrate the novel finding that TAF15 is required for dorsoventral patterning via the repression of *ventx2.1*. Ventx2 and BMP4 function in an autocatalytic positive feedback loop to specify ventral tissue and antagonize organizer function. Following *taf15* depletion, *ventx2.1* expression is expanded in the neural ectoderm and embryos exhibit a BMP overexpression phenotype: reduction in head, and dorsal, and posterior fin structures, with an increase in ventral tissue. Unlike the findings in chapter two, in this study, both maternal and zygotic TAF15 function to suppress *ventx2.1* expression. These findings place TAF15 in the regulatory network of dorsoventral patterning and suggest that maternal and zygotic TAF15 control expression of *ventx2.1* in a similar manner but do not rule out differential mechanisms of this control. Currently, it is unknown if TAF15 represses *ventx2.1* expression directly or if TAF15 is required to activate a repressor of *ventx2.1*.

In the fourth chapter of this thesis I describe studies that serve as a resource for future investigations into the role of microRNAs (miRNAs) in *Xenopus* development. DiGeorge syndrome critical region 8 (DGCR8) is a subunit of the microprocessor complex required for miRNA biogenesis. Unlike most members (e.g. Dicer, Argonaute2) of the RNA interference biogenesis pathway, DGCR8 is required specifically for miRNA biogenesis. Furthermore, unlike previous studies in mice and zebrafish that have depleted maternal *dgcr8* throughout oogenesis to look at the role of miRNAs during embryogenesis, the antisense oligodeoxynucleotide (ODN) that I have designed can be used in host transfer assays to assess the effects of maternal *dgcr8* depletion once oogenesis is complete, specifically during embryogenesis. Additionally, I have designed a splice-blocking morpholino (MO) antisense oligonucleotide that targets zygotic *dgcr8* for depletion. Using these two tools (ODN and MO), the first studies can be performed that tease apart the role of maternal versus zygotic DGCR8 during embryogenesis.

The work presented in this thesis exemplifies the value of carefully assessing biological functions of genes that are both maternally deposited and zygotically transcribed. The surprising finding that TAF15 utilizes distinct molecular mechanisms to control conserved target genes depending on whether this protein is maternally deposited or zygotically expressed demonstrates a new level of molecular complexity that future studies must address. Additionally, these studies further support the motivation to investigate RNA-binding proteins in development and disease as they continually prove to be multifaceted players in molecular biology.

For my husband and classmate
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with whom I shared this journey and has been a fountain of encouragement, support, laughter, and love,

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and for my siblings
Alex and Sonja DeJong
who make my face hurt from laughing.

In loving memory of
Marjorie Lucas
a woman of strong will with a thirst for knowledge

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Chapter 1: Introduction

How one cell, a fertilized egg, develops into an organism composed of multiple cell types, each with different functions and behaviors, is a question that has inspired the field of developmental biology since its inception.

Section 1.1 A brief history of developmental biology.

For centuries, the question of how a single cell, a fertilized egg, develops into an organism has racked the minds of scientists and philosophers alike. Beginning with Paracelsus' homunculus in the 1500's, later followed by Hartsoeker's illustration of spermatozoon (1695) and Malpighi's observation that an early chicken embryo shares remarkable physical similarities with its adult form (1673), we see the stirrings of an explanation for development in the concept of preformation; a view that an organism is preformed and development is simply the growth of a miniature being into adult form (Horder, 2010). Due to the small size and general inaccessibility of embryos, it was not until the 1800's, with Haeckel's contribution of detailed drawings comparing the development of eight different vertebrates across three embryological stages, that we get an introduction to the dynamic natures of embryogenesis. In Haeckel's work we see a glimpse of the contribution developmental biology could have to the field of evolution; it was around this time that embryology combined with comparative anatomy to explore ideas of morphology and scientists began to explain development through epigenesis, where an organism is not preformed but is formed gradually through shape changes and acquires adult features over time (Horder, 2010). The theory of epigenesis was first originated by Aristotle c.350 BC (On the Generation of Animals, 350 B.C.) but was not given much credibility until the 1800's due to the dominant creationist theories of the origin of life. During the period between 1901 and 1906, using frog lenses, Hans Spemann identified the concept of induction: that a group of cells is able to influence the developmental fate of neighboring cells (Spemann, 1938) (Saha, 1991) (Gilbert,). By the 1920's, Spemann and Mangold had applied what Spemann learned from lens-induction to understand cell determination at gastrulation which would lead to their discovery of the Spemann-Mangold organizer, garnering Spemann the Nobel Prize for physiology and medicine in 1935 (Sander & Faessler, 2001). With this, we learn about the requirement of inter-cellular signaling in specifying and differentiating cells of a developing embryo (Horder, 2010) (Spemann & Mangold, 1924).

Section 1.2 Xenopus as a model organism for vertebrate development.

As development biologists found increasing value in studying amphibian embryos, by the 1960's, they turned to the South African clawed frog, *Xenopus laevis* (*X. laevis*) (Gurdon & Hopwood, 2000). Embryologists were not the first scientists to use *X. laevis*, instead, it was through more fortuitous events that the two united. In the early 19th century, *X. laevis* were first described by a French naturalist, and by the turn of the 20th century, a British zoologist cultured the embryos in the laboratory. By the 1930's, *X. laevis* became popular in European and American laboratories; made so by Lancelot Hogben for their use in the field of endocrinology and subsequently as the preferred bioassay for early detection of pregnancy (Gurdon & Hopwood, 2000). Following the injection of urine from a pregnant woman, female *X. laevis* would ovulate, releasing mature eggs. By 1935, it was established that coupling of *X. laevis* could be induced outside of the mating season by injecting pregnancy urine into males and females; as a result, fertilized eggs and embryos could be generated year-round (Gurdon & Hopwood, 2000). It was later shown that human chorionic gonadotropin was the active ingredient of urine from a pregnant woman that could induce mating of *X. laevis* year round. Once it was established that ovulation and mating could be induced at any time, and that the *X. laevis* were hardy, with embryos that could be cultured in great numbers in the lab, these animals became the organism of choice for embryologists seeking large amounts of synchronized materials for cellular and biochemical assays (Gurdon & Hopwood, 2000). In the 1950's, a normal table of *X. laevis* development was established by Pieter Nieuwkoop and their use grew in laboratories worldwide (Gurdon & Hopwood, 2000) (Nieuwkoop & Faber, 1994).

Developmental biologists readily embraced *Xenopus laevis* for use in cell biology and biochemistry due to their large egg size (1-1.3mm, containing 4ug of total RNA) and the ability to synchronously and externally fertilize 3000-5000 embryos (Xenbase). Additionally, the embryos are easy to manipulate. The yolk that sustains an embryo is evenly distributed to each cell and, as a result, cells can be explanted or "cut and pasted" within and/or transferred between embryos. Additionally, scientists are able to overexpress or deplete genes of their interest in embryos by injecting RNAs, proteins, morpholino antisense oligonucleotides (see section 1.5), or bathing them in small molecules. These assays have revealed profound biological properties of molecules, cells, and tissues (Sive et al., 2000). Further, due to the short time required to develop from one cell to a tadpole (~three days post fertilization at 23°C) biologists can observe the fruits of their experimental manipulations within a reasonable amount of time. It should also be noted that *Xenopus* phylogenetically lies between teleost fish and amniotes and is therefore a good model for vertebrate development. Lastly, there is a great strength to studying the biology of molecules, cells, and tissues in a whole organism as part of a system, largely un-derived from their natural state and environment.

With the turn of the 20th century, the field of biology entered the genomic era and frog embryologists wanted to ask tractable genomic questions of their *Xenopus* system; with this came the introduction of the closely related *Xenopus tropicalis* (Amaya et al., 1998). *X. laevis* and *X. tropicalis* last shared a common ancestor 50 million years ago (Hellsten et al., 2007) (Grainger, 2012). About 40 million years ago, as a result of the merging of two diploid progenitors, *X. laevis* underwent an allotetrapoidization and, as such, has 36 chromosomes (2N) and ~3 gigabase (Gb) genome; nearly twice the number and size of *X. tropicalis* chromosomes, 20 (2N), and genome, ~1.5Gb. Furthermore, it is estimated that the *X. laevis* genome has retained 25-50% of these duplicated genes (Hellsten et al., 2007); extra gene copies that greatly complicate genetic studies. Because *X. tropicalis* has a diploid genome, a shorter generation time (four months compared to 1 year for *X. laevis*), and still shares many of the advantages of *X. laevis* system (although its eggs are smaller, ~0.75mm), it is the clear choice as the *Xenopus* genetic model (Xenbase). By 2005, genetic screens for natural mutations in wild caught and inbred *X. tropicalis* lines were underway (Noramly et al., 2005) (Grammer et al., 2005) (Grainger, 2012). Now numerous transgenic *X. laevis* and *X. tropicalis* stocks are available to researchers through the National Xenopus Resource.

In addition to being an excellent system to ask any number of questions relating to the fields of embryology and genomics, *Xenopus* is also well suited to address the phenomenon known as the maternal effect on developmental.

Section 1.3 The maternal effect on development.

The maternal effect on development is a phenomenon in which molecular determinants, such as mRNA, microRNAs, and proteins, are derived from the maternal genome and loaded into the egg (Anderson & Nüsslein-Volhard,1984) (Driever & Nüsslein-Volhard, 1988) (Armisen et al., 2009). This information is present at fertilization (at which time the maternal and paternal genomes combine to generate the zygotic genome) and is required for the first stages of embryogenesis until the zygotic genome is activated and new RNAs and proteins are transcribed to carry the embryo through the rest of development. Both the plant and animal kingdoms depend on these maternally contributed molecules for development as they are inherited by any embryo that develops from a fertilized egg (Li & Li, 2015). Importantly, within the animal kingdom, organisms from a wide range of taxa will vary in the degree to which their development depends on maternal factors (Tadros & Lipshitz, 2009) (Table 1.).

Section 1.4 Examples of maternal effect genes.

Christiane Nüsslein-Volhard has been a foremost contributor to the body of research showing that maternally derived gene products, also known as maternal effect genes, are required for embryonic patterning. Maternal effect genes are gene products, RNA or protein, that are produced maternally and are deposited in the oocyte or are present in the fertilized egg or embryo before expression of zygotic genes is initiated (Marlow, 2010). They are defined by showing phenotypes in embryos derived from homozygous mothers, even if the paternal contrition is wild type. Using *D. melanogaster*, Nüsslein-Volhard showed that dorsal-ventral patterning determinants are stored in maternal mRNA (Anderson & Nüsslein-Volhard,1984). Later, Nüsslein-Volhard published that *bicoid* mRNA is localized to the anterior tip of the oocyte and early embryo and that this asymmetric localization is required to set up a gradient of Bicoid protein, organizing anterior development (Driever & Nüsslein-Volhard, 1988). Since this time, numerous model systems have been used to demonstrate that maternal effect genes are required for a number of developmental processes. These include: oocyte maturation (meiosis), egg activation, fertilization, animal-vegetal polarity (mRNA localization), maternal regulators of imprinting, cleavage (mitosis), maternal to zygotic transition (zygotic genome activation), epiboly (tissue cohesiveness), patterning and morphogenesis, lineage specification, adhesion/cohesion, germline specification and maintenance (Marlow, 2010).

Section 1.5 Xenopus as a system to study the maternal and zygotic effect on development.

Although teasing apart the different biological activities of a maternally versus zygotically derived gene product will always be challenging, *Xenopus* is well suited to ask these types or questions. As I have previously described, *Xenopus* is the closest vertebrate model system to amniotes, their eggs are externally fertilized in large brood sizes and are easily manipulated, and important for the study of maternal effect genes, zygotic genome activation does not occur until the 12th cleavage cycle. A number of tools have been developed in *Xenopus* to address what the maternal and zygotic gene contributions are to embryogenesis.

To address the maternal contributions to development, Heasman and Wylie used short (18-mer) antisense oligodeoxynucleotides (ODNs) to deplete maternal mRNAs from oocytes (Wylie & Heasman, 1997). This technique depletes target mRNAs by harnessing the endogenous activity of RNAse-H, active in oocytes, which degrades RNA:DNA hybrids. In this system, oocytes are surgically removed from donor ovaries, de-folliculated, injected with ODNs, and incubated for 24 hours to allow degradation. Along with the ODN injection, the oocytes are dyed to label injected oocytes, and following the incubation step these dyed oocytes are surgically placed into the body cavity of a recipient female who is induced to ovulate. In this manner the recipient female is made to release eggs depleted of specific maternally contributed transcripts that can be fertilized and assayed for changes in development. Using ODNs, Heasman and Wylie have been able to show that maternal mRNAs are essential regulators of embryonic patterning and processes such as dorsal mesoderm induction (β-catenin), endoderm differentiation and primary germ layer specification (VEGT), and mesoderm induction (Vg1) (Heasman et al., 1994) (Wylie et al., 1996) (Zhang et al., 1998) (Birsoy et al., 2006).

While Heasman and Wylie used ODNs to clearly and robustly show the requirement for maternal mRNAs in *Xenopus* development, the use as an everyman's tool never took off; the technical and advanced skills required for execution have been difficult to reproduce outside of their lab. Furthermore, while ODNs effectively deplete maternal mRNAs from an entire embryo, there are some cases where this is not the desired outcome. One great advantage of the *Xenopus* system is that upon the first cell cleavage, the embryo is often split into its left and right halves (Danilchik & Black, 1988). It is at this point that one of the two cells can be injected with a reagent (mRNA, protein, small molecules) and the cell that was not injected will serve as an internal control (Figure 1.1A). With each subsequent cell division, injecting any single cell will affect a more specific and finite cell lineage, allowing scientists to ask how specific and individual areas of the embryo are affected. In 1997, the morpholino antisense oligonucleotide was designed (Summerton & Weller, 1997) and used for this exact purpose, depleting mRNAs from specific cells at specific times; eventually used to deplete mRNA from only 1 cell of a 32 cells embryo, allowing for the most specific depletion in *Xenopus* (Heasman et al., 2000).

Morpholino antisense oligonucleotides (MOs) are synthetic oligonucleotides composed usually of 25 subunit chains that are similar to DNA and RNA except that instead of a five-membered ribose ring, they have a six-membered morpholine ring. MOs bind to their complementary target RNA through Watson-Crick base pairing and are resistant to nucleases, making them very stable (Eisen & Smith, 2008). Unlike ODNs, MOs do not act through an RNAseH mechanism (Summerton, 1999). Instead, to deplete target gene products, MOs bind to RNA and either sterically block the movement of the translation initiation complex (translation-blocking MO) or the proper splicing of pre-mRNA (splice-blocking MO), resulting in intron retention and the inclusion of missense codons and likely a premature stop codon (Draper et al., 2001) (Figure 1.1B). In this way, if a MO targets a translation start site, then both maternal and zygotic mRNA will be targeted. If, however, a MO targets a splice site, then only the zygotic mRNA will be targeted as maternal mRNAs are already spliced. With these tools, scientists have now been able to tease apart the developmental roles of maternally contributed versus zygotically derived gene products.

Section 1.6 An example of differing maternal and zygotic effects on development.

A classic example of a gene with separable maternal and zygotic developmental roles is β-catenin. As previously mentioned, depletion of maternal β-catenin from the oocyte, and subsequent embryo, leads to a complete failure of dorsal mesoderm induction (Heasman et al., 1994). However, using dorsal vegetal injections of translation-blocking morpholino, at various stages, Heasman and Wylie were able to dissect the activities of maternal and early zygotic function in specific lineages: 2- and 4-cell stage blocks dorsal axis formation, 8-cell stage blocks head formation, and A-tier injection at the 32-cell stage results in abnormal cement gland formation (Heasman et al., 2000). Importantly, zygotic transcription is not activated until the 12th cleavage cycle and thus these studies were blocking only maternally contributed β-catenin. At the time of these experiments, splice-blocking morpholinos were not yet available to test exclusive zygotic gene function. In this example, we see that, at the time of fertilization, β-catenin activity is required for dorsal axis formation and that later in development, it is required more specifically for dorsoanterior fates. Thus, this example shows developmental differences in maternally and zygotically contributed β-catenin.

Section 1.7 Maternally deposited and zygotically derived RNA-binding proteins as potent regulators of development.

The main body of work that has examined the maternal contribution to development in vertebrates has focused on transcription factors and signaling molecules (Marlow, 2010). It has been proposed since the late 1960's that RNAs (e.g. masked maternal mRNAs) and RNA-binding proteins could be potent regulators of development (Lifton & Kedes, 1976) (Bandziulis et al., 1989). Since this time, it has been shown in *C. elegans*, *Drosophila*, *Xenopus*, and mice that maternal RNA-binding proteins are important for post-transcriptional regulation and are required for splicing (*C. elegans*) and the RNA-interference pathway (mouse) to maintain maternal steady state levels in germ-line development as well as maternal transcript turnover during the maternal to zygotic transition (MZT) of genome transcription (*Drosophila*, *Xenopus*) (Hebeisen et al., 2008) (Murchison et al., 2007) (Benoit et al., 2009) (Bentaya et al., 2012). Around the same time that these studies were published, an expression clone screen was performed in *Xenopus* to ask which genes affect neural plate patterning and morphogenesis and found that a surprisingly large percentage of the genes identified were RNA-binding proteins (Dichmann et al., 2008). One of the genes identified in the expression clone screen was the atypical RNA-binding protein Fused in sarcoma (Fus), a member of the FET family of proteins which includes Fus, Ewing's Sarcoma (EWS), and TATA-binding protein-associated factor 15 (TAF15). Fus has since been shown to be required for *Xenopus* development through the splicing of fibroblast growth factors (FGFs) and cadherins, developmental regulators critical to mesoderm induction and cell adhesion in *Xenopus* (Dichmann & Harland, 2012).

Due to the growing body of evidence that both maternally deposited and zygotically transcribed RNA-binding proteins are potent regulators of development, I have chosen to focus my thesis work on two RNA-binding proteins that are both present at fertilization and are also transcribed upon zygotic genome activation: TAF15 and DGCR8.

Section 1.8 The FET family of atypical RNA-binding proteins.

The FET family of atypical RNA-binding proteins includes Fused in sarcoma (Fus), Ewing's sarcoma (EWS), and the TATA-binding protein-associate factor 15 (TAF15). The FET proteins are heterogeneous nuclear ribonuclear particle (hnRNP) proteins that are abundantly expressed and contain both RNA- and DNA-binding domains, this family is also known to interact with thousands of transcripts and affect multiple steps of mRNA biogenesis (Schwartz et al., 2015) (Figure 1.2). To a varying degree, these family members are present in plants, nematodes, insects, and vertebrates. Invertebrates and plants encode one FET protein while vertebrates have three. One speculation is that the FET proteins evolved to facilitate the complex coupling of transcription and mRNA processing that occurs in multicellular organisms (Schwartz et al., 2015) (Kato et al., 2012) (Schwartz et al., 2013).

The FET family of genes is most noted for their incidences in disease states. Following abnormal chromosomal translocations, FET protein N-terminal low-complexity/activation domains are found fused to various DNA-binding proteins, contributing to the formation of various cancers (Tan & Manley, 2009) (Delattre et al., 1992) (Crozat et al., 1993) (Rabbitts et al., 1993) (Martini et al., 2002) (Panagopoulos et al., 1999) (Sjögren et al., 1999) (Kovar, 2011). This family is also implicated in neuromuscular degenerative diseases. Causative and correlated point mutations in the C-terminal nuclear localization signal of Fus and TAF15, respectively, are found in patients with familial amyotrophic lateral sclerosis (FALS) and frontotemporal lobar dementia (Kwiatkowski et al., 2009) (Vance et al., 2009) (Schwartz et al., 2015) (Kovar, 2011). A recent study identifying amyotrophic lateral sclerosis (ALS) risk genes and pathways reported that variants in Fus explained 4% of reported FALS and 1% of spontaneous ALS (SALS), while variants in TAF15 and EWS explained <1% of reported FALS and SALS (Cirulli et al., 2015).

The work examining the FET proteins has been carried out almost exclusively in cell lines. Previous reports show that all three FET proteins exhibit nuclear expression and in addition, TAF15 and Fus are found in the cytoplasm of most cell types. FET proteins have both distinct and overlapping patterns in human tissues. FET proteins are targeted to stress granules following heat shock and oxidative stress, and are associated with regulating numerous cellular activities including: cell proliferation, cell cycling, cell death, transcription, splicing, microRNA processing, RNA-transport, signaling, and maintenance of genomic integrity (Ballarino et al., 2012) (Andersson et al., 2008) (Shiohama et al., 2007) (Gregory et al., 2004). Using photoactivatable ribonucleoside-enhanced cross-linking and immunoprecipitation (PAR-CLIP), FET proteins were predominantly found to bind to intronic regions as well as the 3'UTR of genes (Hoell et al., 2011).

Among vertebrates, the three FET members are highly conserved from fish to mammals, suggesting an independent and specialized requirement for each protein (Schwartz et al., 2015). Interestingly, depletion studies looking at the role of FET proteins in vertebrates suggest that this family of atypical RNA-binding proteins are differentially required for development in *Xenopus* and mice. Somewhat paradoxically, given the evolutionarily conserved FET family structures, it is thought that the FET family may actually act redundantly in mice. Fus is required for some of the earliest stages of development in *Xenopus*, as shown by depleted embryos exhibiting gastrulation and cell adhesion defects (Dichmann & Harland, 2012). However, the requirement for Fus in mice does not appear to be until later in development as pups depleted of Fus die neonatally as a result of defects in B-lymphocyte development and genomic instability (Hicks et al., 2000). Mice deficient for EWS also exhibit defects in B-cell development, in addition to meiosis, suggesting that the more mild phenotype observed in early mouse development, as compared to *Xenopus*, could be explained by overlapping FET functions (Li et al., 2007). Currently, no studies have looked at the role of TAF15 in mice or *Xenopus*.

Little is known about the role of TAF15 in development. TAF15 is not considered a canonical TATA-binding protein associated factor (TAF) as it is not associated with all human TFIID complexes and has no ortholog in non-vertebrate species (Ballarino et al., 2012). However, it is this non-ubiquitous association with the core transcriptional machinery that is most interesting to me as this supports the hypothesis that TAF15 may be more selective in the transcripts it regulates and, as a result, may have more specified roles in development. TAF15 would not be the first TAF to be shown to have a specific role in development. TAF3 has been shown to be required for endoderm lineage differentiation and preventing the premature specification of neurectoderm and mesoderm in embryonic stem cells (Liu et al., 2011).

Section 1.9 microRNA biogenesis and the role of DGCR8.

microRNAs (miRNAs) are small 22 nucleotide non-coding RNAs encoded in plants, animals, virus genomes, and single-celled eukaryotes that function as guide molecules in RNA interference and silencing (Griffiths-Jones et al., 2007) (Ha & Kim, 2014). miRNAs are transcribed by RNA polymerase II as primary miRNAs (pri-miRNAs) and can initially vary in size from a few hundred bases up to a tens of kilobases and have a 5' 7-methylguanosine cap and a 3' polyadenylated (poly(A)) tail (Saini et al., 2007). As such, from the time of transcription to carrying out its post-transcriptional regulatory function, a miRNA undergoes extensive processing (Yoontae et al., 2002) (Figure 1.3).

Single stranded pri-miRNA transcripts form double stranded stem loop structures that contain mature miRNA sequences. Each stem loop is made up of approximately 35 base pairs and a terminal loop. Flanking the base of each stem loop is single stranded RNA. The nuclear RNA-binding protein, DiGeorge syndrome critical region 8, DGCR8, binds to the base of a stem loop at single stranded-double stranded RNA junctions. With the DGCR8 cofactor Drosha, a nuclear RNAse III-type endonuclease that specifically cleaves double-stranded RNA, DGCR8 and Drosha form the microprocessor complex. Drosha initiates the miRNA maturation process by cropping the stem-loop and releasing a ~65 nucleotide hairpin RNA structure, this is called the pre-miRNA. Once cleaved by the microprocessor, the pre-miRNA is exported to the cytoplasm by Exportin 5 where Dicer, a cytoplasmic RNAse III-type endonuclease, cleaves the terminal loops generating a small RNA duplex. This RNA duplex is then loaded onto the Argonaute2 (Ago2) protein, which subsequently unwinds the RNA, forming the RNA-induced silencing complex (RISC) (Ha & Kim, 2014). In their mature form, microRNAs are single stranded 22 nucleotide RNAs that recognize and bind to complementary sequences in the 3' untranslated region of target mRNAs and, in doing so, guide the RNA-induced silencing complex (RISC) complex to repress translation.

Of the factors involved in miRNA biogenesis, DGCR8 is the only one currently known to be miRNA-specific (Wang et al., 2007) (Suh et al., 2010). In addition to being integral to miRNA processing, Drosha is reported to have a role in ribosomal RNA processing, and Dicer and Ago2 are required for the processing of short interfering RNAs (siRNAs) and endogenous small hairpin RNAs (endo-shRNAs) (Wu et al., 2000) (Bernstein et al., 2003)(Ha & Kim, 2014).

There are many zygotically transcribed miRNAs with specific expression patterns that are known to play roles in *Xenopus* development (Walker & Harland, 2008) (Walker & Harland, 2009) (Lund et al., 2009) (Rosa et al., 2009). In addition to these, it is known that a population of miRNAs are maternally deposited (Armisen et al., 2009). miRNAs have been well studied, but in regards to the maternal/zygotic contribution of miRNAs in development, two outstanding questions remain: which miRNAs are dependent on maternal versus zygotic DGCR8 and do maternally contributed miRNAs play a role in development?

Section 1.10 The goals of this thesis.

Due to the growing body of evidence that both maternally deposited and zygotically transcribed RNA-binding proteins are potent regulators of development, I have chosen to focus my thesis work on two RNA-binding proteins that are both present at fertilization and are transcribed upon zygotic genome activation: TAF15 and DGCR8.

Table 1.1 Comparison of the variation of zygotic genome activation in several model organisms, focusing on the time post fertilization and developmental stage.
Adapted from Tadros & Lipshitz, 2009.

	S. purpuratus	C. elegans	D. melanogaster	D. rerio	X. laevis	M. musculus	H. sapien
Cleavage cycle	~8	6 to 7	14	10	12	1	2
Time (hours)	15	3 to 3.5	2.5	2.75	5	22	48

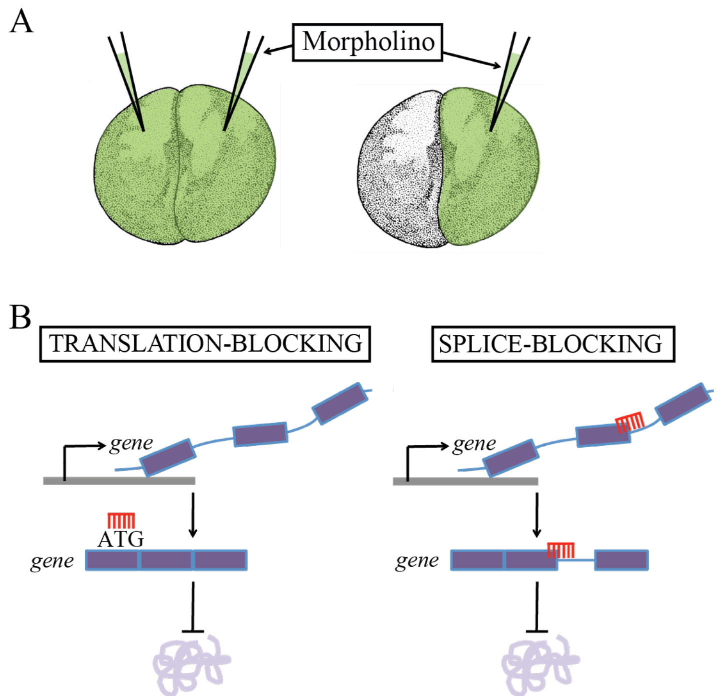


Figure 1.1 Experimental design to deplete embryos of a target gene. (A) Schematic showing injections targeting either two of two cells, to deplete a target gene from the entire embryo, or one of two cells, to deplete from one half with the uninjected side remaining as an internal control. (B) Schematic showing morpholinos designed to deplete both maternal and zygotic, translation-blocking, or zygotic-only, splice-blocking, gene.

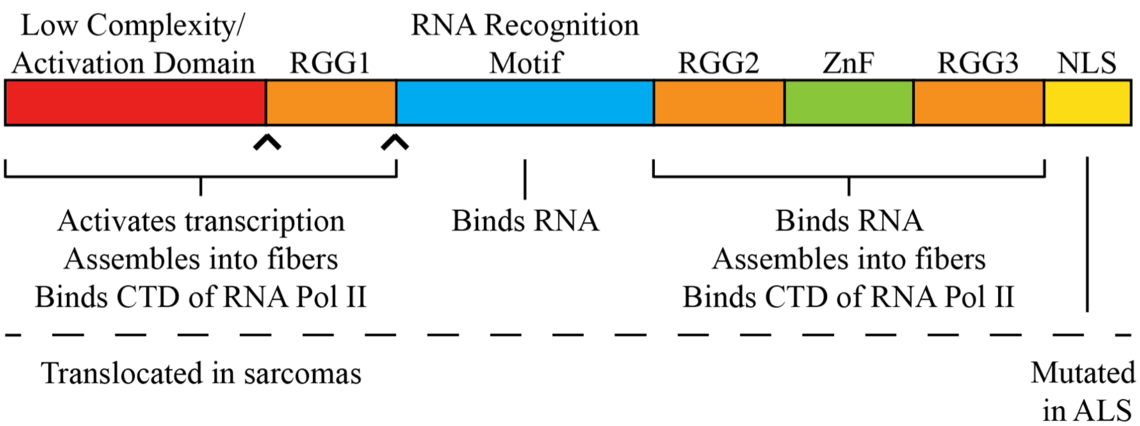


Figure 1.2 FET protein domains: biological functions and disease drivers. Comments above the dashed line describe normal function and those listed below are found in disease states. Arrowheads indicate sarcoma breakpoints. Adapted from Schwartz, et al., 2015 and Tan & Manley, 2009.

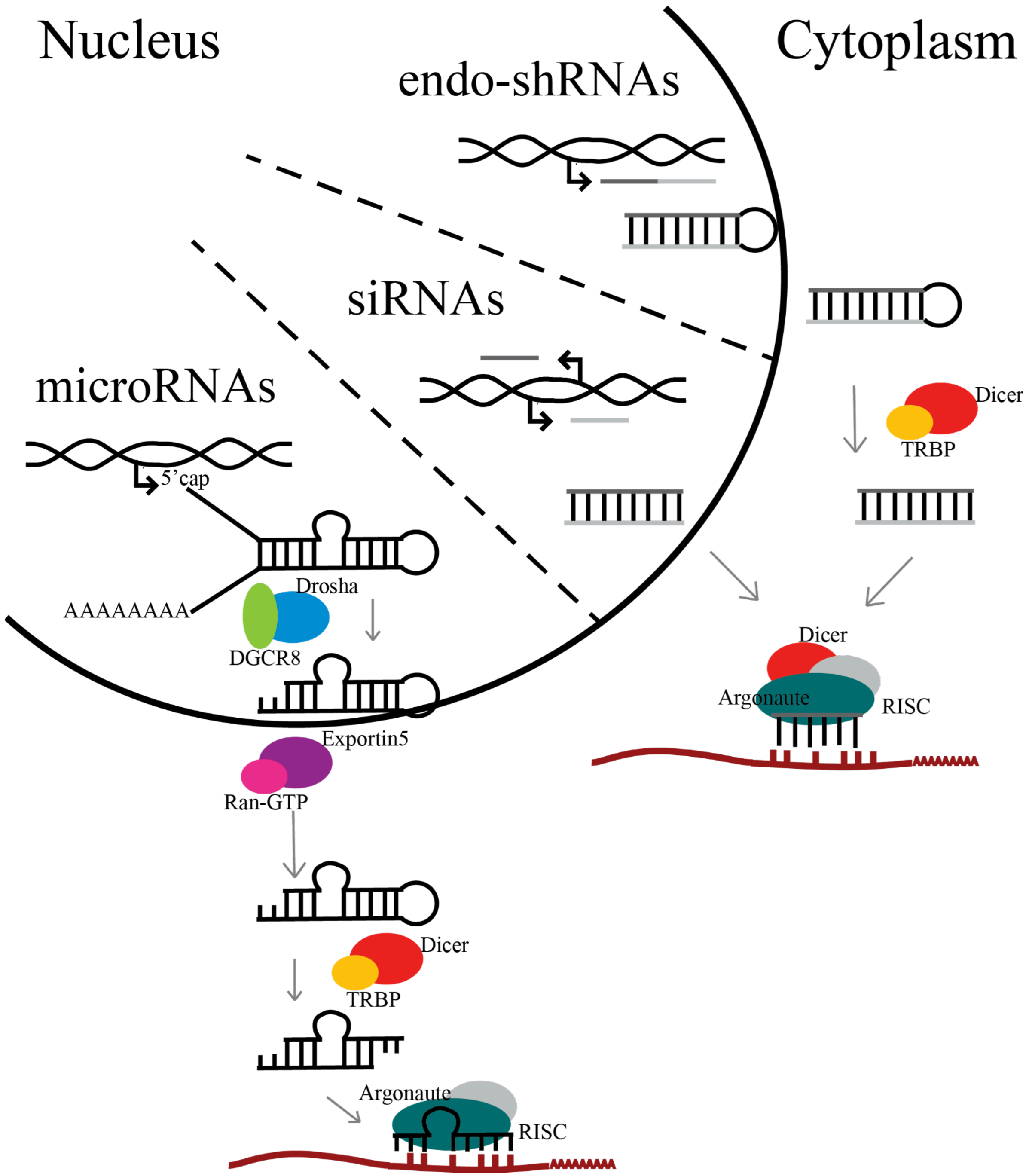


Figure 1.3 RNA interference biogenesis pathways. Dicer and Argonaute2 are necessary for miRNA, siRNA, and endo-shRNA biogenesis pathways. DGCR8 is specific to the miRNA biogenesis pathway.

Chapter 2: The atypical RNA binding protein, TAF15, regulates target genes at both the transcriptional and post-transcriptional level.

Section 2.1: Summary

Maternally contributed molecular determinants are required for the embryonic development of animals from a wide range of taxa. This maternal information will drive development until the stage where the embryo undergoes zygotic genome activation, transcribing nascent RNA from the zygotic genome. Few studies have worked to tease apart if and what the different developmental activities are concerning maternally contributed versus zygotically derived genes. In this work, I have found that the atypical RNA binding protein, TATA-binding protein-associated factor 15 (TAF15), has different biological activities depending on if it is maternally contributed or zygotically transcribed; interestingly, while utilizing different molecular mechanisms, the target genes of maternal or zygotic TAF15 are the same.

Section 2.2: Introduction

The FET family of atypical RNA-binding proteins is comprised of three members: Fused in sarcoma (Fus), Ewing's sarcoma (EWS), and TATA-binding protein-associated factor 15 (TAF15). These proteins have been primarily investigated in the clinical setting as they were initially discovered in 1992 as components of fusion oncogenes; found to play a role in various cancers such as sarcomas, leukemias, as well as neuronal degenerative diseases (Kovar, 2011) (Neumann et al., 2011) (Tan & Manley, 2009) (King et al., 2012) (Vance et al., 2009). It has only been in relatively recent studies that the functions of these proteins have been examined in their full length, "wild-type", form (Tan & Manley, 2009) (Schwartz et al., 2015) (Dichmann & Harland, 2012). From the studies that have looked at the structural, functional, and biochemical properties of this family, it was determined that these proteins have the functional capabilities akin to a molecular Swiss army knife; containing domains for transcriptional activation, RNA-binding, DNA-binding, and functioning in both RNA Polymerase II-mediated transcription and pre-mRNA splicing (Tan & Manley, 2009) (Schwartz et al., 2015). One exciting speculation is that the FET proteins may function to connect transcription and splicing.

A recent study examining the role of Fus in *Xenopus* development found that embryos depleted of Fus exhibit mesoderm differentiation defects and epithelial dissociation (Dichmann & Harland, 2012). The underlying mechanism of these phenotypes was intron retention in *fibroblast growth factor 8* (*fgf8*), *fibroblast growth factor receptor 2* (*fgfr2*), and *cadherin 1* (*cdh1*) transcripts. In all reported cases, every intron throughout the transcripts were retained (Dichmann & Harland, 2012). This study clearly showed that Fus is required for transcript processing in *Xenopus* development. It has been shown in mouse that both Fus and EWS mutants exhibit B-cell development defects, suggesting potential for redundancy of FET protein function (Hicks et al., 2000) (H. Li et al., 2007). Given the important role of FUS in development, the potential for function redundancy of FET family members, and a lack of basic research on normal functions, TAF15 is an interesting RNA binding protein that is likely to play an important role in early *Xenopus* development.

It has been well established that TAF15 is associated with a distinct population of transcription factor (TF)IID, a multiprotein complex composed of a variety of TATA-binding proteins (TBP) and TBP-associated factors (TAFs); well known for its role in transcriptional regulation and core-promoter recognition (Bertolotti et al., 1996). Additionally, TAF15 contains an RNA-recognition motif, suggesting a role as an RNA-binding protein (Bertolotti et al., 1996). In a more recent study, aimed at identifying RNAs associated with TAF15, it was found that the most abundant TAF15-associated RNA was U1 small nuclear RNA (snRNA) (Jobert et al., 2009) (Kugel & Goodrich, 2009). U1 snRNA is classically known as a component of the splicing machinery where it functions within a protein-RNA complex termed the U1 small nuclear ribonucleoprotein particle, which associates with the 5' splice site to initiate the process of splicing introns from precursor messenger RNAs (pre-mRNAs) (Kugel & Goodrich, 2009). This interaction with U1 snRNA again suggests a role for TAF15 in controlling post-transcriptional RNA splicing events (Kugel & Goodrich, 2009).

Classical RNA splicing can be separated in two functional groups, constitutive and alternative splicing. Constitutive splicing refers to the process by which introns are removed (spliced), stitching together exons in the same order that they are found in the genome, producing one gene product (Boutz, Bhutkar, & Sharp, 2015) (Perales & Bentley, 2009) (Pandya-Jones, 2011). Alternative splicing refers to the process by which exons of a gene may be included or excluded, producing numerous gene products (isoforms) and increasing gene product diversity and complexity (Grabowski & Black, 2001) (Black, 2003). It is thought that alternative splicing as mechanisms for expanding protein diversity could facilitate increased organismal complexity (Dichmann et al., 2015) (E. T. Wang et al., 2008). Both constitutive and alternative splicing occurs co-transcriptionally, prior to the transcriptional termination and polyadenylation of pre-mRNAs (Pandya-Jones & Black, 2009). A number of proteins facilitate RNA splicing (Chen & Cheng, 2012) but one factor, the serine/arginine-rich (SR) protein, *SR splicing factor 4* (*srsf4*), a member of the SR family of RNA-binding factors, that is important for both constitutive and alternative splicing, is of novel interest (Boutz et al., 2015) (Zhou & Fu, 2013). In addition to co-transcriptional splicing, there is also post-transcriptional splicing. It has been previously shown that the retention of individual introns in poly-adenylated pre-mRNAs serves as a mechanism for controlling gene expression; transcripts with retained introns will remain in the nucleus, preventing translation of the transcript, but following a cellular signal (e.g. osmotic or heat stress), the intron is excised and the protein is quickly translated (Boutz et al., 2015) (Ninomiya et al., 2011). Recently, SRSF4 was found to be important for the post-transcriptional splicing of single introns (Boutz et al., 2015).

In this study, I show that TAF15 is required for both proper RNA splicing and transcriptional regulation of genes during *Xenopus* development and that TAF15/*taf15* is expressed both maternally and zygotically (Xenbase and Figure 2.1). In order to differentiate the molecular mechanism of maternally and zygotically contributed TAF15, I used two different antisense morpholinos (MOs): either a translation-blocking MO to deplete both maternal and zygotic *taf15* (M+Z *taf15* depletion) or a splice-blocking MO to deplete only zygotic *taf15* (Z-only *taf15* depletion). I generated RNA-sequencing libraries from M+Z *taf15* depleted embryos to obtain an unbiased list of candidate genes affected by *taf15* depletion. From these libraries I was able to find genes with either affected transcript levels (described in Chapter 3) or with splicing defects (examined here in Chapter 2). Unexpectedly, I found that M+Z *taf15* depletion leads to a specific intron retention in a number of target genes, including the RNA splicing factor *srsf4*, while Z-only *taf15* depletion leads to a downregulation in transcription of the same target genes with no detectable intron retention. These data suggest that maternal and zygotic TAF15 regulate the same target genes, but surprising, through different molecular mechanisms.

The data in this chapter propose a model where maternal TAF15 cooperates with maternal SRSF4 to regulate the expression of maternally deposited mRNAs. In the time before zygotic genome activation, TAF15/SRSF4 control the timing of single intron excision, preventing the translation of all maternally deposited mRNAs at once. As will be described in more detail in chapter three, upon zygotic genome activation TAF15 cooperates with the core transcriptional machinery and is required for the transcriptional activation of target genes. Surprisingly, the same genes that are post-transcriptionally regulated by maternal TAF15 are transcriptionally regulated by zygotic TAF15. These data demonstrate that gene regulation by TAF15 occurs at both the post-transcriptional and transcriptional level and that this regulation is dependent on temporally expressed cofactors.

Section 2.3: Results

Section 2.3.1: taf15 is both maternally deposited, zygotically transcribed, and exhibits a specific gene expression pattern.

To study the role *taf15* in *Xenopus* development I first determined where the gene was expressed. To do this, I performed RNA *in situ* hybridization (ISH) on various embryonic stages (Figure 2.1A). From this assay I was able to observe the localization of maternally deposited *taf15* to the animal pole in the egg as well as in the 2- and 4-cell stage embryos. After zygotic genome activation (ZGA), during gastrulation (stage 11), *taf15* is seen in the ectodermal and underlying mesodermal germ layers but appears to be absent from the endoderm, or at least not detectable above background by ISH. During early neurulation (stage 13), *taf15* expression remains in the ectoderm but continues to become more specific, expressed dorsally throughout the neural plate and by late neurulation (stage 18), after the neural tube has closed, throughout the dorsal central nervous system, sensory placodes, and neural crest. By the tailbud stage (stage 26), expression is restricted to the dorsoanterior tissues of the embryo, specifically the brain, branchial arches, and placodes of the ear, eye, and kidney. Lastly, in the early tadpole (stage 35/36), *taf15* is seen specifically expressed in many tissues including the fore-, mid-, and hindbrain, central nervous system, otic vesicle, branchial arches, intermediate tubules of the kidney, and hypaxial muscle.

In addition to observing the expression pattern of *taf15* throughout different stages of embryogenesis, I also wanted to look at protein levels to validate that *taf15* is not only transcribed, but also translated (Figure 2.1B). Looking by Western blot, from the 2-cell to late tailbud stage, TAF15 is maternally deposited with a significant increase in protein expression following ZGA. This is consistent with *taf15* expression assayed by ISH (Figure 2.1A). It is important to note that many different species of TAF15 are observed in Western blots at each developmental stage. While the exact modifications remain to be determined, these species are likely the results of post-translational modifications to TAF15 (e.g. ubiquitylation, sumoylation, phosphorylation, etc.).

Section 2.3.2: taf15 depletion leads to gross morphological defects.

ISH identified the tissue types that express *taf15*, suggesting a role for *taf15* in many aspects of development. To elucidate the function of *taf15* in development I undertook a depletion study using antisense morpholinos specific for *taf15*. ISH demonstrated that *taf15* is both maternally deposited and zygotically transcribed; therefore I designed a translation blocking morpholino (MO) to ask how total loss of *taf15* effects embryogenesis (Figure 2.2A). Following depletion of both maternal and zygotic *taf15*, embryos exhibit gross morphological defects including: shortened anterior-posterior axis, loss of dorsal and posterior fin structures, reduced dorso-anterior head structures, and increased ventral tissue. It should be noted that the ventral-anterior fate of the cement gland appears unaffected. Additionally, embryos depleted of *taf15* exhibit defects in touch response; using a pipet tip, I can puncture a stage 31-equivalent embryo and they will remain completely unresponsive (data not shown). A normal touch response would be for an embryo to swim away the instant they are poked, this is what I observe with uninjected controls (data not shown). The phenotypes observed by depletion of maternal and zygotic *taf15* were consistent with the expression patterns observed by ISH (Figure 2.1A). As a MO specificity control, I injected some embryos with the same dose of a five mismatch morpholino and found that embryos injected with a five mismatch morpholino do not phenocopy those injected with *taf15* translation blocking morpholino, suggesting the effects of the translation blocking morpholino are specific to *taf15* depletion (Figure 2.2A).

To determine the efficiency of *taf15* depletion, I performed Western blot analysis to measure total TAF15 (Figure 2.2B). By this method, I can measure that in stage 15-equivalent embryos, TAF15 is reduced to 20-30% of control levels following injection of a translation-blocking morpholino (targeting maternal and zygotic *taf15*) or a splice-blocking morpholino (targeting zygotic *taf15* only).

Section 2.3.3: Measuring changes in gene expression following taf15 depletion.

To assess how *taf15* depletion affects gene expression, I generated single-embryo RNA-sequencing (RNA-seq) libraries from embryos injected with translation blocking morpholino (Figure 2.3A). Using a standardized RNA-seq analysis pipeline, the Tuxedo Suite (Trapnell et al., 2012), and DESeq (Love, Huber, & Anders, 2014), a list of statistically significant differentially expressed gene transcripts between morpholino-injected and uninjected embryos was generated (Appendices 1 and 2). Ultimately, I generated two sets of RNA-seq libraries. The first RNA-seq libraries were made from three uninjected and three M+Z *taf15* depleted *X. tropicalis* embryos, stage 15. For the first set of libraries, because there were no known transcripts specifically affected following *taf15* depletion in *Xenopus*, I assessed morpholino injection by the presence of fluorescein tracer. Following RNA-seq analysis of this first library, I assessed expression level changes of all samples and determined that one of the stage 15 equivalent M+Z *taf15* depleted libraries had expression levels equivalent to uninjected embryos. This suggests insufficient M+Z *taf15* depletion and this library was eliminated from subsequent analysis. A stage 15 uninjected and M+Z *taf15* depleted sample was remade with the second set of RNA-seq libraries. The second set of RNA-seq libraries were made from three uninjected and three M+Z *taf15* depleted *X. tropicalis* embryos, stage 10, and one uninjected and one M+Z *taf15* depleted *X. tropicalis* embryo, stage 15. For the second set of libraries, because analysis of the first set of libraries gave a list of transcripts specifically affected following *taf15* depletion, I assessed the extent of depletion by measuring *ventx2.1*, *sp5l*, and *fgfr4* intron 1 transcript levels by qPCR. Embryos with a significant increase in *ventx2.1*, *sp5l*, and *fgfr4* intron 1 expression were selected to make the second set of libraries. Fus, another FET family member, is known to regulate splicing in *Xenopus* (Dichmann & Harland, 2012). Given the previous connection to gene splicing, concurrent with analyzing transcript abundance, I was interested in determining if TAF15 played a role in splicing and therefore analyzed differential intron-exon usage between morpholino-injected and uninjected embryos. To do this, I used the Bioconductor package, DEXSeq (Reyes et al., 2014). This chapter will focus on the role of TAF15 in proper splicing, from data generated from the DEXSeq analysis, while chapter 3 will focus on total changes in gene expression levels, from data generated from the Tuxedo Suite and DESeq analysis.

Section 2.3.4: Maternal and zygotic depletion of taf15 leads to retention of specific introns.

Using DEXSeq to assay the RNA-seq libraries for differential intron-exon usage, I was able to determine that embryos depleted of both maternal and zygotic *taf15* retain introns in a select set of genes, a subset of which are featured in Figure 2.4. Although the DEXSeq data supports that >1000 genes have differential intron-exon usages when comparing morpholino-injected to uninjected embryos, upon manual inspection, the majority of these results were determined to be minor splice changes, not detectable at the transcript level (Figure 2.5). By viewing the RNA-seq read alignments in the Integrative Genomics Viewer (IGV), I could verify differences in intron usage totaling ~8 (UC) versus ~16 (M+Z *taf15* depleted) reads (e.g. *srsf1*) (Figure 2.5). Although this is a significant two-fold difference, and the differences are potentially real, read numbers like these are similar to background levels and they could be false positives. For this reason, I was interested in following up on major intron retention changes, <10 (UC) versus 650 (M+Z *taf15* depleted) (e.g. *fgfr4*), and will focus on four genes with verified intron retentions: *fgfr4*, *isl1*, *pax8*, and *srsf4* (Figure 2.4 and Figure 2.10A). Because there are too many DEXSeq results to manually filter out minor versus major splice changes (and this would be subjective), current work is ongoing to try different bioinformatics approaches to filter out minor splice changes and obtain a list of genes with transcripts containing only major intron retentions.

Section 2.3.5: Maternal and zygotic TAF15 regulate fgfr4 expression through different mechanisms.

The receptor tyrosine kinase, *fibroblast growth factor receptor 4* (*fgfr4*) was found by RNA-seq analysis to have an intron retention following maternal and zygotic depletion by translation-blocking *taf15* morpholino (M+Z depleted) (Figure 2.6). Using quantitative (qPCR), I was able to validate this RNA-seq result and measure that intron 1 of *fgfr4* is retained at a six fold higher level in M+Z depleted embryos compared to uninjected embryos. Interestingly, however, when a splice-blocking morpholino is used to deplete zygotic-only *taf15* (Z depleted), no intron retention is observed (Figure 2.6A). However, looking at the total *fgfr4* transcript levels, I also observe differences when comparing M+Z to Z depleted *taf15* embryos. Here I see that the total transcript level of *fgfr4* is reduced in Z depleted embryos, and that this reduction is significantly reduced from the total *fgfr4* expressed in M+Z depleted embryos (Figure 2.6A). Consistent with the qPCR data, RNA *in situ* hybridization for total *fgfr4* transcript shows no reduction of *fgfr4* expression in the side of the embryo depleted for M+Z *taf15* whereas in the side depleted for Z *taf15*, there is a readily observed reduction (Figure 2.6B). Seeing that M+Z *taf15* depletion results in an intron retention in *fgfr4*, and that Z-only *taf15* depletion leads to a reduction in total *fgfr4*, I wanted to ask how these depletion conditions affect overall FGFR4 expression (Figure 2.7A). As expected, by Western blot, I am able to see a reduction in TAF15 to ~20% in both M+Z and Z-only *taf15* depleted embryos (Figure 2.7A). Consistent with the data that *fgfr4* is regulated by both M+Z TAF15, when I blot for FGFR4 after either M+Z or Z-only *taf15* depletion, I see a reduction in total FGFR4 to 35% and 52% respectively (Figure 2.7A). Further support for a role of *taf15* specifically regulating *fgfr4* is that FGFR4 reduction can be rescued in *taf15* depleted embryos that are coinjected with human *TAF15* (Figure 2.7B).

fgfr4 signaling regulates mid/hindbrain development as the injection of dominant negative FGFR4 suppresses the homeobox transcription factor, *engrailed 2* (*en2*), which marks the mid/hindbrain boundary (Hongo et al., 1999). Another gene, the paired box transcription factor, *paired box 2* (*pax2*), is also expressed in the mid/hindbrain region and is known to act upstream of *en2* (Koenig et al., 2010). To functionally test if both depletion conditions of *taf15* disrupt mid/hindbrain development, I analyzed *pax2*; in both cases, *pax2* expression is reduced (Figure 2.6B).

These data suggest that both M+Z TAF15 regulate *fgfr4*, but through different mechanisms: M+Z *taf15* depletion (translation-blocking MO) disrupts *fgfr4* expression through intron retention, and Z-only *taf15* depletion (splice-blocking morpholino) disrupts *fgfr4* expression by reducing transcript levels. These results suggest that maternal TAF15 is sufficient for the proper splicing of *fgfr4* whereas zygotic TAF15 is required for transcriptional activation. To my knowledge, this is the first example of a factor having a different mechanism of activity based on whether it is produced maternally or zygotically.

To further test my hypothesis that maternal and zygotic TAF15 regulate the same set of target genes, but through different mechanisms, I performed functional studies on two more genes shown by RNA-seq analysis to have intron retention following M+Z *taf15* depletion.

Section 2.3.6: Maternal and zygotic TAF15 regulate isl1 expression through different mechanisms.

The homeodomain transcription factor, *ISL LIM homeobox 1* (*isl1*) provides a second example found by RNA-seq analysis to have an intron retention following M+Z *taf15* depletion (Figure 2.8). Just as with *fgfr4*, I was able to use qPCR to validate the RNA-seq result and measure that intron 3 of *isl1* is retained at a five fold higher level in M+Z *taf15* depleted embryos compared to uninjected embryos. Again, following Z-only *taf15* depletion, no intron retention was observed (Figure 2.8A). The total transcript level of *isl1* was reduced in Z depleted embryos, and this reduction was significantly different from the total *isl1* expressed in M+Z depleted embryos, which was unaffected (Figure 2.8A). Consistent with these qPCR data, RNA *in situ* hybridization for total *isl1* transcript shows less reduction of *isl1* expression in an embryo with one side depleted for M+Z *taf15* compared to the an embryo with one side depleted for Z *taf15* (Figure 2.8B).

The early differentiation of sensory neurons requires *isl1* (Pavan & Raible, 2012). To perform a functional test to assay how intron retention in *isl1* following M+Z *taf15* depletion affects *isl1* activity, I performed immunohistochemistry and stained for sensory neurons. In embryos where half the embryo was depleted of M+Z *taf15*, and the other half was uninjected as an internal control, staining for sensory neurons (tor 219.2.13, Chapter 5: Whole-mount Immunohistochemistry) on the M+Z *taf15* depleted side was significantly reduced and effectively missing, with no observable extended axons (Figure 2.8C). This result is consistent with the observation that *taf15* depleted embryos fail to respond to touch.

Section 2.3.7: Maternal and zygotic TAF15 regulate pax8 expression through different mechanisms.

The paired box transcription factor, *paired box 8* (*pax8*) provides a third gene found by RNA-seq analysis to have an intron retention following M+Z *taf15* depletion (Figure 2.9). As with *fgfr4* and *isl1*, I used qPCR, to validate the RNA-seq results and determined that intron 6 of *pax8* was retained at a five fold higher level in M+Z *taf15* depleted embryos compared to uninjected embryos. Similar to *fgfr4* and *isl1*, intron retention is only observed after M+Z *taf15* depletion and Z-only *taf15* depletion showed no intron retention (Figure 2.9A). Unlike *fgfr4* and *isl1*, the total transcript level of *pax8* is reduced in both M+Z and Z-only depleted embryos, although expression is more greatly reduced with Z-only depletion (Figure 2.9A).

Pronephric tubule development requires *pax8* (Buisson et al., 2015). During *Xenopus* tailbud stages, *foxj1.2* is expressed in the presumptive nephrostomes of the pronephros (Choi et al., 2006). To functionally test if *taf15* depletion disrupts *pax8*-dependent pronephros development I looked *in situ* at the *pax8* target gene, *foxj1.2* (Figure 2.9B). Importantly, in both M+Z and Z-only *taf15* depletion condition, *foxj1.2* expression is reduced demonstrating that the molecular activity of TAF15 is upstream of *pax8*, *foxj1.2*, and controls the proper formation of the pronephric tubule (Figure 2.9B).

Section 2.3.8: Maternal TAF15 may function with SRSF4 to regulated splicing.

The alternative splicing factor, *serine/arginine-rich splicing factor 4* (*srsf4*) provides a fourth gene found by RNA-seq analysis to have an intron retention with M+Z *taf15* depletion (Figure 2.10A). Just as with *fgfr4*, *isl1*, and *pax8*, qPCR analysis validated the RNA-seq results and demonstrated that intron 5 of *srsf4* is retained almost six fold in M+Z *taf15* depleted embryos compared to uninjected embryos. Interestingly, and consistent with the previous genes identified to have intron retentions, the intron retention in *srsf4* was only identified after M+Z *taf15 depletion and* Z-only *taf15* depletion led to no detectable intron retention (Figure 2.10A).

Surprisingly, total *srsf4* transcript levels showed that all morpholino-injected embryos had a significant decrease in *srsf4* abundance, a trend not seen for *fgfr4*, *isl1*, or *pax8* (Figure 2.10B). The overall decrease in *srsf4* transcripts following all MO injections may be due to an overall sensitivity of the *srsf4* transcript to the stresses of embryonic manipulation. Because I do not see splicing defects with Z-only *taf15* depletion or injection of a five mismatch MO, the significant decreases in total *srsf4* expression that are observed are different from the previous examples. Although the levels of *srsf4* in M+Z *taf15* versus Z *taf15* depleted embryos are not significantly different from each other, the M+Z *taf15* depleted embryos (the condition where I see intron retention) consistently showed the lowest levels of *srsf4*. This result is the opposite of what was observed with *fgfr4*, *isl1*, and *pax8*, where Z-only *taf15* depletion resulted in the greatest decrease in transcript. It is unlikely that *srsf4* is more sensitive to Nonsense Mediate Decay (NMD) than *fgfr4*, *isl1*, and *pax8* because transcripts with intron retentions are retained in the nucleus and not substrates of NMD (Boutz et al., 2015).

SRSF4 is required for the post-transcriptional excision of single introns from target genes (Boutz et al., 2015). The splicing activity of *srsf4* is modulated by the LAMMER dual specificity kinase, *CDC-like kinase 1* (CLK1). CLK1-dependent phosphorylation of SRSF4 facilitates the release of SRSF4 from nuclear speckles and subsequent recruitment of this splicing factor to nascent pre-mRNAs (Naro & Sette, 2013). In mammalian cells, CLK1 levels are themselves controlled by retention of introns 3 and 4 (Ninomiya et al., 2011). Retention of these introns is proposed to hold *clk1* transcripts in a "ready state" that can be rapidly matured by splicing, while preventing premature translation (Ninomiya et al., 2011). I therefore propose a hypothesis that intron retention in *srsf4* caused by M+Z *taf15* depletion leads to a decrease in total SRSF4 activity and a loss of splicing activity, which the cell compensates for by increasing CLK1 protein, the activator of SRSF4. Thus, upon depletion of M+*Z taf15*, both *clk1* mRNA and protein levels would increase. Interestingly, upon M+Z *taf15* depletion there is an increase in the levels of mature *clk1* transcript, and a decrease in the retention of intron 3 consistent with increased production of CLK1 and increased activation of SRSF4 (Figure 2.11B). Thus, it appears that there are two mechanisms to increase CLK1 levels, first by increased translation via removing the retained intron 3 and second by increased overall transcription of the *clk1* gene. These increases in total *clk1* were only observed with M+Z *taf15* depletion, and not with Z-only *taf15* depletion or injection of a five mismatch MO, consistent with the conditions that severely reduce the level of functional *srsf4* mRNA.

Given the increased intron retention after depletion of *taf15*, I hypothesized that SRSF4 was a splicing cofactor with TAF15. Using western blot analysis I showed that SRSF4 is maternally deposited into the embryo (stage 6) and is present in the embryo following zygotic genome activation during gastrulation (stage 10) and neurulation (stage 15) (Figure 2.12A). The expression profile of SRSF4 (Figure 2.12A) and TAF15 (Figure 2.1B) indicate that TAF15 and SRSF4 are expressed at the right time to be cofactors. Given that TAF15 and SRSF4 are coexpressed, I wanted to assay for their interaction. I undertook immunoprecitation (IP) experiments with TAF15 to determine if SRSF4 could be pulled down with TAF15 (Figure 2.12B). While I was able to see a band in my TAF15 IP samples that does not appear to be present in the control rabbit IgG IP samples, the size of the band is different than the predicted molecular weight of SRSF4. One explanation for this size shift could be any covalently bound post-translational modification of SRSF4. While the shift seems to be greater than what would be expected of phosphorylation, this is a possibility, as well as any other modification such as sumoylation, glycosylation, or ubiquitylation. While these data are preliminary, they do suggest that TAF15 and SRSF4 could be found in a complex together and supports the hypothesis that SRSF4 is a RNA splicing cofactor of TAF15.

These results presented here suggest the perplexing and circular idea that TAF15 and SRSF4 could act as splicing cofactors, responsible for the splicing defects seen in *srsf4* itself, *fgfr4*, *isl1*, and *pax8*. However, because *srsf4* is misspliced following M+Z depletion of *taf15*, it is also possible that the *srsf4* missplicing is responsible for the splicing defects of *fgfr4, isl1, and pax8*. If the missplicing events in *srsf4*, *fgfr4*, *isl1*, and *pax8* were all due to loss of TAF15 as a cofactor to SRSF4, this would suggest that rescuing the loss of TAF15 would lead to an equal rescue of splicing defects in *srsf4*, *fgfr4*, *isl1*, and *pax8*. However, when M+Z *taf15* depletion is rescued by injecting human *TAF15*, only *srsf4* shows reduced intron retention while *fgfr4, isl1,* and *pax8* intron retentions are not rescued (Figure 2.13). These data suggest that the splicing defects of *fgfr4*, *isl1*, and *pax8* may be downstream of the (assumed) loss of SRSF4 following

M+Z depletion of *taf15,* and since the rescue of *srsf4* splicing by human *TAF15* is incomplete, the levels of SRSF4 may be too weak to rescue these secondary splicing defects.

Section 2.3.9: A comparison of the gross morphological defects observed following taf15 overexpression and depletion.

In addition to studying the gross morphological phenotypes of *taf15* depletion, I also wanted to examine how overexpression (o.e.) *taf15* affects *Xenopus* development (Figure 2.14). Following injection of a total of 300pg into two cell embryos, embryos were allowed to develop to a stage where changes in gross morphology were readily observed. Both *taf15* depleted and overexpressing embryos have a shorted anterioposterior axis with reduced or lost dorsal and posterior fin structures. Unlike M+Z *taf15* depleted embryos however, *taf15* overexpressing embryos have relatively unaffected eye and head development. Additionally, some *taf15* overexpressing embryos exhibit mild morphogenetic defects resulting in failed posterior neural tube closure. Lastly, unlike *taf15* depleted embryos that do not respond to touch, *taf15* overexpressing embryos respond to touch in an uncontrolled and spastic manner, twitching and swimming in circles long after stimulation (data not shown). It has been previously shown in cell culture that the overexpression of TAF15-GFP (as well as Fus-GFP and EWS-GFP) causes stress granule formation and that the the FET-GFP proteins localize to these stress granules (Andersson et al., 2008). It is possible that the uncontrolled touch response of *taf15* overexpressing embryos is due to the subcellular mislocalization of TAF15 and possible plaque-like formations. It seems that the *taf15* overexpression phenotype is somewhat reminiscent of neuromuscular dysfunction.

Section 2.4: Discussion

From these data, the following model can be proposed (Figure 2.15). In the embryonic environment preceding zygotic genome activation, the translation of maternally deposited mRNAs is regulated, in order to prevent all maternal mRNAs from being translated at once. When a single intron is retained, this keeps the mRNA in the nucleus in a “ready to go” state. Once translation of this message is required, the intron is quickly excised through the RNA binding activity of TAF15 and the splicing cofactor SRSF4 and the mRNA is exported to the cytoplasm. Thus, in this environment, where there is no active transcription but only maternally deposited mRNAs, this provides a mechanism to temporally and spatially control the translation of specific transcripts. In the embryonic environment where zygotic genome activation has occurred, and therefore active transcription occurs, I propose that TAF15 associates with the core promoter, using either its N-terminal low complexity domain or RNA-binding domains to bind the C-terminal domain of RNA pol II, and activate transcription of specific targets. The data presented here is the first example, to my knowledge, where a set of target genes is regulated through two different molecular mechanisms (post-transcriptionally or transcriptionally), depending on if the regulatory protein (TAF15) is maternally deposited or zygotically transcribed.

A perplexing result is the lack of zygotic effect, as measured by transcriptional downregulation, following M+Z *taf15* depletion. Looking at the qPCR data for *fgfr4*, *isl1*, and *pax8*, there is a greater decrease in total transcript levels with Z-only *taf15* depletion, as compared to M+Z *taf15* depletion. One explanation for this phenomenon could have to do with when, and to what level, a target gene is transcribed (and if the target gene is maternally deposited) (Figure 2.16). Maternal TAF15 will affect the splicing of a target gene. It has been previously shown that transcripts with detained introns are retained in the nucleus and are not subject to nonsense mediate decay, resulting in total transcript levels that do not decrease. Zygotic TAF15 will affect the total transcript levels of a target gene, resulting in total transcript levels that will decrease. The later a gene is transcribed (e.g. *pax8*), the less effect maternal TAF15 will have on its regulation and the more the effect of zygotic *taf15* depletion, and therefore decrease in transcript level, will be observed (Figure 2.16).

The data presented here clearly show that the FET family of atypical RNA proteins, unlike in mouse, do not function redundantly in *Xenopus* development. As it has been previously published, Fus is required to excise all introns from a target transcript, functioning as a regulator of constitutive splicing (Dichmann & Harland, 2012). It cannot be ruled out, however, that Fus functions at the transcriptional level, as levels of gene expression were not closely studied (Dichmann & Harland, 2012). In this work, I have found that maternal TAF15 functions post-transcriptionally, likely with a partner such as SRSF4, and is required to excise single introns from a target transcript; a mechanism that has been shown retain transcripts in the nucleus preventing transcript translation, thus regulating the timing of gene expression. Zygotic TAF15, on the other hand, functions at the transcriptional level to regulate target genes.

Future studies will aim to resolve the biochemical mechanism underlying the different biological functions of maternal and zygotic TAF15. By mutating different domains of TAF15, I hope to resolve which domains are required for splicing (maternal TAF15) or transcriptional regulation (zygotic TAF15). Additionally, to investigate if the splicing targets of TAF15 are direct I will perform RNA-immunoprecipitations (IP). Using a TAF15 antibody I will IP for TAF15 and assay for *fgfr4*, *isl1*, *pax8*, and *srsf4*. I will also further resolve the relationship of TAF15 and SRSF4 as splicing cofactors. In addition to repeating the experiments that immunoprecipitated (IP) TAF15 and Western blotted for SRSF4, I will also IP for SRSF4 and blot for TAF15. It is also important to resolve if SRSF4 decreased only in M+Z *taf15* depleted embryos, where I see splicing defects, or if it is also decreased in Z *taf15* depleted embryos, where I do not see splicing defects; the qPCR for total *srsf4* transcripts has generated some confusing data (Figure 2.10B). Furthermore, I will look at the abundance of TAF15 at earlier stages in M+Z versus Z-only *taf15* depleted embryos. I would predict that the maternal product would be depleted in M+Z *taf15* depleted embryos and affect splicing of new transcripts following zygotic genome activation (ZGA). Moreover, if TAF15 is required to regulate the timing of maternal mRNA translation by modulating splicing before zygotic genome activation, then I should see these introns retained by qPCR before ZGA, independent of embryonic manipulation. Lastly, using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) genome editing system, I will target zygotic *taf15* and validate that zygotic *taf15* mutants (CRISPR/Cas9-targeted) phenocopy the transcriptional downregulation observed in Z *taf15* depleted embryos injected with splice-blocking morpholino.

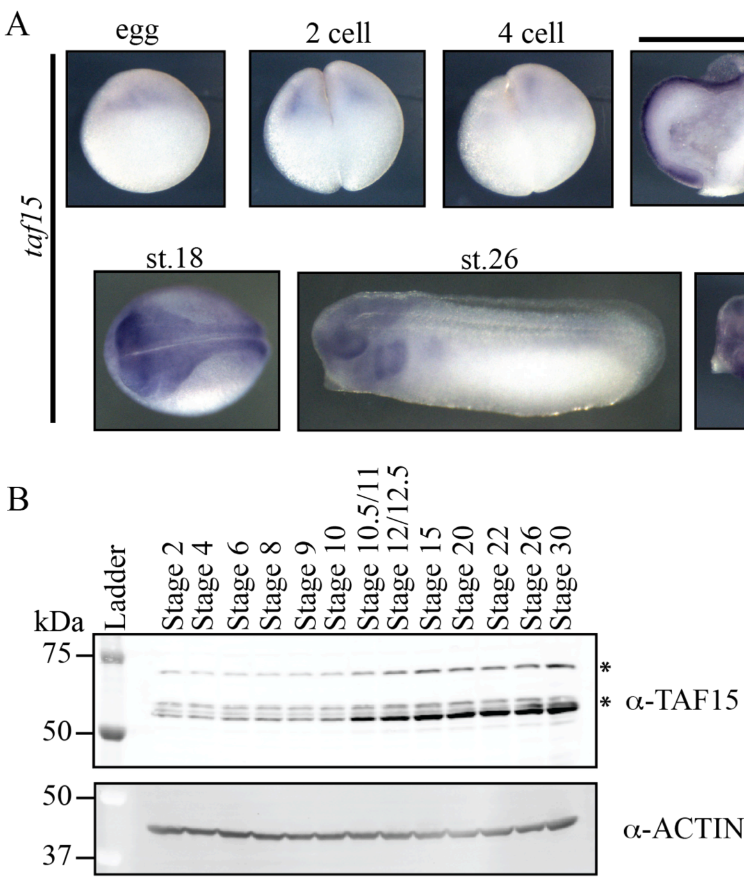


Figure 2.1 Expression of *taf15*/TAF15 in *Xenopus tropicalis*. (A) *In situ* RNA hybridization for *taf15*, fertilized egg to early tadpole. Egg, 2 cell, 4 cell, and stage 11, cross sections. Stage 13 and 18, dorsal view, anterior to the left. Stage 26 and 35/36, lateral view, anterior to the left. (B) Western blot for TAF15 and ACTIN loading control, two cell to early tadpole. * Indicates potential post-translational modification.

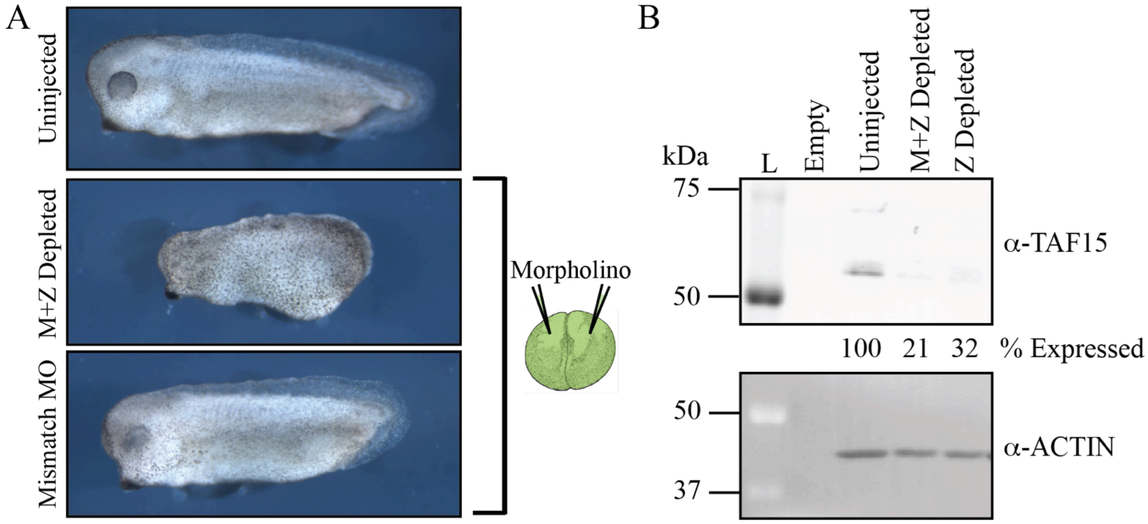


Figure 2.2 ***Xenopus tropicalis taf15*** **depletion.** (A) Brightfield images of stage 31 embryos, uninjected or following injection of 34ng of translation-blocking morpholino (M+Z Depleted) or mismatch morpholino (Mismatch MO). (B) LI-COR images of Western Blots for TAF15 and ACTIN loading control. Lysates collected from stage 15 uninjected embryos (Uninjected), and stage 15 equivalent embryos injected with 34ng translation blocking morpholino (M+Z Depleted), and 16ng splice-blocking morpholino (Z Depleted). Percent TAF15 expression in morpholino-injected embryos compared to uninjected (% Expression).

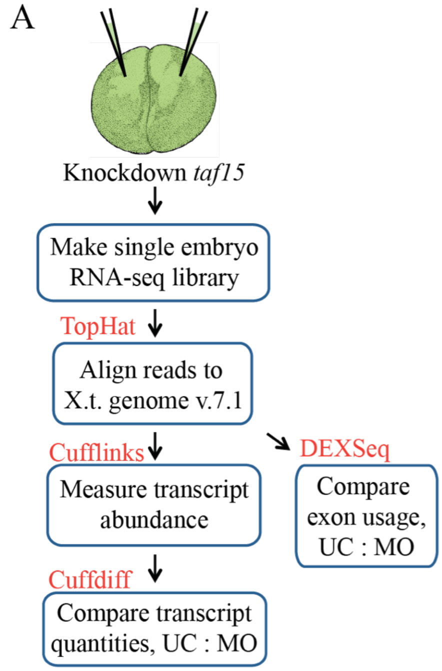


Figure 2.3 Workflow to deplete embryos of *taf15* and measure expression levels of target genes. (A) Schematic showing the approach to generate and sequence *taf15* depleted embryos and use bioinformatics to analyze changes in quantities and species of taf15 target genes.

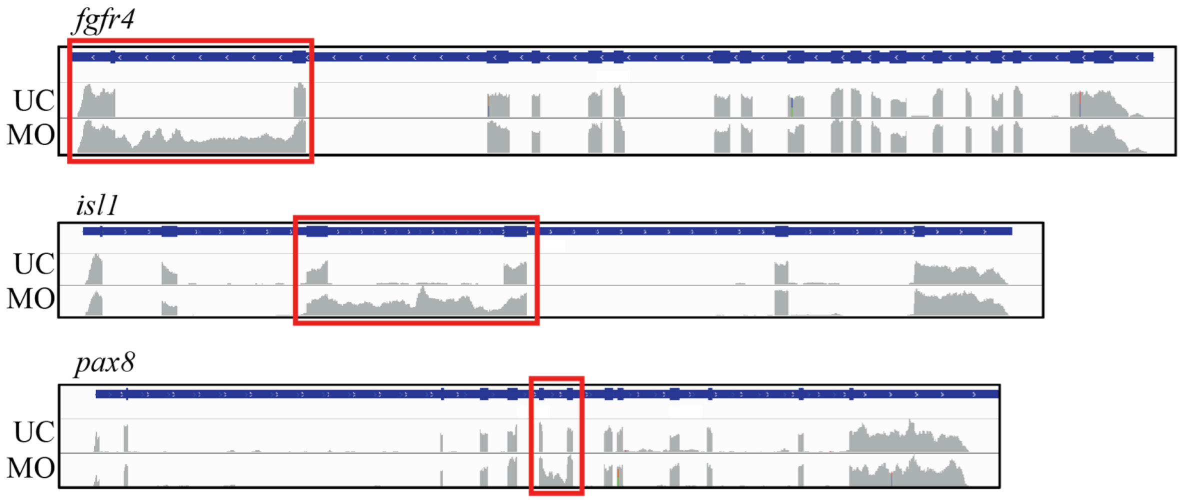


Figure 2.4 Maternal and zygotic depletion of *taf15* results in single intron-retention in target genes. Three representative genes, *fgfr4*, *isl1*, and *pax8*, that exhibit a single intron retention. For each gene, RNA-seq read alignments from an uninjected (UC) stage 15 embryo, are the top alignments, and read alignments from maternal and zygotic *taf15* depleted (MO) stage 15 equivalent embryo, are the bottom alignments. Reads aligning to a retained intron are boxed in red. Images are from the Integrative Genomics Viewer (IGV). Above the UC alignments is the gene model in blue oriented 5’ to 3’.

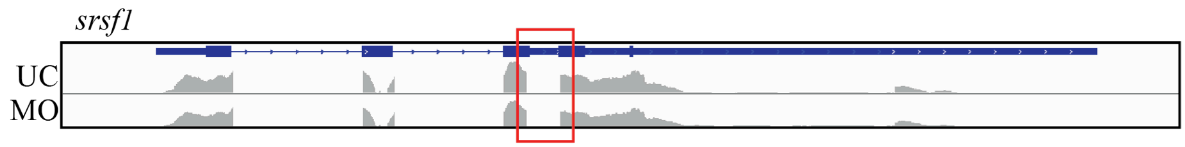


Figure 2.5 Example of minor splice changes following maternal and zygotic depletion of *taf15*. A representative gene, *srsf1*, that exhibits minor splice changes. RNA-seq read alignments from an uninjected (UC) stage 15 embryo, are the top alignments, and read alignments from maternal and zygotic *taf15* depleted (MO) stage 15 equivalent embryo, are the bottom alignments. Minor splice changes boxed in red, not visible at the whole transcript level. Images are from the Integrative Genomics Viewer (IGV). Above the UC alignments is the gene model in blue oriented 5' to 3'.

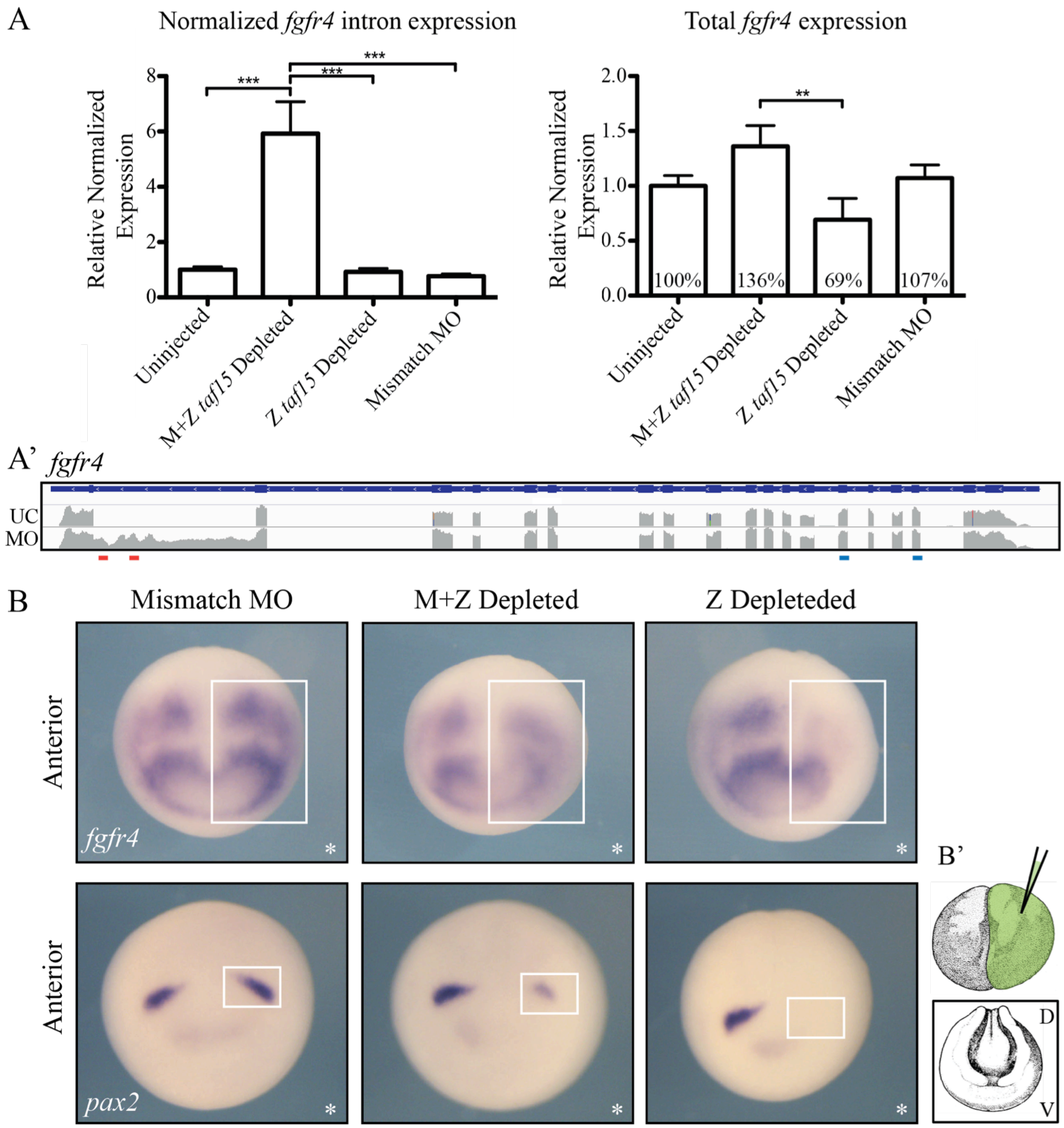

A
Normalized fgfr4 intron expression
Relative Normalized Expression
8
6
4
2
0
***
***
***
Uninjected
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO
Total fgfr4 expression
2.0
1.5
1.0
0.5
0.0
**
100%
136%
69%
107%
A' fgfr4
UC
MO
B
Mismatch MO
M+Z Depleted
Z Depleteded
Anterior
fgfr4
pax2
B'
D
V

Figure 2.6 Expression of *fgfr4* and *pax2* upon *taf15* depletion. (A) Quantitative RT-PCR measuring *fgfr4* intron and total expression. Uninjected stage 15 *Xenopus tropicalis* embryos (uninjected) and stage 15 equivalent embryos injected with 34ng translation-blocking morpholino (M+Z *taf15* Depleted), 16ng splice-blocking morpholino (Z *taf15* depleted), and 34ng mismatch morpholino (Mismatch MO). *** $p<0.0001$, ** $p<0.005$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses. (A') Schematic showing primer loci to measure intronic (red bars) and total (blue bars) *fgfr4* transcript. Gene model oriented 5' to 3'. Same RNA-seq alignments as used in Figure 2.4. (B) RNA in situ hybridization to *fgfr4* and the *fgfr4* target gene *pax2*. Anterior view, dorsal up, embryos injected 1 of 2 cells with morpholino, * = injected side, white boxes mark the expected gene expression domain on the injected side. (B') Schematic of 1 of 2 cell injection and anterior view of stage 15 *Xenopus embryo*, dorsal (D), ventral (V).

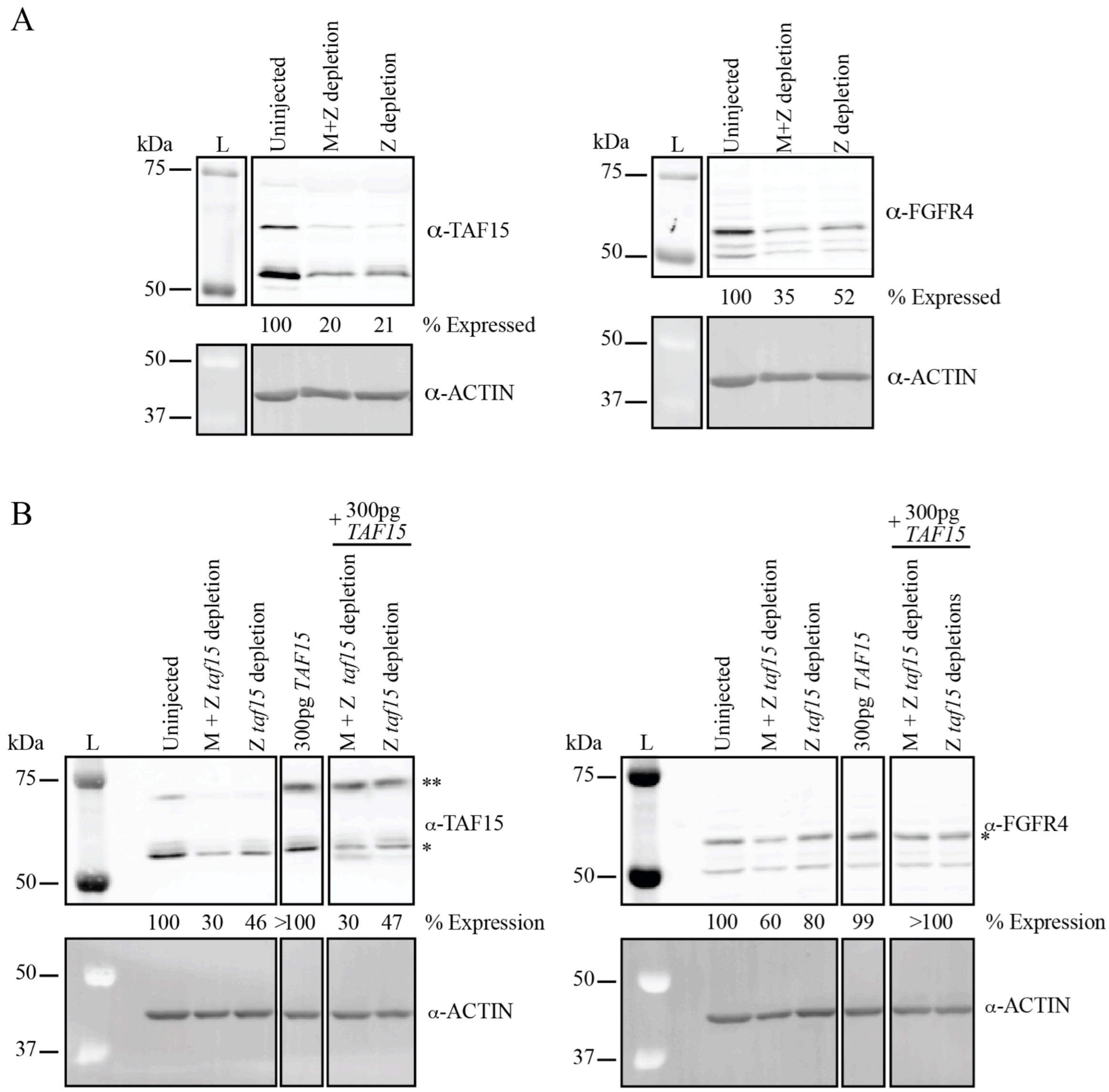


Figure 2.7 Depletion and rescue of TAF15 and FGFR4. (A) LI-COR images of Western Blots for TAF15, FGFR4, and ACTIN loading control. Lysates collected from stage 15 uninjected embryos (Uninjected), and stage 15 equivalent embryos injected with 34ng translation blocking morpholino (M+Z Depleted), and 16ng splice-blocking morpholino (Z Depleted). Percent TAF15 or FGFR4 expression in morpholino-injected embryos compared to uninjected (% Expression). (B) In addition to measuring TAF15 and FGFR4 depletion, as in (A), rescue of TAF15 and FGFR4 was analyzed using lysates from embryos injected with 300pg human *taf15* (TAF15). ** Indicates TAF15 translated from human TAF15. * Indicates the band used to quantify protein expression.

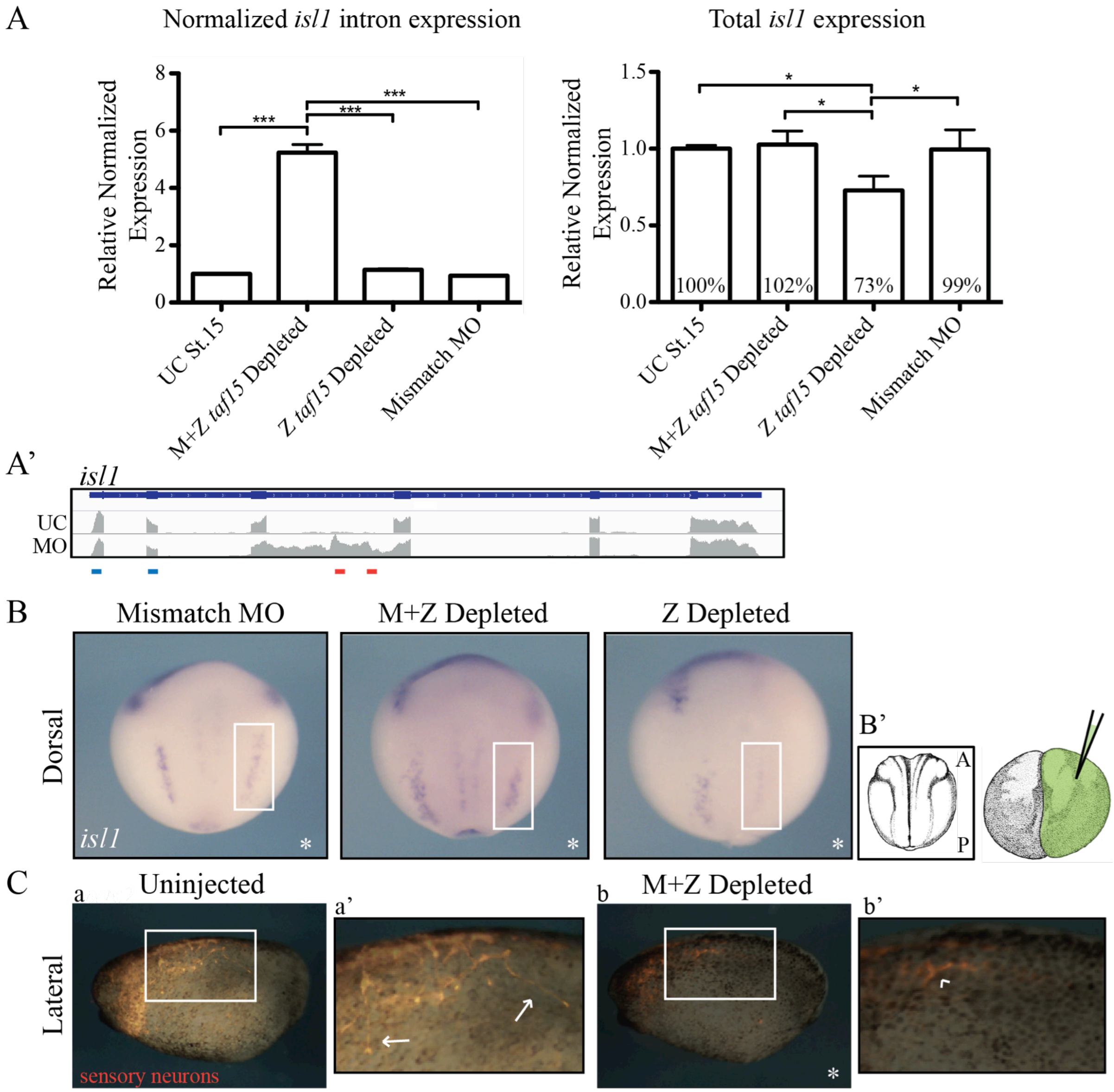

A
Normalized isl1 intron expression
Relative Normalized Expression
8
6
4
2
0
***
***
***
UC St.15
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO
Total isl1 expression
Relative Normalized Expression
1.5
1.0
0.5
0.0
*
*
*
100%
102%
73%
99%
UC St.15
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO
A'
isl1
UC
MO
B
Mismatch MO
M+Z Depleted
Z Depleted
Dorsal
isl1
B'
A
P
C
a
Uninjected
a'
b
M+Z Depleted
b'
Lateral
sensory neurons

Figure 2.8 Expression of *isl1* and sensory neurons upon *taf15* depletion. (A) Quantitative RT-PCR measuring *isl1* intron and total expression. Uninjected stage 15 *Xenopus tropicalis* embryos (uninjected) and stage 15 equivalent embryos injected with 34ng translation-blocking morpholino (M+Z taf15 Depleted), 16ng splice-blocking morpholino (Z taf15 depleted), and 34ng mismatch morpholino (Mismatch MO). *** $p<0.0001$, * $p<0.05$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses. (A') Schematic showing primer loci to measure intronic (red bars) and total (blue bars) *isl1* transcript. Gene model oriented 5' to 3'. Same RNA-seq alignments as used in Figure 2.4. (B) RNA *in situ* hybridization to *isl1*. Dorsal view, anterior up, embryos injected 1 of 2 cells with morpholino, * = injected side, white boxes mark the expected gene expression domain on the injected side. (B') Schematic of 1 of 2 cell injection and anterior view of stage 15 *Xenopus embryo*, dorsal (D), ventral (V). (C) Antibody staining for *isl1*-derived sensory neurons. (a,b) Lateral views of the Uninjected and M+Z Depleted (vertically reflected) sides of the same embryo, anterior to left. (a',b') Blown up images of boxed region in (a) and (b). Arrows point to Rohon-Beard cells, arrowhead point to undifferentiated sensory neurons.

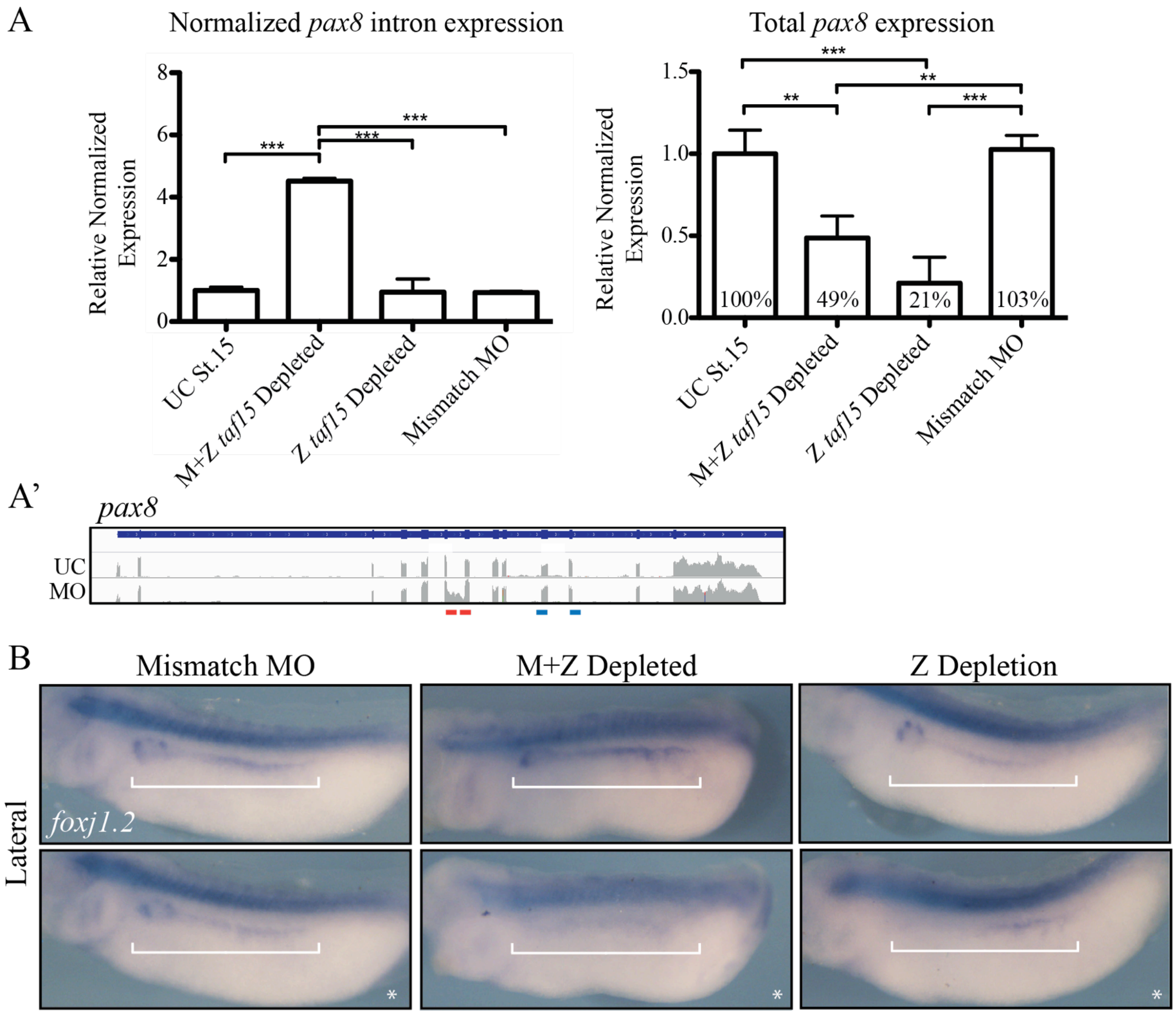


Figure 2.9 Expression of *pax8* and *foxj1.2* upon *taf15* depletion. (A) Quantitative RT-PCR measuring *pax8* intron and total expression. Uninjected stage 15 Xenopus tropicalis embryos (uninjected) and stage 15 equivalent embryos injected with 34ng translation-blocking morpholino (M+Z taf15 Depleted), 16ng splice-blocking morpholino (Z taf15 depleted), and 34ng mismatch morpholino (Mismatch MO). *** $p<0.0001$, ***$p<0.0002$ (total pax8), ** $p<0.005$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses. (A') Schematic showing primer loci to measure intronic (red bars) and total (blue bars) *pax8* transcript. Gene model oriented 5' to 3'. Same RNA-seq alignments as used in Figure 2.4. (B) RNA *in situ* hybridization to the *pax8 target* gene *foxj1.2*. Lateral views of the uninjected and morpholino-injected (vertically reflected) sides of the same embryo for each condition, anterior to left, embryos injected 1 of 2 cells with morpholino, * = injected side, white brackets mark the expected gene expression domain on the injected side.

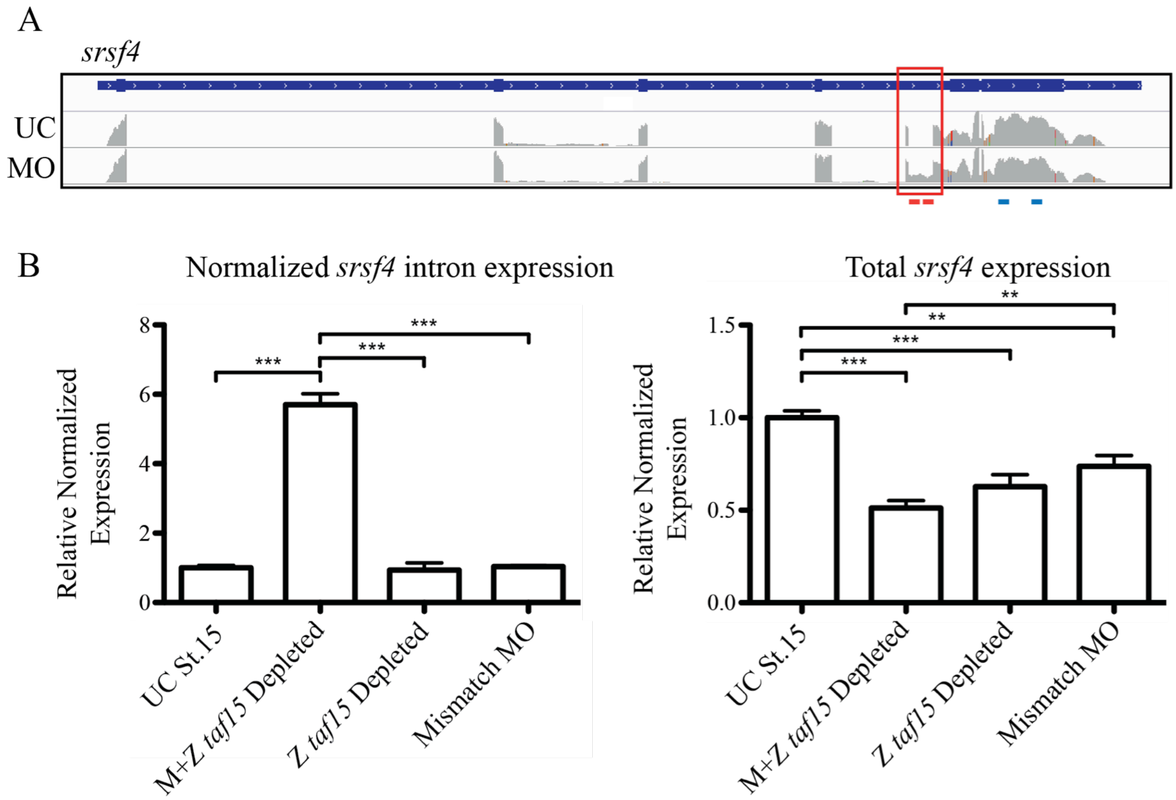


Figure 2.10 Expression of *srsf4* upon *taf15* depletion. (A) RNA-seq read alignments showing intron retention in *srsf4* transcript. RNA-seq read alignments from an uninjected (UC) stage 15 embryo, are the top alignments, and read alignments from maternal and zygotic *taf15* depleted (MO) stage 15 equivalent embryo, are the bottom alignments. Reads aligning to a retained intron are boxed in red. Above the UC alignments is the gene model in blue oriented 5' to 3'. Image is from the Integrative Genomics Viewer (IGV). Schematic showing primer loci to measure intronic (red bars) and total (blue bars) *srsf4* transcript. (B) Quantitative RT-PCR measuring *srsf4* intron and total expression. Uninjected stage 15 *Xenopus tropicalis* embryos (uninjected) and stage 15 equivalent embryos injected with 34ng translation-blocking morpholino (M+Z taf15 Depleted), 16ng splice-blocking morpholino (Z *taf15* depleted), and 34ng mismatch morpholino (Mismatch MO). *** $p<0.0001$, ** $p<0.005$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses.

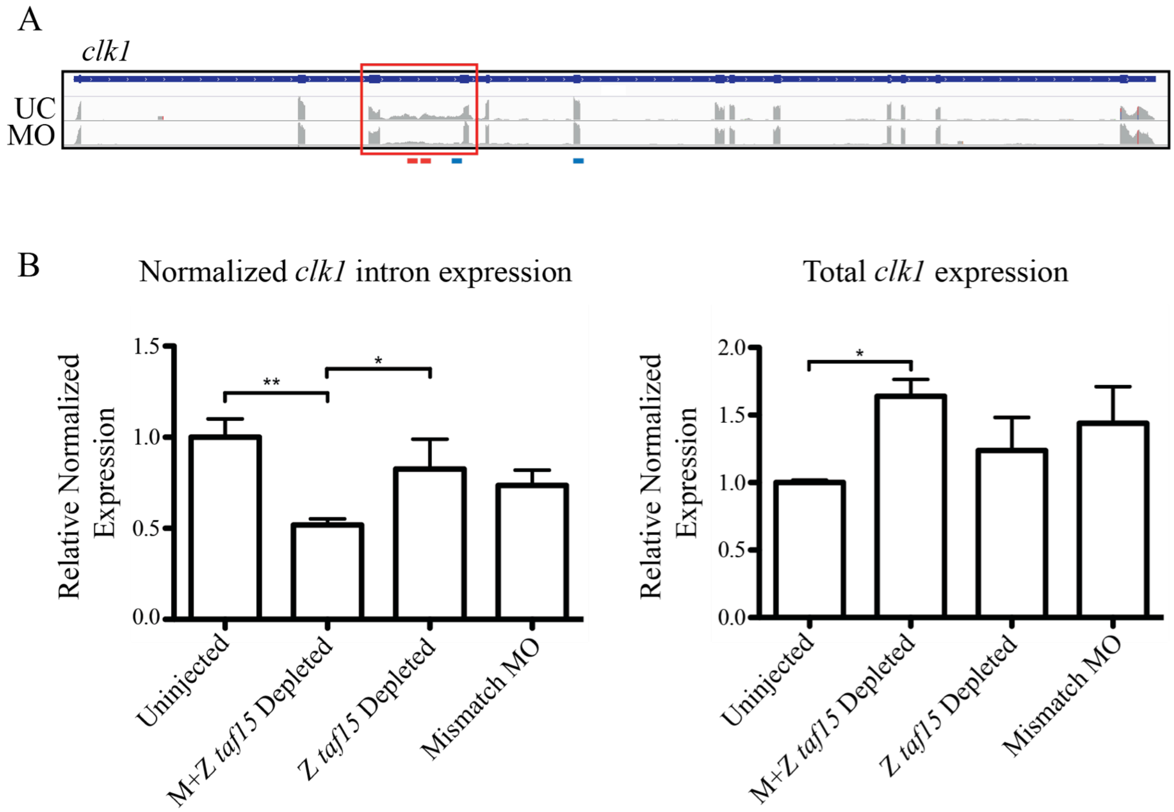


Figure 2.11 Expression of *clk1* upon *taf15* depletion. (A) RNA-seq read alignments showing intron retention in *clk1* transcript. RNA-seq read alignments from an uninjected (UC) stage 15 embryo, are the top alignments, and read alignments from maternal and zygotic *taf15* depleted (MO) stage 15 equivalent embryo, are the bottom alignments. Reads aligning to a retained intron are boxed in red. Above the UC alignments is the gene model in blue oriented 5' to 3'. Image is from the Integrative Genomics Viewer (IGV). Schematic showing primer loci to measure intronic (red bars) and total (blue bars) *clk1* transcript. (B) Quantitative RT-PCR measuring *clk1* intron and total expression. Uninjected stage 15 *Xenopus tropicalis* embryos (uninjected) and stage 15 equivalent embryos injected with 34ng translation-blocking morpholino (M+Z taf15 Depleted), 16ng splice-blocking morpholino (Z taf15 depleted), and 34ng mismatch morpholino (Mismatch MO). * $p<0.05$, ** $p<0.005$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses.

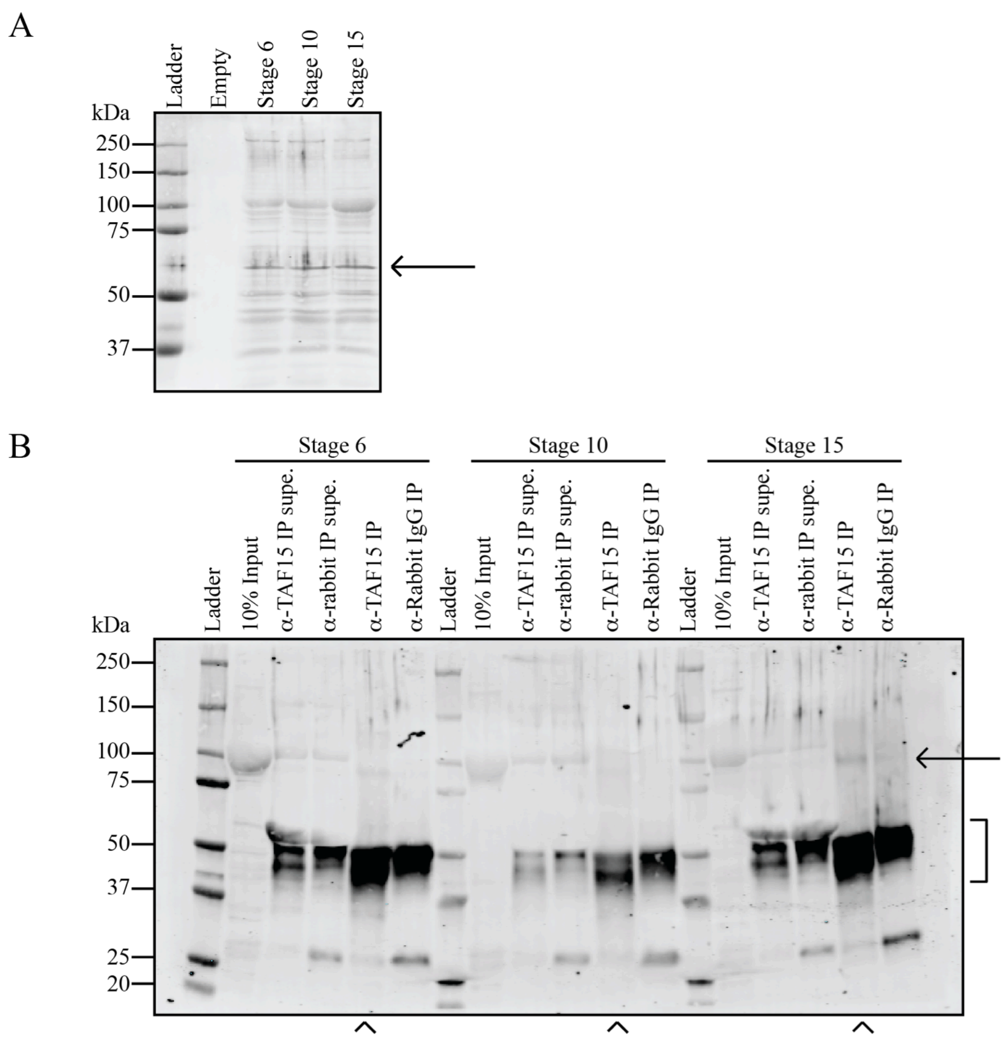
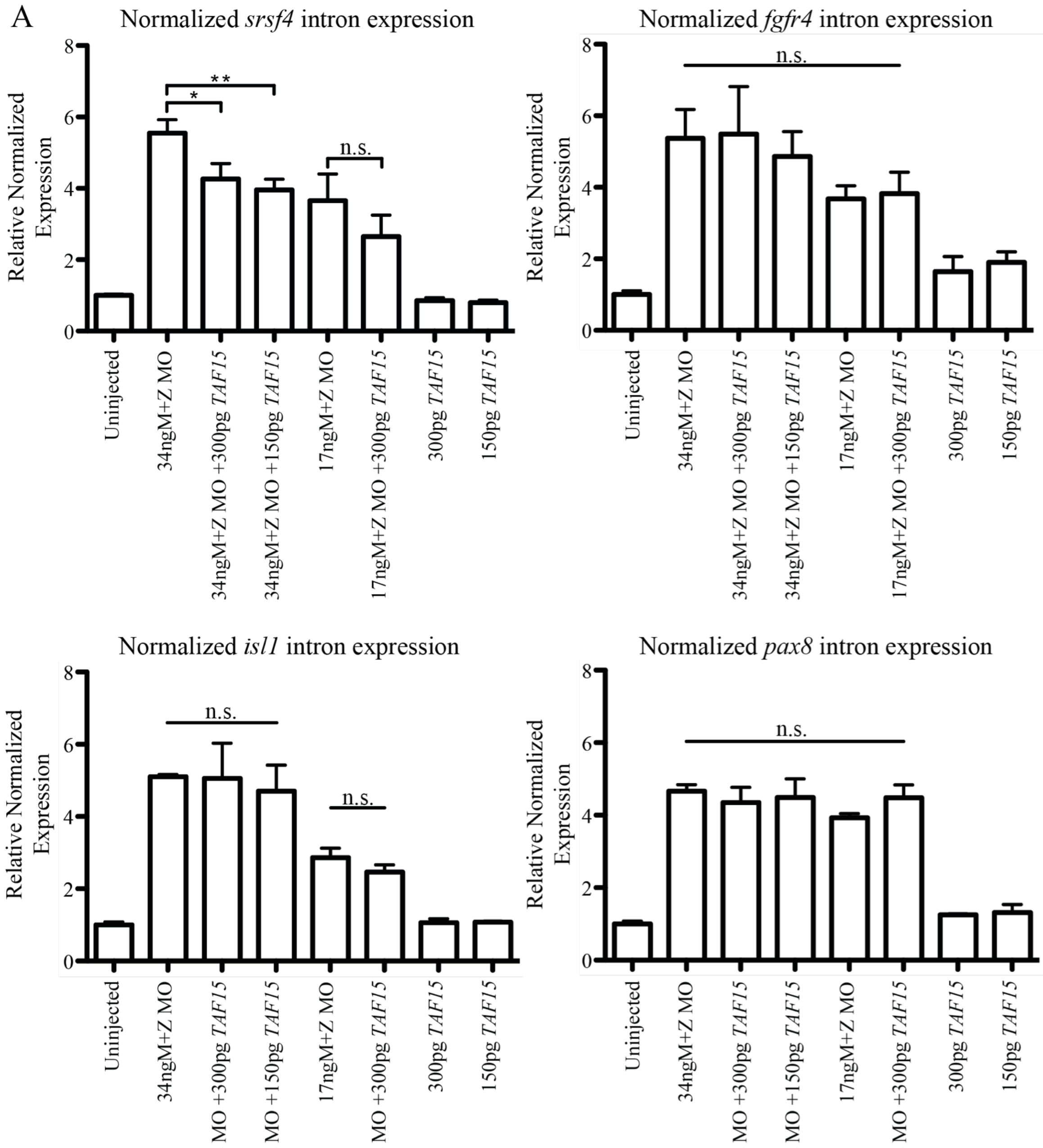


Figure 2.12 SRSF4 Detection in *Xenopus tropicalis* embryos. (A) Western blot for SRSF4. Arrow indicates predicted molecular weight of SRSF4. (B) Western blot for SRSF4 following TAF15 immunoprecipitation. Arrow heads indicate lanes with lysate from a-TAF15 immunoprecipitation (a-TAF15 IP). Arrow indicates molecular weight where a band is found with a-TAF15 IP but not with control a-Rabbit IgG IP. Bracket indicates protein IgG bands.

A



Normalized *srsf4* intron expression
Relative Normalized Expression
0
2
4
6
8
*
**
n.s.
Uninjected
34ngM+Z MO
34ngM+Z MO +300pg *TAF15*
34ngM+Z MO +150pg *TAF15*
17ngM+Z MO
17ngM+Z MO +300pg *TAF15*
300pg *TAF15*
150pg *TAF15*
Normalized *fgfr4* intron expression
Relative Normalized Expression
n.s.
Normalized *isl1* intron expression
Relative Normalized Expression
n.s.
n.s.
Normalized *pax8* intron expression
Relative Normalized Expression
n.s.

Figure 2.13 Rescue of *srsf4* intron retention with TAF15. (A) Quantitative RT-PCR measuring *srsf4*, *fgfr4*, *isl1*, and *pax8* intron expression. Uninjected stage 15 *Xenopus tropicalis* embryos (Uninjected) and stage 15 equivalent embryos injected with translation-blocking morpholino (M+Z MO), translation-blocking morpholino and human taf15 (M+Z MO + TAF15), and human taf15 (TAF15). ** $p<0.005$, * $p<0.05$, n.s. = not significant, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses.

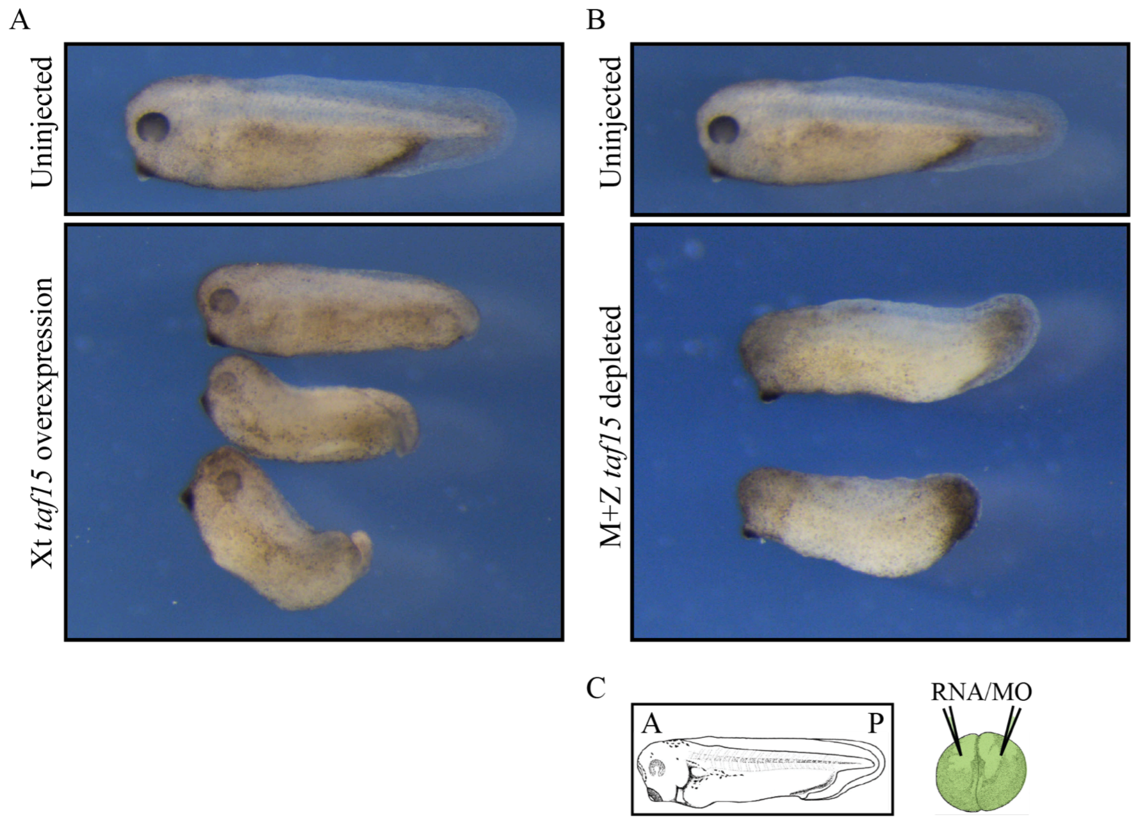


Figure 2.14 *Xenopus tropicalis taf15* overexpression and depletion. (A) Brightfield images of stage 33-34 embryos, uninjected or following injection of 300pg of *X. tropicalis* RNA, anterior left. (B) Brightfield images of stage 33-34 embryos, uninjected or following injection of 34ng of translation-blocking morpholino (M+Z Depleted), anterior left. (C) Lateral view of stage 33-34 Xenopus embryo, anterior (A), posterior (P), schematic of 2 cell injection.

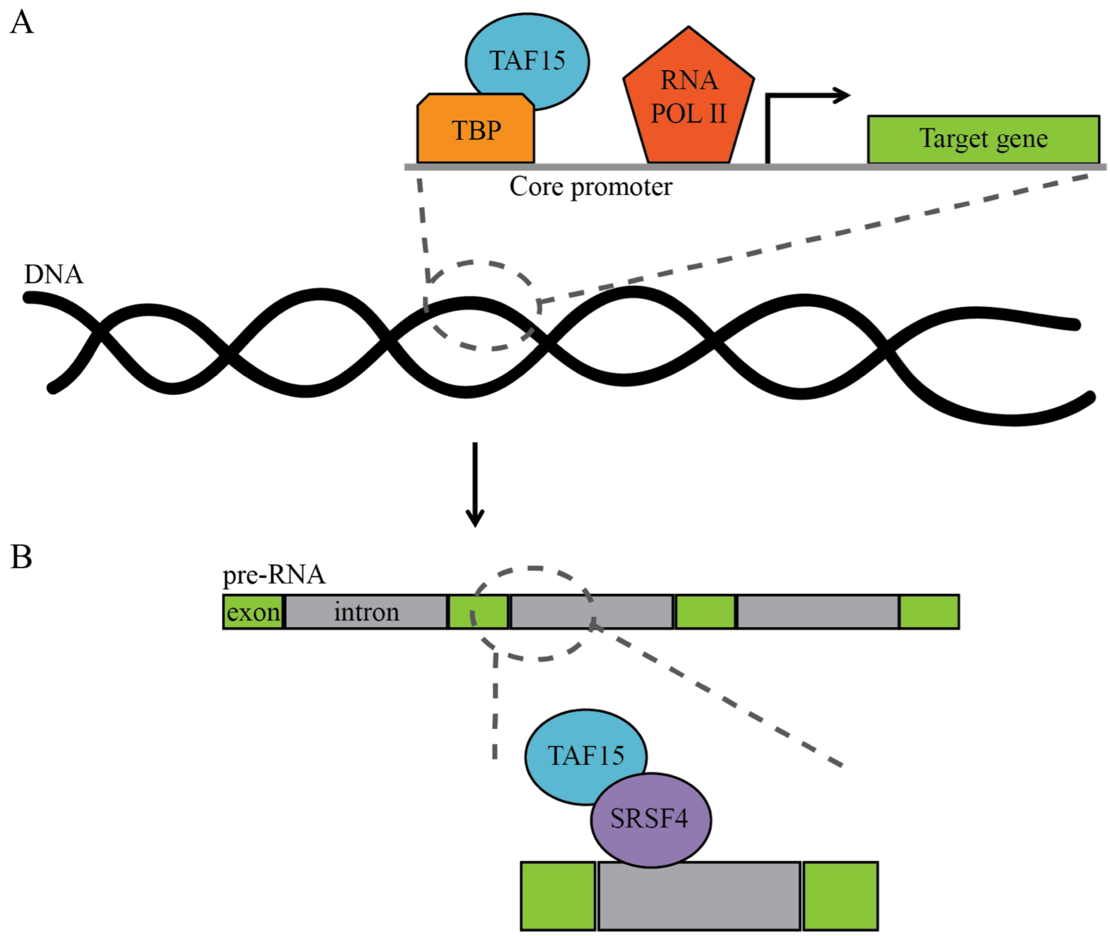


Figure 2.15 Model of transcriptional regulation for either maternal or zygotic TAF15. (A) Transcription of target genes. Zygotic TAF15 associates with the core promoter, regulating target gene expression at the transcriptional level. (B) Splicing of target genes. Maternal TAF15 associates with a splicing factor, such as SRSF4, regulating target gene expression at the post-transcriptional level.

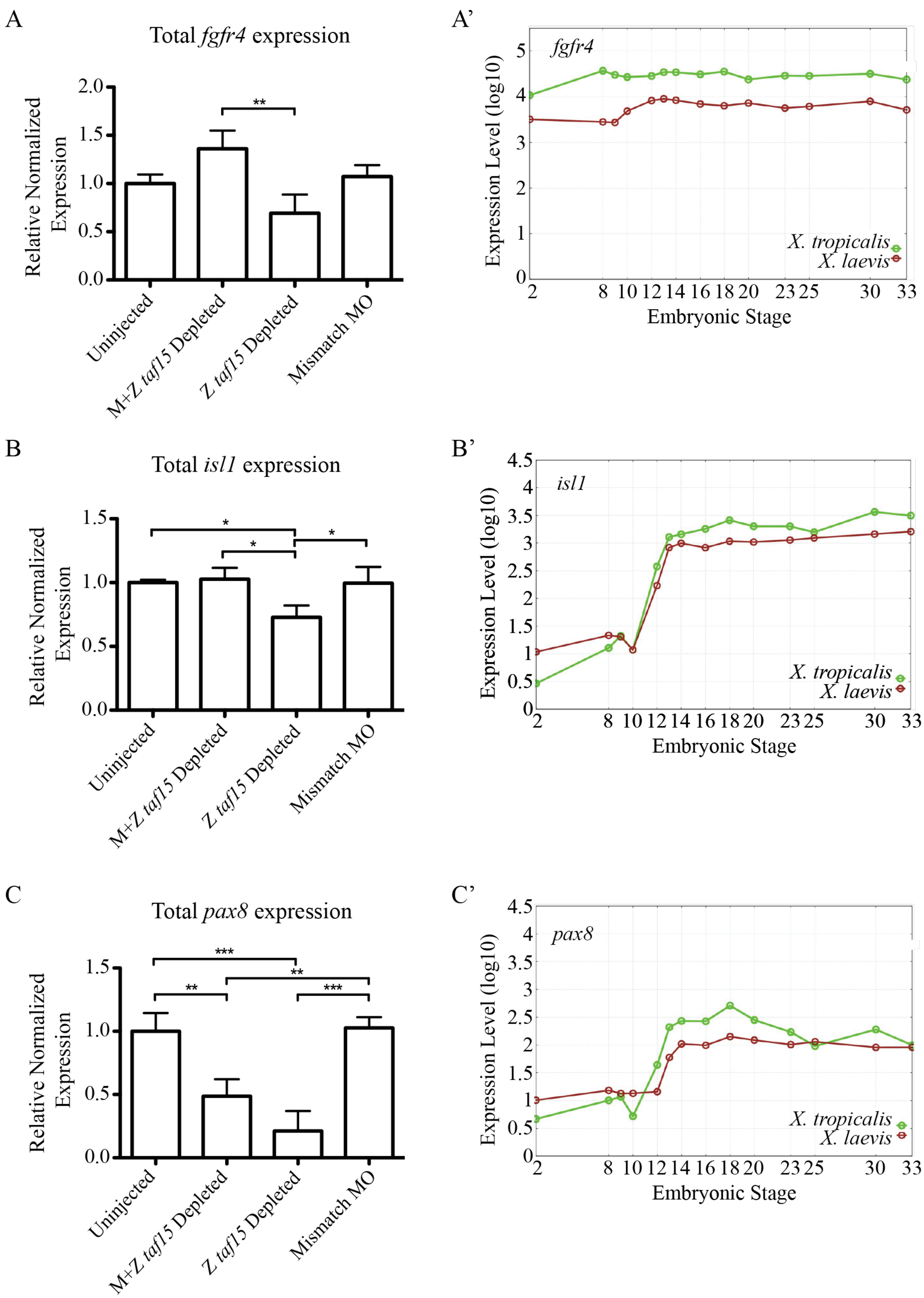

A
Total fgfr4 expression
Relative Normalized Expression
2.0
1.5
1.0
0.5
0.0
**
Uninjected
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO
A'
fgfr4
Expression Level (log10)
X. tropicalis
X. laevis
Embryonic Stage
2 8 10 12 14 16 18 20 23 25 30 33
B
Total isl1 expression
Relative Normalized Expression
1.5
1.0
0.5
0.0
*
*
*
Uninjected
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO
B'
isl1
Expression Level (log10)
X. tropicalis
X. laevis
Embryonic Stage
2 8 10 12 14 16 18 20 23 25 30 33
C
Total pax8 expression
Relative Normalized Expression
1.5
1.0
0.5
0.0
***
**
**
***
Uninjected
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO
C'
pax8
Expression Level (log10)
X. tropicalis
X. laevis
Embryonic Stage
2 8 10 12 14 16 18 20 23 25 30 33

Figure 2.16 A comparison of the levels of total gene expression following *taf15* depletion to the developmental timing of expression. (A) (B) (C) Quantitative RT-PCR measuring total *fgfr4*, *isl1*, and *pax8* expression, respectively. Uninjected stage 15 Xenopus tropicalis embryos (uninjected) and stage 15 equivalent embryos injected with 34ng translation-blocking morpholino (M+Z taf15 Depleted), 16ng splice-blocking morpholino (Z taf15 depleted), and 34ng mismatch morpholino (Mismatch MO). * $p<0.05$, ** $p<0.005$, *** $p<0.0002$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses. Same qPCR data, measuring total transcript levels, as used in Figure 2.6A (*fgfr4*), Figure 2.8A (*isl1*), and Figure 2.9A (*pax8*) (A') (B') (C') Schematics of gene expression levels throughout embryonic development. Expression images adapted from Xenbase.

Chapter 3: The atypical RNA binding protein, TAF15, regulates dorsoventral patterning by repressing the *ventx* family of transcription factors.

Section 3.1: Summary

The Ventx family of homeobox transcription factors are known to work with BMPs and play an essential role in ventral patterning of the embryo. In this study, I have found that TAF15 is required for the repression of one *Xenopus ventx* paralog, *ventx2.1*, specifically in the dorsal tissues of the neural ectoderm.

Section 3.2: Introduction

It has been well established that at 30 minutes post-fertilization the *Xenopus* egg undergoes subcortical rotation of the cytoplasm; this subcortical rotation is required to establish the primary dorsoventral (DV) axis of the embryo (Heasman, 2006) (Vincent & Gerhart, 1987) (Hikasa & Sokol, 2013) (Sive, 1993). The 30° cortical rotation of the cytoplasm is integrally important for development and leads to the microtubule-dependent localization of β-catenin to a region that will define the future dorsal axis of the embryo (Houliston & Elinson, 1992) (Vincent & Gerhart, 1987) (Hikasa & Sokol, 2013). Wnt/ β-catenin signaling is responsible for the activation of many target genes required for Spemann organizer formation, the major signaling center in amphibians that induces the development of the central nervous system (R. Harland & Gerhart, 1997) (Heasman, 2006). In addition to the maternally contributed Wnt/ β-catenin-dependent dorsal pre-patterning, the zygotically transcribed bone morphogenetic proteins (BMP), members of the transforming growth factor β (TGFβ) superfamily, are required to pattern the tissue that will define the future ventral axis of the embryo (R. M. Harland, 1994). Upon zygotic genome activation there is a very complex network of instructive signals required to form the three germ layers and progression of gastrulation. At least four major signaling pathways are involved in the development of the three germ layers and gastrulation, including: BMP, Activin-type TGFβ, Wingless-Int (Wnt), and Fibroblast growth factor (FGF) (Heasman, 2006). These signaling pathways are essential to activate the signal transducers Smad1, Smad2, β-catenin, and MAPK (Heasman, 2006). In this chapter, I will explore the role of BMP signaling in patterning the ventral axis of the *Xenopus* embryo, focusing specifically on the BMP target gene *ventx*, a family of homeobox transcription factors.

Upon zygotic genome activation, downstream of maternal BMP2 and BMP7, BMP signaling is activated in the ventral equatorial zone and animal cap of the blastula and is specifically restricted from the dorsal region of the embryo (Heasman, 2006) (Schohl & Fagotto, 2007) (Faure et al., 2000). Exclusion of BMP from the future dorsal regions of the embryo is thought to be the result of the early activation of the BMP-antagonists *chordin* and *noggin* (Heasman, 2006) (De Robertis & Kuroda, 2004) (Piccolo et al., 1996) (Smith & Harland, 1992) (Zimmerman et al., 1996). During this time, in what will be the future ventral region of the embryo, there is activation of the BMP-dependent epidermal regulatory network. This includes the activation of *ventx2* and *msx1* which activate the epidermal pathway and suppress pro-neural genes (Heasman, 2006) (Onichtchouk et al., 1996) (Onichtchouk et al., 1998) (Suzuki et al., 1997). Furthermore, *ventx2* is downstream of BMP4 signaling and is required to specify ventral mesodermal fates and antagonize organizer function (Onichtchouk et al., 1996). Additionally, while *ventx2* is activated by BMP2/4, Ventx2 activates BMP4 transcription, resulting in an autocatalytic positive feedback loop (Schuler-Metz et al., 2000).

In this study, I show that TAF15 is necessary for the repression of *ventx2.1* from the dorsal neurectoderm of the *Xenopus* embryo. I show that as early as gastrulation (stage 10), *ventx2.1* and *taf15* begin to have complementary RNA expression patterns *in situ*. *taf15* is expressed predominantly in the dorsal marginal zone of the gastrula whereas *ventx2.1* is expressed predominantly in the ventral marginal zone. This expression pattern becomes more defined and complementary as the embryo develops. During the mid neurula stage (stage 15), *taf15* is expressed throughout the ectodermal and dorsal neurectodermal tissues whereas *ventx2.1* is expressed in the underlying lateral mesoderm with very faint expression in the dorsal neurectoderm. Following depletion of *taf15* from the embryo, *ventx2.1* expression increases significantly and specifically in the dorsal neurectoderm. The data presented in this chapter suggest that TAF15 is upstream of *ventx2.1* and is required for dorsoventral axial patterning.

Section 3.3: Results

Concurrent with my RNA-seq analysis looking at differential intron-exon usage following *taf15* depletion, as discussed in Chapter 2, I also used RNA-seq analysis to compare changes in transcript levels between uninjected embryos and those depleted of maternal and zygotic *taf15*. For a complete list of statistically significant differentially expressed gene transcripts see Appendices 1 and 2.

Section 3.3.1: Maternal and zygotic depletion of taf15 leads to increased ventx expression.

Following M+Z *taf15* depletion, *Xenopus* embryos fail to form dorsal structures such as their dorsal fins and have more ventral tissue (Figure 2.2A). A positive feedback loop of the bone morphogenetic proteins (BMP), a family of TGF-β related peptide growth factors, and the VENT homeobox (Ventx) genes, homeodomain transcription factors, is required to specify the ventral axis of a *Xenopus* embryo (Onichtchouk et al., 1998) (Sander et al., 2007). RNA-seq analysis from 15 embryos indicated that all six of the *ventx* paralogs, *ventx1.1/1.2/2.1/2.2/3.1/3.2*, are significantly upregulated in M+Z *taf15* depleted embryos (Figure 3.1A). The increased expression of the *ventx* paralogs following M+Z *taf15* depletion explains the increased ventrally fated tissues, at the expense of dorsal tissues, seen in these morphant embryos (Figure 2.2A). Using the Integrative Genomics Viewer (IGV, Broad Institute), to visualize RNA-seq read alignments, it is clear that, unlike the M+Z *taf15* targets discussed in chapter 2, *ventx* genes do not exhibit splicing defects (Figure 3.1B and Figure 3.2A). Of the six *ventx* family members, *ventx2.1* is known to act upstream of all other *ventx* genes (Schuler-Metz et al., 2000). For this reason, and due to the expression pattern of endogenous *ventx2.1* (as well as *ventx2.1* expression following *taf15* depletion, discussed in the following sections), I have decided to focus on how *taf15* affects *ventx2.1* expression. Using q-PCR, I was able to validate the RNA-seq results and saw that *ventx2.1* expression significantly increases ~2 fold following M+Z *taf15* depletion. This significant increase is observed by qPCR as early as stage 10 and is maintained through stage 15 (Figure 3.1C). Furthermore, unlike the trend that was observed in chapter 2, both M+Z and Z-only *taf15* depletion results in a significant increase in *ventx2.1* expression (Figure 3.1C). It should be noted that increased *ventx2.1* expression is not observed with Z-only *taf15* depletion until stage 15. A reasonable explanation for this is that the effects of a *taf15* splice-blocking morpholino (used to deplete zygotic *taf15*) cannot be seen as early as stage 10 because zygotic genome transcription has only just begun, and there would still be maternal TAF15 present at this time, able to act on and regulate zygotic genome transcription (See discussion section of Chapter 2).

Section 3.3.2: Some taf15 and ventx2.1 expression domains are complementary.

I next wanted to compare the expression domains of *taf15* and *ventx* genes. RNA-seq and qPCR analysis indicated that *ventx* genes are upregulated following *taf15* depletion, suggesting that *taf15* is required for the suppression of *ventx* genes. If *taf15* suppresses the expression of *ventx*, it would be expected that *taf15* and the *ventx* genes would exhibit at least some complementary expression patterns. Interestingly, *ventx2.1* indeed has a complementary expression patter to *taf15* (Figure 3.3A) while the remaining *ventx2.1* family members show a distinct, non-complementary, expression pattern (data not shown).

As early as gastrula stage 10, a developmental stage shortly following zygotic genome activation where the future dorsal and ventral tissues of the embryo are actively being established, I *taf15* transcript is enriched in the cells that will make up future dorsal tissues while and *ventx2.1* transcript is expressed in cells that will make up future ventral tissues (Figure 3.3A & B). As can be observed after cross-sectioning these embryos, *taf15* and *ventx2.1* are clearly beginning to be complementarily expressed and are both expressed in the deep cells and not in the superficial cells.

By neurula stage 15, the expression domains of *taf15* and *ventx2.1* are strikingly complementary (Figure 3.4A). Here *taf15* is expressed predominantly in the neural plate whereas the strongest *ventx2.1* expression is seen laterally and ventrally. It is also of note that in the presumptive cement gland, *taf15* expression is absent while *ventx2.1* expression is strong. As discussed in chapter two, and consistent with the expression data described in this chapter, M+Z *taf15* depleted embryos have well-formed cement glands but lose dorsal structures and gain ventral tissue (Figure 2.2A). These data suggest that *taf15* does not play a role in regulating *ventx2.1* expression in the presumptive cement gland. To gain more detailed knowledge of the extent of complementary *taf15* and *ventx2.1* expression, I cross-sectioned these embryos and revealed distinct complementary expression of *taf15* and *ventx2.1* (Figure 3.4B). In the cross-sections of ISH embryos, it is clear that *taf15* is mainly expressed in the overlying ectoderm, present in the neural, and both epithelial, and sensorial layers of the ectoderm whereas *ventx2.1* is mainly expressed in the underlying lateral plate mesoderm with very faint expression in the neural ectoderm. These data, along with the expression data described above, suggest that TAF15 controls the levels of *ventx2.1* during *Xenopus* development.

Section 3.3.3: Maternal and zygotic depletion of taf15 leads to expanded ventx2.1 expression into the neural ectoderm.

Having established that *ventx2.1* expression increases with *taf15* depletion, and that *taf15* and *ventx2.1* have some complementary expression domains, I next wanted to look *in situ* at *ventx2.1* expression in *taf15* depleted embryos. Embryos with reduced *taf15* levels had increased *ventx2.1* expression and expansion of the expression pattern into regions that would normally have *taf15* expression (Figure 3.5A & B). When M+Z or Z-only *taf15* is depleted, *ventx2.1* expression increases in the neural ectoderm, a region where *taf15* is normally highly expressed and *ventx2.1* is very weakly expressed. Again, unlike what was observed in chapter two where maternal and zygotic *taf15* regulate the same targets through different mechanisms, here, both maternal and zygotic *taf15* are capable of supressing the dorsal expression of *ventx2.1* (Figure 3.5C) with no change in intron retention (Figure 3.2A).

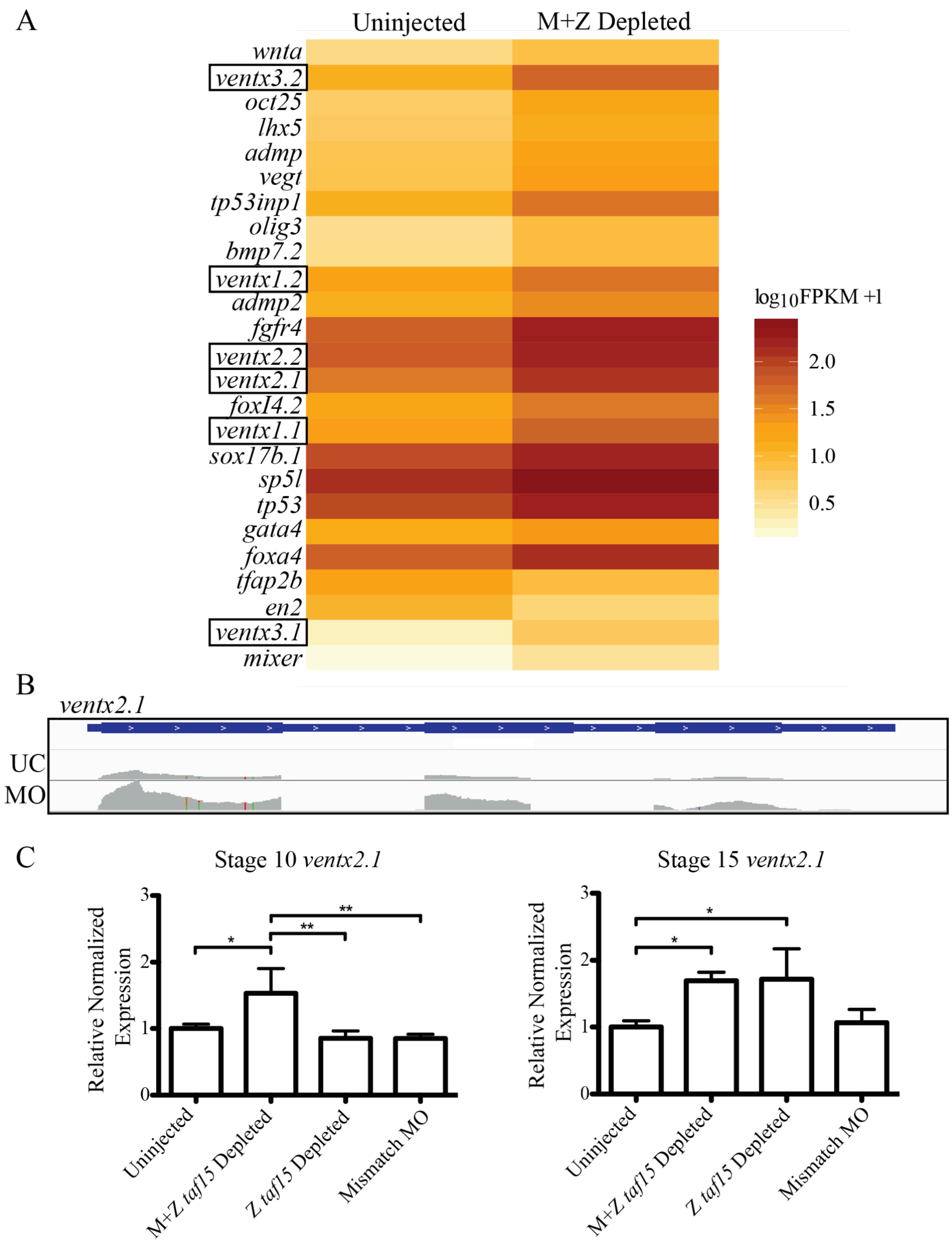
Section 3.4: Discussion

These data clearly illustrate the role of TAF15 in regulating dorsoventral patterning. I propose a model where TAF15 represses *ventx2.1* from the dorsal marginal zone of the gastrula and this repression continues through neurulation, as we see TAF15 repressing *ventx2.1* from dorsal neural ectodermal tissue (Figure3.6). Without knowing if the *ventx* genes are direct transcriptional targets of TAF15, it is impossible to conclude if the innate function of TAF15 is to repress *ventx* expression or to activate a repressor of *ventx* expression. However, the RNA-seq results show that there is no intron retention in the *ventx* genes which supports the conclusion that the RNA splicing activity of TAF15 does not control the *taf15*-dependent repression of *ventx2.1*.

Xenopus embryos depleted of the BMP-antagonist *chordin*, have a phenotype strikingly similar to what I observe when embryos are depleted of *taf15* (Bruno et al., 2005). Both *chordin* and *taf15* depletion results in ventralized embryos with reduced head and eye structures as well as reduced dorsal and posterior fin and tail structures. Just as with *taf15* depletion, *chordin*-depleted embryos have a relatively normal cement gland and increased ventral tissue. Interestingly, according to my RNA-seq data, *taf15*-depleted embryos do not have a decrease in *chordin* expression. However, by stage 15, M+Z *taf15* depleted embryos do exhibit a significant increase in *bmp4* expression and, just like the *chordin*-depleted embryos, a significant increase in the BMP4 target gene, *sizzled*. It is known that *chordin* is a dedicated BMP antagonist and therefore the increased *sizzled* expression observed in *chordin*-depleted embryos is thought to be due to an increase in BMP activity (Bruno et al., 2005). Given the phenotypic similarities seen between depletion of *chordin* and *taf15,* it is intriguing to suggest that TAF15 may be a downstream effector of Chordin, important for repressing BMP signaling. However, because *taf15* is expressed in many more tissue types than is *chordin* (Chapter 2, Figure 2.1) (Xenbase: chordin), and based on the phenotype and complementary expression data I have described for both *taf15* and *ventx2.1*, it is more likely that *taf15*-depleted embryos phenocopy the increased BMP activity seen in *chordin*-depleted embryos via the failure of TAF15 to repress *vent*, and subsequently, the BMP/Vent positive feedback loop (Schuler-Metz et al., 2000).

Interestingly, the human Vent-like homeobox gene *VENTX*, a putative homolog of the *Xenopus ventx2* gene is aberrantly expressed in CD34+ cells of acute myeloid leukemia patients (Rawat et al., 2010). Furthermore, the leukemia-associated TAF15 fusion protein, TAF15-CIZ/NMP4, is found in acute myeloid leukemia (Alves et al., 2009). Although *ventx* has been lost in mouse, the function of *ventx* in repressing dorsal fates is well conserved between fish and frogs (Rawat et al., 2010) (Imai et al., 2001). Given the relationship I have observed of increased *ventx* expression following *taf15* depletion, the coincidence of TAF15 dysfunction and increased *VENTX* in acute myeloid leukemia, and the fact that Ventx is required for proper mesenchyme and blood differentiation in *Xenopus*, it is possible that TAF15-dependent negative regulation of *ventx* is a conserved mechanism (D Onichtchouk et al., 1998).

The entire family of *ventx* genes is clustered together in the *Xenopus* genome (Integrative Genomics Viewer of my RNA-seq alignments). It is possible that this genomic organization is the reason I see all of the *ventx* genes upregulated following *taf15* depletion, even though *ventx2.1* is the only member that exhibits a functional expression dynamic with TAF15. Future studies will aim to test if the regulation of the *ventx* family of homeobox transcription factors by TAF15 is direct or indirect. Additionally, using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) genome editing system, I will target zygotic *taf15* and validate that zygotic *taf15* mutants (CRISPR/Cas9-targeted) phenocopy the *ventx* transcriptional upregulation observed in M+Z and Z *taf15* depleted embryos injected with translation-blocking and splice-blocking morpholino. Lastly, I will also attempt to rescue the *taf15* depletion phenotype with morpholinos designed to deplete *ventx2.1*.



A
Uninjected
M+Z Depleted
wnta
ventx3.2
oct25
lhx5
admp
vegt
tp53inp1
olig3
bmp7.2
ventx1.2
admp2
fgfr4
ventx2.2
ventx2.1
foxl4.2
ventx1.1
sox17b.1
sp5l
tp53
gata4
foxa4
tfap2b
en2
ventx3.1
mixer
log10FPKM +1
2.0
1.5
1.0
0.5
B
ventx2.1
UC
MO
C
Stage 10 ventx2.1
Stage 15 ventx2.1
Relative Normalized Expression
Uninjected
M+Z taf15 Depleted
Z taf15 Depleted
Mismatch MO

Figure 3.1 Expression of *ventx* upon *taf15* depletion. (A) Heatmap of developmental regulators that are significantly differently expressed between M+Z *taf15* depleted and uninjected *Xenopus tropicalis* embryos. *ventx* paralogs are boxed. Results generated from the first RNA-seq library: three stage 15 uninjected *Xenopus tropicalis* embryos and two M+Z *taf15* depleted stage 15 equivalent *Xenopus tropicalis* embryos. (B) Integrative Genomics Viewer visualization of *ventx2.1* RNA-sequening read alignments. RNA-seq read alignments from an uninjected (UC) stage 15 embryo, are the top alignments, and read alignments from maternal and zygotic *taf15* depleted (MO) stage 15 equivalent embryo, are the bottom alignments. Above the UC alignments is the gene model in blue oriented 5' to 3'. (C) Quantitative RT-PCR measuring *ventx2.1* total expression. Stage 10 or stage 15 emrbyos. Uninjected *Xenopus tropicalis* embryos (uninjected) and embryos injected with 34ng translation-blocking morpholino (M+Z *taf15* Depleted), 16ng splice-blocking morpholino (Z *taf15* depleted), and 34ng mismatch morpholino (Mismatch MO). ** $p<0.005$, * $p<0.05$, error bars = standard deviation. All means were compared by one-way ANOVA followed by Tukey post-hoc analyses.

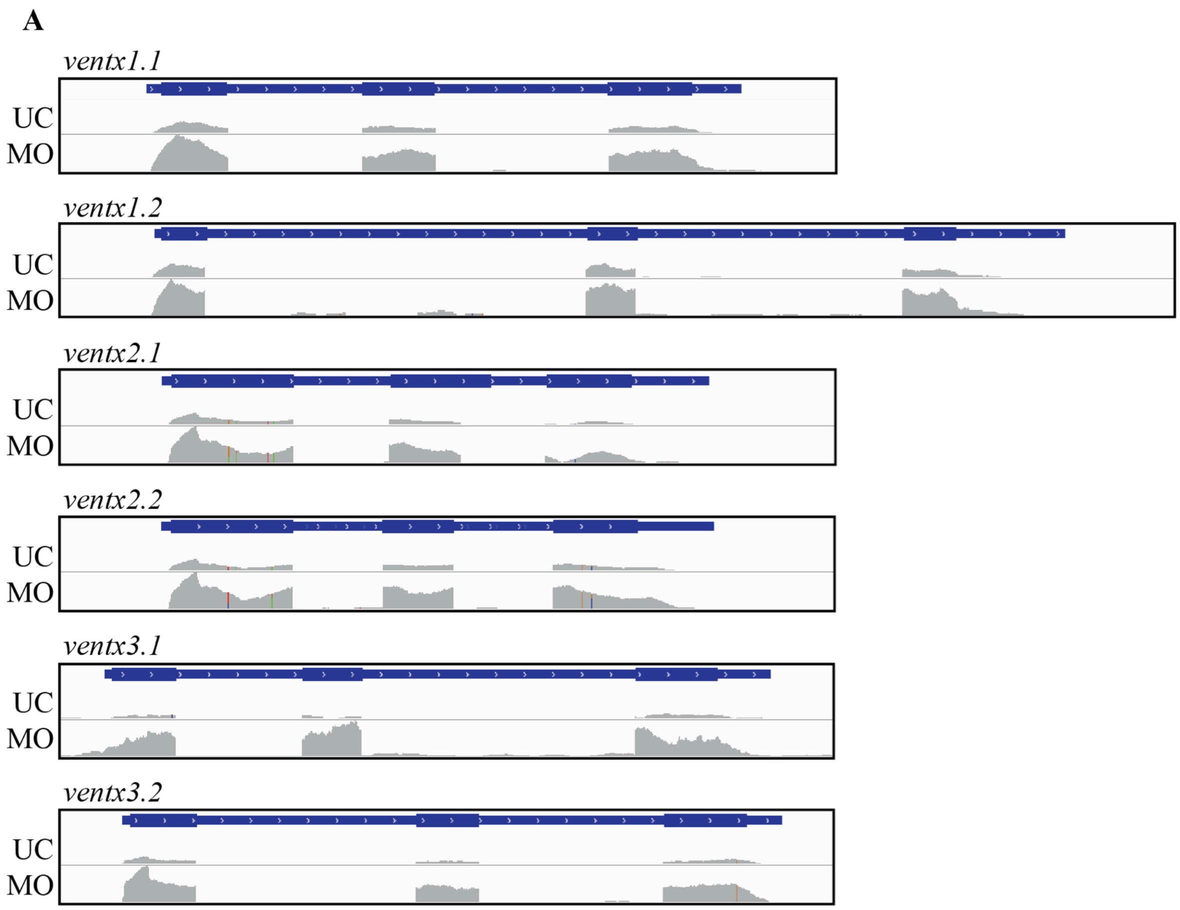


Figure 3.2 RNA-seq alignments of all *ventx* family members following *taf15* depletion. Integrative Genomics Viewer visualization of *ventx1.1*,*ventx1.2*, *ventx2.1*, *ventx2.2*, *ventx3.1*, *ventx3.2* RNA-sequening read alignments. For each gene, RNA-seq read alignments from an uninjected (UC) stage 15 embryo, are the top alignments, and read alignments from maternal and zygotic *taf15* depleted (MO) stage 15 equivalent embryo, are the bottom alignments. Above the UC (uninjected control) alignments is the gene model in blue oriented 5' to 3'. *ventx2.1* is the same RNA-seq alignment as was used in Figure 3.1B.

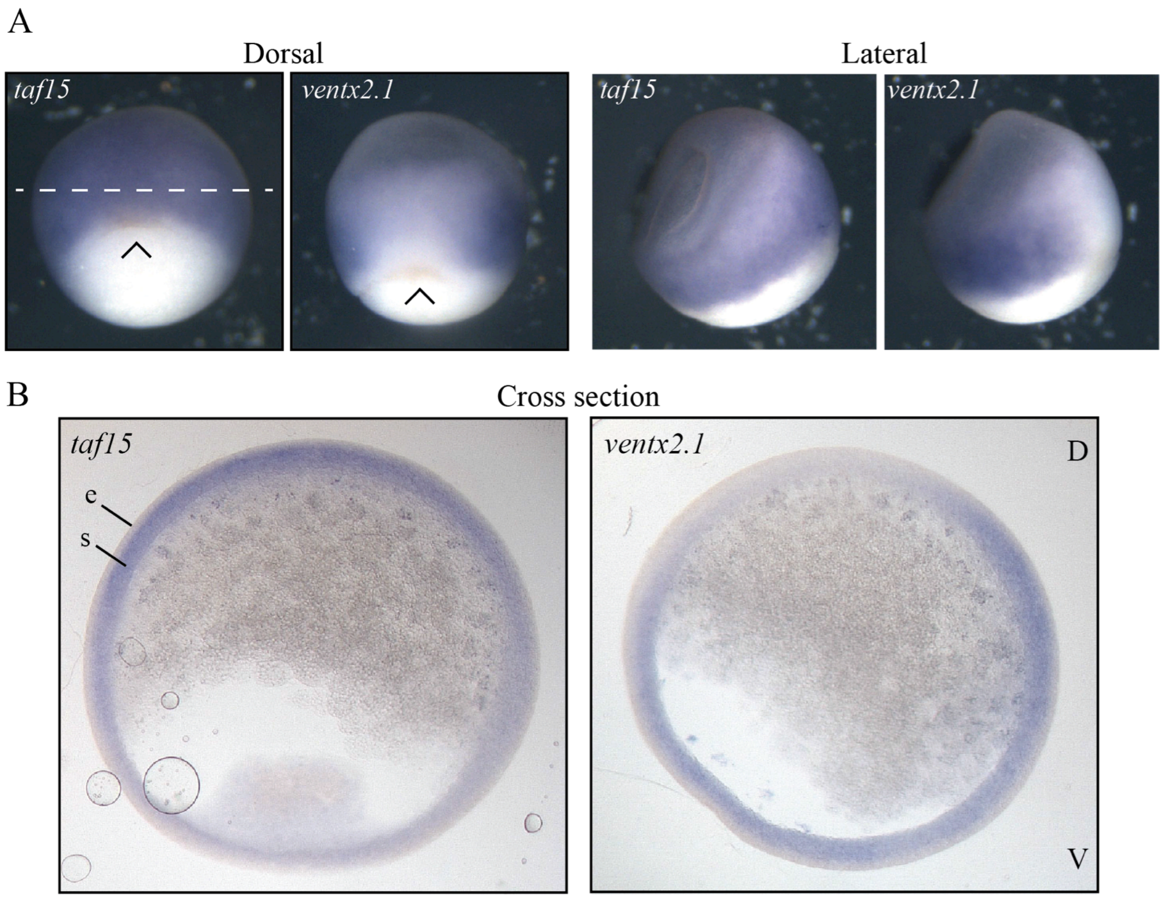


Figure 3.3 Complementary expression domains of *taf15* and *ventx2.1*. (A) RNA *in situ* hybridization for *taf15* and *ventx2.1* in stage 10 *Xenopus tropicalis* embryos. Dorsal view, dotted white line indicates where the cross section was made, arrow head points to blastapore lip. Lateral view, dorsal right. (B) Cross-sections of RNA *in situ* hybridization for *taf15* and *ventx2.1*. 50um sections. Abbreviations: epithelial (e) and sensorial (s) layers, dorsal (D), ventral (V).

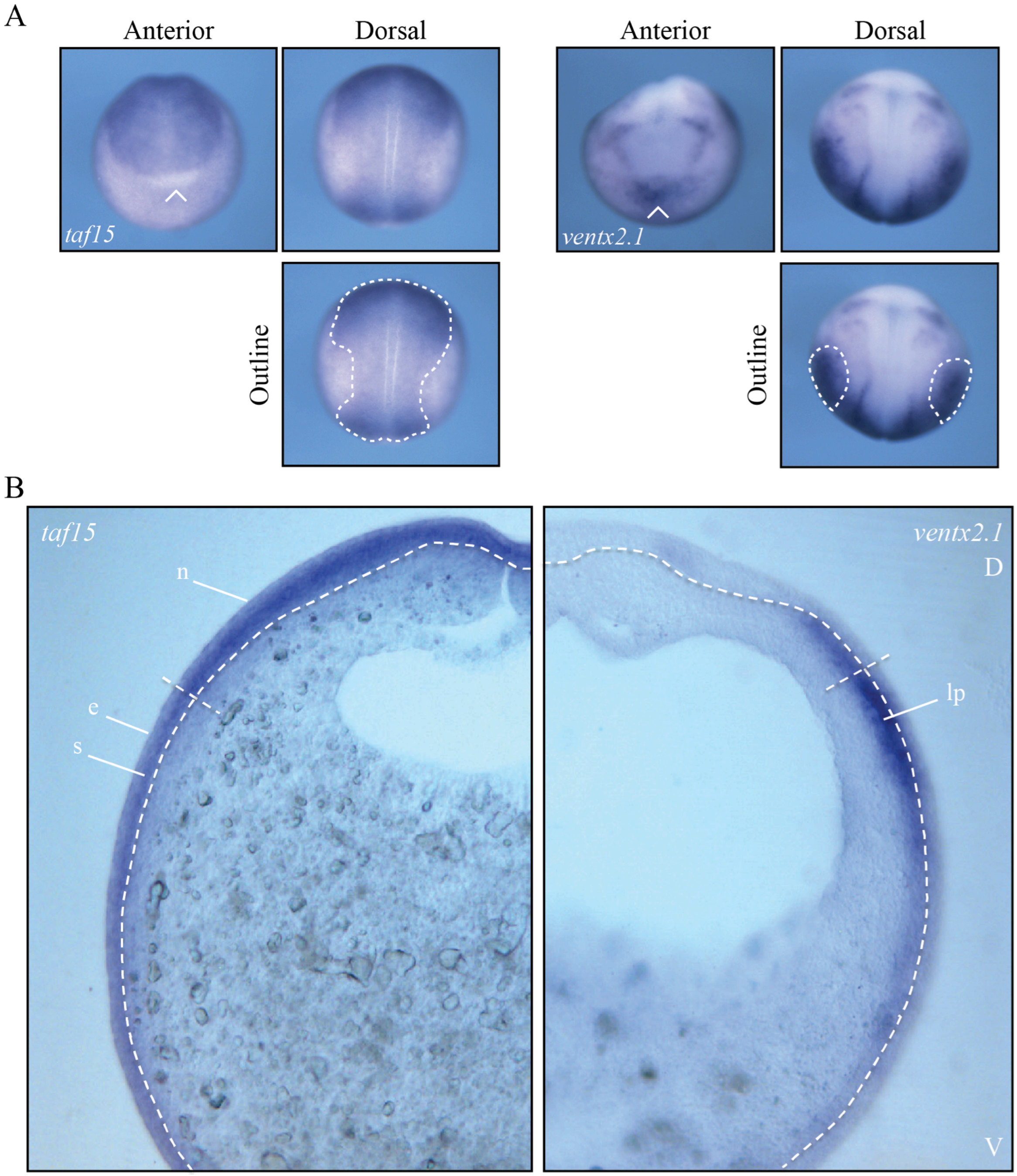

A
Anterior
Dorsal
Anterior
Dorsal
taf15
ventx2.1
Outline
Outline
B
taf15
ventx2.1
n
e
s
lp
D
V

Figure 3.4 Complementary expression domains of *taf15* and *ventx2.1* in uninjected embryos. (A) RNA *in situ* hybridization for *taf15* and *ventx2.1* in stage 15 *Xenopus tropicalis* embryos. White arrow heads in anterior view indicate future cement gland. White dotted lines in the dorsal outline views highlight the complementary expression domains of *taf15* and *ventx2.1*. Dorsal and Outline panels are the same pictures. In dorsal views, anterior is up. (B) Cross-sections of RNA *in situ* hybridization for *taf15* and *ventx2.1*. 50um sections. Abbreviations: neural ectoderm (n), epithelial (e) and sensorial (s) layers of the epidermal ectoderm, lateral plate mesoderm (lp), dorsal (D), ventral (V). Dotted white lines delineate high taf15 expressing tissues from low or non-expressing tissues, as well as neural from non-neural ectoderm.

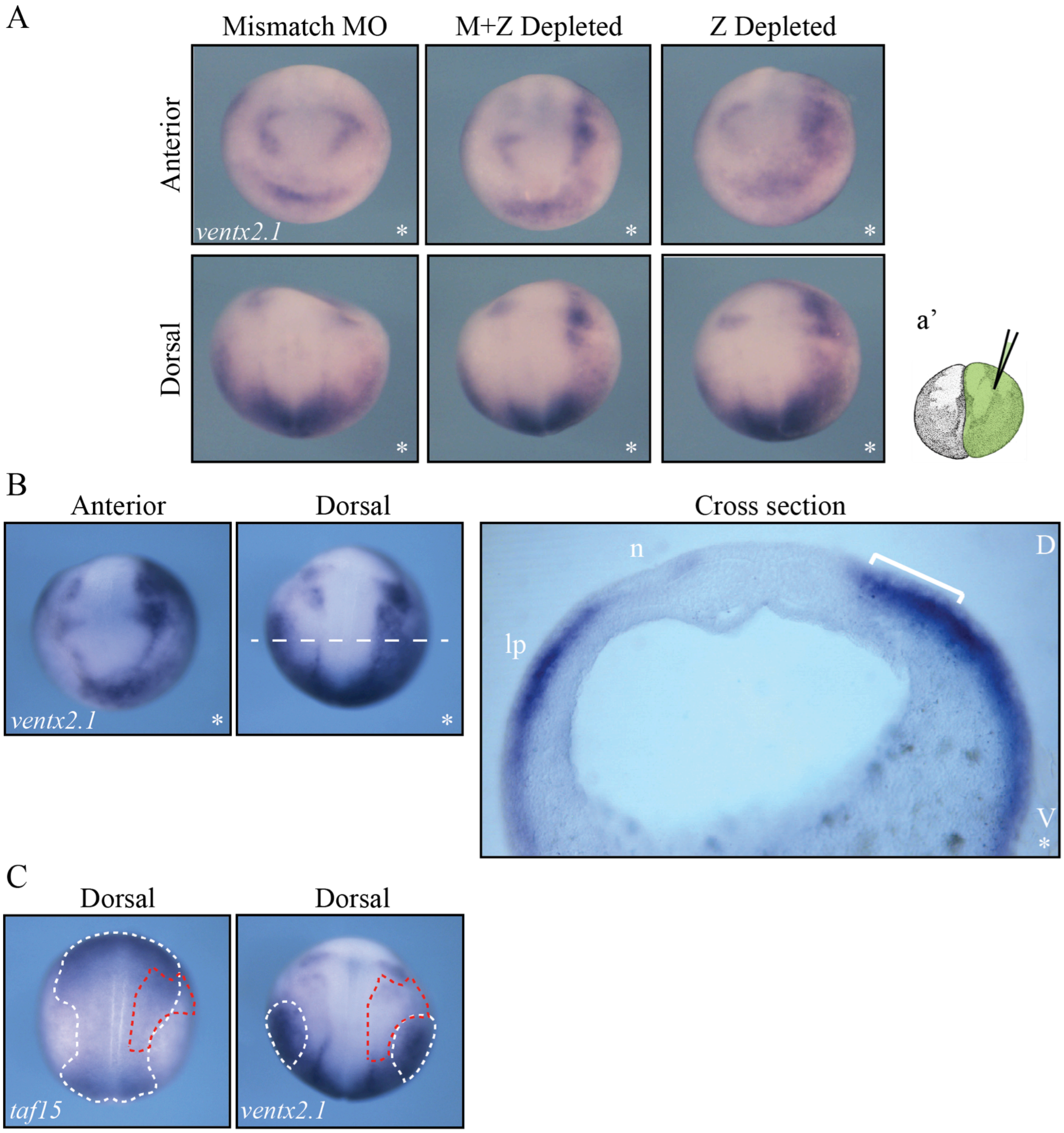

A
Mismatch MO
M+Z Depleted
Z Depleted
Anterior
Dorsal
ventx2.1
a'
B
Anterior
Dorsal
Cross section
ventx2.1
n
lp
D
V
C
Dorsal
Dorsal
taf15
ventx2.1

Figure 3.5 Increased *ventx2.1* expression with *taf15* depletion. (A) RNA *in situ* hybridization for *ventx2.1* upon injection of mismatch morpholino (Mismatch MO), 17ng translation-blocking morpholino (M+Z *taf15* Depleted), and 8ng splice-blocking morpholino (Z *taf15* Depleted), into one of two cells at the two cell stage. * = injected side. (a') Morpholino injection schematic. (B) RNA in situ hybridization for *ventx2.1* after injection of 17ng translation-blocking morpholino into one of two cells at the two cell stage. * = injected side. White line in dorsal view indicates where cross section was made. White bracket in cross section marks increased *ventx2.1* in neural ectoderm. Abbreviations: neural (n) ectoderm, lateral plate (lp) mesoderm, dorsal (D), ventral (V). Same cross section as was used in Figure 3.4B, *ventx2.1.* (C) Red dotted lines indicate where *ventx2.1* expression increases with *taf15* depletions. White dotted lines indicate complementary expression domains of endogenous *taf15* and *ventx2.1*. Panels in (C) are the same pictures as used in Figure3.4A, dorsal and outline. In all dorsal views, anterior up.

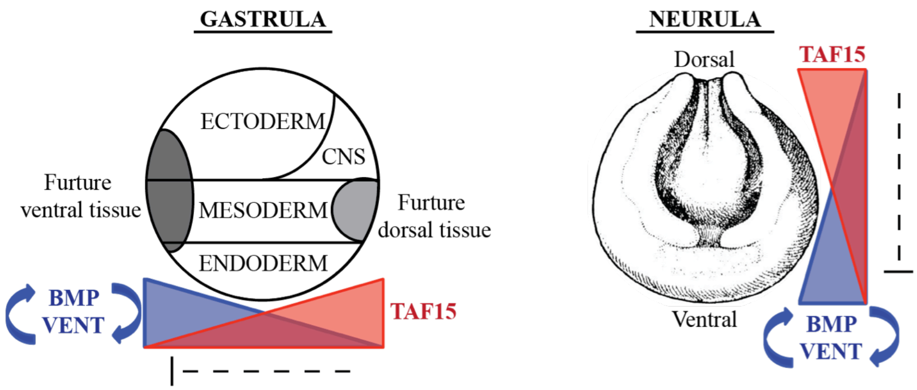


Figure 3.6 Model of TAF15 suppression of ventral fates. Gastrula. As early as stage 10 of *Xenopus* development, *taf15* begins to be preferentially expressed in the furture dorsal tissues whereas *ventx* genes are preferentially expressed in the future ventral tissues of the embryo. Abbreviation: central nervous system (CNS), bone morphogenetic protein (BMP). Gastrula schematic adapted from De Robertis & Kuroda, 2004. Neurula. At stage 15 of *Xenopus* development, *taf15* is expressed throughout ectodermal tissues whereas *ventx2.1* is expressed in the underlying ventral mesoderm. At this stage, *taf15* represses *ventx2.1* from regions of the neural ectoderm.

Chapter 4: Tools for maternal and zygotic *dgcr8* depletion to investigate the role of microRNAs in *Xenopus laevis* embryogenesis.

Section 4.1: Summary

This chapter serves as a resource for anyone who wants to parse apart the different effects that maternal verses zygotic *dgcr8* may have on development. Although only preliminary results, this chapter describes the tools that I generated to independently deplete maternal and/or zygotic *dgcr8*. Surprisingly, in these preliminary studies I found that the components of the microRNA biogenesis pathway do not all have overlapping expression patterns.

Section 4.2: Introduction

Early *Xenopus* development is dependent on the proper placement and delicate balance of maternal factors (White & Heasman, 2008). In the egg, these factors designate the animal/vegetal axis and the dorsal/ventral axis following fertilization. Additionally, maternal mRNAs and proteins drive mesoderm, ectoderm, and endoderm differentiation prior to the major wave of zygotic transcription. microRNAs (miRNAs) have been shown to be maternally deposited in *Xenopus* eggs (Armisen et al., 2009). However, the functional role of maternal miRNAs in *Xenopus* development have not been investigated. In frog and fish, studies have shown a role for zygotic miRNAs in modulating developmental signaling pathways by striking a balance between Nodal agonists and antagonists (Choi et al., 2007) (Rosa et al., 2009) (Martello et al., 2007) (Martin & Kimelman, 2007). As early development requires tight signal regulation, and zygotic miRNAs are known to balance signaling pathways, it is likely that maternally deposited miRNAs play an important role in early development.

miRNAs are approximately 22 nucleotide non-coding RNAs that regulate gene expression by base pairing with the 3' untranslated region (3'UTR) of target gene mRNAs (Figure 1.3). miRNA binding can either repress translational of the mRNA target, or induce degradation of the target mRNA (Figure 1.3). miRNAs are initially transcribed as pri-miRNAs which consist of a 100-1,000 base pair sequence. These transcripts contain a stem loop flanked by single stranded RNA. DiGeorge syndrome critical region 8, DGCR8, a double-stranded RNA-binding protein, forms a "microprocessor" complex with the RNase III enzyme Drosha and guides Drosha to cleave and remove the flanking single stranded RNA from the pri-miRNA stem loop generating pre-miRNAs (Ghildiyal & Zamore, 2009). Exportin5 exports the pre-miRNAs from the nucleus (Ghildiyal & Zamore, 2009). Once in the cytoplasm, Dicer, another RNase III enzyme, cleaves the stem loop, generating the mature duplexed miRNA. Argonaute2 (Ago2) then binds the duplexed miRNA and incorporates it into the RNA induced silencing complex (RISC) to be guided to target mRNAs (Ghildiyal & Zamore, 2009).

miRNAs have been found to have important roles in development (Kim et al., 2009) (Walker & Harland, 2009). In C. elegans, lin-4 and let-7 are important for development during the larval stages as well as the larval-to-adult transition, respectively (Lee, Feinbaum, & Ambros, 1993). In *Xenopus*, zygotic miR-427, the miRNA with the earliest described role in *Xenopus* development, targets Nodal/Lefty signaling as well as accelerates the degradation of maternal cyclins during the midblastula transition (Rosa et al., 2009) (Lund et al., 2009). The miR-427 ortholog in zebrafish, miR-430, is involved in brain morphogenesis as well as accelerating maternal transcript degradation during the midblastula transition (Giraldez et al., 2006).

Recently the expression of small RNAs throughout oogenesis in *Xenopus* was examined which revealed an abundant population of miRNAs (Armisen et al., 2009). Two of the miRNAs, miR-101a and miR-148a, were highly expressed during oogenesis, absent from follicle cells, and deposited maternally to the egg (Armisen et al., 2009). The expression level and timing of expression of maternal miR-101a and miR-148a expression, specifically their placement in the egg, makes these miRNAs attractive candidates to play a role in early development. Surprisingly, little attention has been given to maternally deposited miRNAs and their role in early embryogenesis.

Previous studies in zebrafish and mice have investigated the role of miRNAs in early embryonic development via loss of function alleles of Dicer1 during oogenesis (Giraldez et al., 2006) (Bernstein et al., 2003) (Akhtar et al., 2015) (Tang et al., 2007). Given the previously used methods, the role of *dicer1* in germline versus embryonic development could not be differentiated. However, in *Xenopus* it is possible to knockdown maternal factors once oocyte development is complete, allowing for examination of maternal signals specifically during embryogenesis (Hulstrand et al., 2010). Additionally, evidence suggests that in addition to miRNA biogenesis, Dicer1 is also essential for the biogenesis of small interfering RNAs (siRNAs) and endogenous short hairpin RNAs (shRNAs) (Suh et al., 2010). Thus, the specific role of miRNAs in early development remains to be elucidated. Importantly, the RNA binding protein DGCR8 is only required in miRNA processing and is therefore a more appropriate target to study the role of miRNAs in embryogenesis (Suh et al., 2010).

Zygotic *dgcr8* deficient mice arrest prior to implantation at the blastula stage E6.5, suggesting a role for DGCR8 and miRNAs in development (Y. Wang et al., 2007). Interestingly similar to zygotic *dgcr8* knockout, maternal and zygotic *dgcr8* mutants show no morphological difference between control and mutant embryos prior to the blastocyst stage, suggesting that in mouse, the earliest differentiation events (leading to the epiblast and trophectoderm lineages) progress normally in the absence of DGCR8-dependent miRNAs (Suh et al., 2010). However, the maternal to zygotic transition occurs at very different stages of embryogenesis, the 2-cell and 4000-cell stage, in mouse and *Xenopus*, respectively (Table 1). Although the data from maternal/zygotic DGCR8 deficient mice suggest that DGCR8-dependent miRNAs are not required for the earliest stages of mouse embryogenesis, due to the later zygotic genome activation in *Xenopus*, maternal DGCR8-dependent miRNAs could play a larger role in early *Xenopus* development.

Unlike in the mouse or zebrafish germline depletion systems, the *Xenopus* host transfer assay can deplete maternal *dgcr8* from mature oocytes without disrupting miRNAs biogenesis during oogenesis. Furthermore, splice-blocking antisense morpholino oligonucleotides can be introduced into embryos prior to zygotic genome activation to specifically target zygotic *dgcr8*. Due to the complete separation of maternal and zygotic *dgcr8* activities afforded by the host transfer assay, and delayed zygotic genome activation, *Xenopus* embryos are the perfect model system to investigate the role of maternal versus zygotic DGCR8-dependent miRNAs in early vertebrate development (Hulstrand et al., 2010) (Giraldez et al., 2006) (Bernstein et al., 2003) (Akhtar et al., 2015) (Tang et al., 2007).

Section 4.3: Results

Section 4.3.1: dgcr8 is both maternally deposited and zygotically transcribed and exhibits a specific gene expression pattern.

To study which tissues might be affected by a total loss of microRNAs (miRNAs), I determined where *dgcr8* is expressed. To do this, I performed RNA *in situ* hybridization (ISH) on various embryonic stages (Figure 4.1). From this assay I was able to observe the localization of maternally deposited *dgcr8* to the animal pole in the egg, 2-, and 4-cell stage embryos. Of all the stages examined, stage 9, during zygotic genome activation (ZGA), had the lowest *dgcr8* expression, not detectable above background. Although this could suggest a lack of miRNA activity and biogenesis, this is not the case because during ZGA, miRNAs are required for the degradation of maternal mRNAs (Lund et al., 2009) (Rosa et al., 2009). One possibility is that maternal, and not zygotic, DGCR8 protein is responsible for the majority of miRNA biogenesis during ZGA. During late neurulation (stage 18), after the neural tube has closed, *dgcr8* expression is increased and enriched within the neural plate. By the late tailbud stage (stage 30), expression is restricted to the dorsoanterior tissues of the embryonic central nervous system, specifically the fore-, mid-, and hindbrain, eye, otic vesicle, branchial arches, and dorsal structures of the trunk; at this stage, *dgcr8* appears to be excluded from the most posterior regions of the embryo. This tissue specific and dynamic *dgcr8* expression data supports the extensive developmental roles miRNAs have been shown to have in *Xenopus* embryogenesis (Walker & Harland, 2008) (Watanabe et al., 2005). A few examples include: miR-24a repressing apoptosis in the developing retina (Walker & Harland, 2009), miR-427 degrading maternal cyclins and regulating Nodal/Lefty signaling (mesendodermal specification) (Lund et al., 2009) (Rosa et al., 2009), as well as components of the miR-17-92 polycistronic oncomir both promoting (miR-92) and antagonizing (miR-19) oncogene-dependent apoptosis (Olive et al., 2009) (Olive et al., 2013).

Section 4.3.2: argonaute2 is both maternally deposited and zygotically transcribed and exhibits a specific gene expression pattern, different from dgcr8.

As a control experiment I set out to look at the expression pattern of another component of the miRNA biogenesis pathway, *argonaute2* (*ago2*). Given the important role of *ago2* and *dgcr8* in miRNA processing it was easy to assume that the expression patterns of these genes would be overlapping. Surprisingly, *ago2* and *dgcr8* transcripts do not have completely overlapping expression patterns (Figure 4.1 and Figure 4.2). While *ago2* and *dgcr8* mRNA is not expressed in overlapping domains it remains formally possible that DGCR8 and Ago2 protein expression is more overlapping. Further experiments are needed to address this possibility.

Using ISH, I was able to visualize *ago2* expression at various embryonic stages (Figure 4.2). From this assay I was able to observe that unlike *dgcr8*, *ago2* is not detected above background until after ZGA. By late neurulation (stage 18), *ago2* expression does overlap with *dgcr8* in the neural plate, although the domain of *ago2* expression is smaller. By the late tailbud stage (stage 30), expression of *ago2* is most readily detected in the dorsoanterior tissues, overlapping with *dgcr8* in the forebrain, eye, otic vesicle, branchial arches. In addition to these tissues, *argonaute2* is also expressed in the pronephros and, unlike *dgcr8* in the posterior dorsal structures of the trunk.

Published work using a *dgcr8* specific morpholino found that embryos depleted of *dgcr8* had affected pronephros development and exhibited reduced tubule formation as a result of a failure of the tissue to differentiate (Agrawal, Tran, & Wessely, 2009). The miRNA responsible for this phenotype was miR-30, required to regulate Xlim1/Lhx1 (Agrawal et al., 2009). In my RNA ISHs for *dgcr8* I do not see expression in the pronephros, but I do see expression of *argonaute2*. This suggests that RNA ISH may not be a sensitive enough assay to detect and extrapolate activity of miRNA processing machinery. However, since the time I performed RNA ISHs for *dgcr8* and *ago2* in 2010, it has been published that *argonaute2*, the catalytic component of the RNA-inducing silencing complex (RISC), is limited during early *Xenopus* development, restricting RNAi and miRNA biogenesis (Lund et al., 2011). This finding does support my RNA ISH data for *ago2* which showed very weak expression during embryonic cleavage stages, as well as my hypothesis that miRNA biogenesis machinery is not expressed in overlapping patterns. Both the *dgcr8* and *ago2* RNA *in situ* hybridizations will need to be repeated and developed for longer to see if I can see additional expression patterns, e.g. *dgcr8* expression in the pronephros, broader *ago2* expression.

Section 4.3.2: Tools to deplete maternal dgcr8 using the host transfer method.

As I stated in the introduction, the approach proven to result in the most stringent depletion of a maternal message from embryogenesis is the use of oligodeoxynucleotides (ODNs) targeting maternal mRNAs, and to perform a host transfer assay. Although I never completed the host transfer method, I did design and test many ODNs and found one that sufficiently depletes maternal *dgcr8*, "ODN2" (Figure 4.3A) (Table 5.2).

Section 4.3.3: Zygotic dgcr8 depletion leads to seemingly mild gross morphological defects.

To parse apart the different developmental contributions of maternal versus zygotic *dgcr8*, I designed a splice-blocking morpholino that successfully leads to an intron retention in zygotic *dgcr8* (Figure 4.3B) (Table 5.1). Following injection of varying amounts of splice-blocking *dgcr8* morpholino into both cells of two cell embryos, embryos exhibit a dose-dependent response to zygotic *dgcr8* depletion (Figure 4.3C). The gross phenotype following zygotic *dgcr8* depletion is surprisingly mild, based on the known requirement of many miRNAs throughout *Xenopus* development. The mild phenotype associated with zygotic *dgcr8* depletion suggests that there must be a significant pool of DGCR8 protein, possibly maternal DGCR8, that is able to process miRNAs and allow for the embryos to develop to later stages. These results may suggest that maternal DGCR8, or miRNAs processed by maternal DGCR8, can persist until embryos are tadpoles. Importantly, the dose-dependent reduction in dorsoanterior structures, specifically of the brain, and the posterior regions of the embryo being less affected, following *dgcr8* depletion, is consistent with the expression data I've observed for *dgcr8*.

Section 4.4: Discussion

The work described in this chapter generated the tools needed to investigate the different developmental contributions of maternal and zygotic *dgcr8*. As assayed by RT-PCR, the method of using oligodeoxynucleotides to deplete maternal *dgcr8* and splice-blocking antisense morpholinos to deplete zygotic *dgcr8* was a success.

The RNA *in situ* hybridization (ISH) expression data for *dgcr8* and *argonaute2* raise some interesting questions about the dependence of miRNAs on both DGCR8 and Ago2. Ago2 is required for small RNA pathways in addition to miRNAs, but this does not explain the seemingly more limited expression domain observed here for *argonaute2* as compared to *dgcr8*. In fact, because Ago2 is required in more small RNA pathways than DGCR8, one would expect the expression domain of *argonaute2* to be more expansive than *dgcr8*. However, as I previously stated, ISH visualizes RNA expression therefore it is possible that DGCR8 and Ago2 protein expression is more overlapping after zygotic genome activation. It is also important to note that while ISH is a fairly sensitive assay, probes can increase in sensitivity with use, thus these ISHs will need to be repeated. Additionally, it cannot be ruled out that *ago2* expression is below the limit of detection for ISH but is still biologically relevant. It will be of interest to look *in situ* at the remaining members of small RNA pathways to examine similarities and differences in expression patterns, both at the RNA and protein level.

Unlike the mouse and zebrafish studies that depleted maternal *dgcr8* throughout oogenesis, the tools described in this chapter allow for the depletion of maternal *dgcr8* from mature *Xenopus* oocytes or zygotic *dgcr8* from embryos. The tools that I have designed in this chapter could be used to generate *dgcr8*-depleted embryos, and will allow for publication of the first study where specific the role of *dgcr8* in embryogenesis could be ascertained.

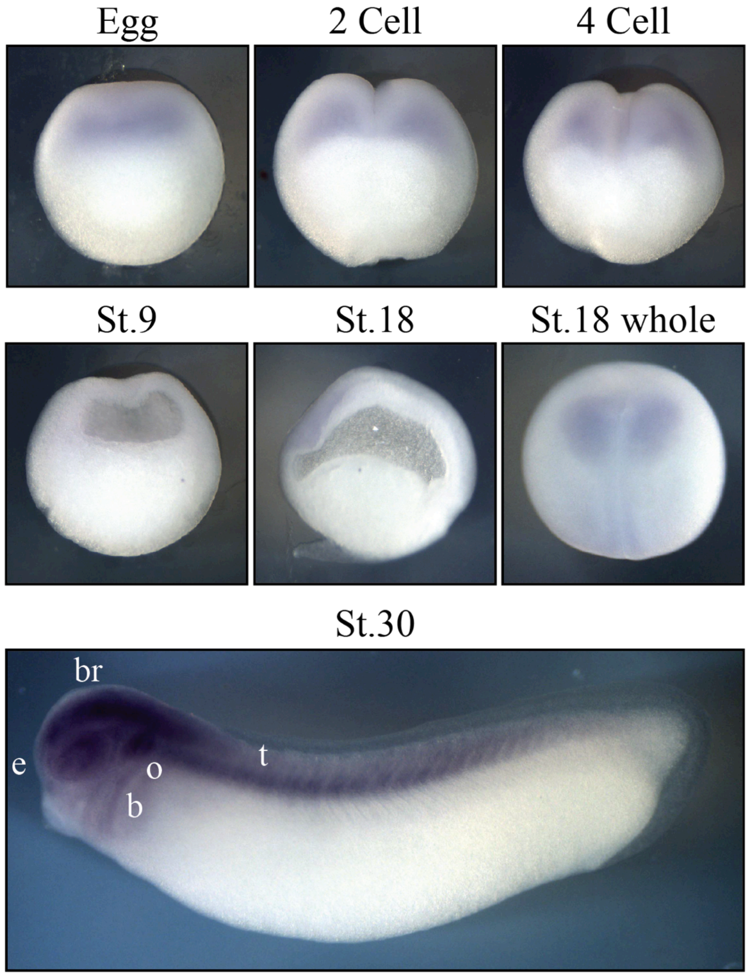


Figure 4.1 Expression of *dgcr8* in *Xenopus laevis*. RNA in situ hybridization of *dgcr8* from fertilized egg to early tadpole. Egg, 2 cell, 4 cell, and stages 9 and 18, cross sections. Stage 18 cross section, anterior left. Stage 18 whole embryo, dorsal view, anterior up. Stage 30, lateral view, anterior left. Fore/mid/hindbrain (br), eye (eye), otic vesicle (o), dorsal structures of the trunk (t), branchial arches (b).

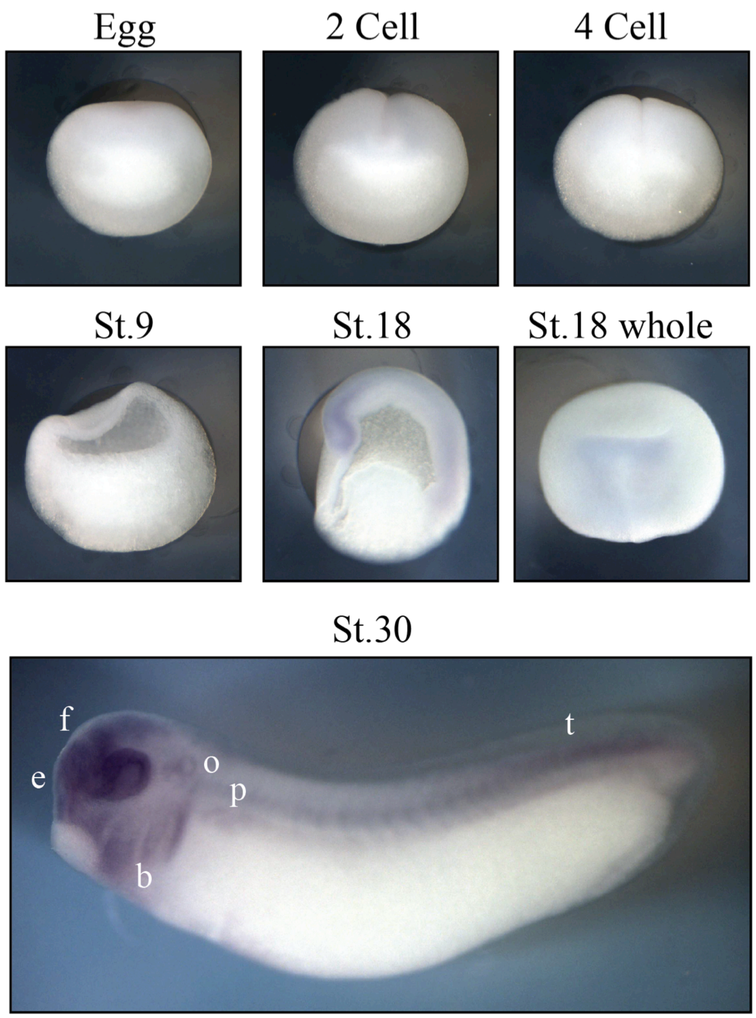


Figure 4.2 Expression of *argonaute2* in *Xenopus laevis*. RNA in situ hybridization of *argonaute2* from fertilized egg to early tadpole. Egg, 2 cell, 4 cell, and stages 9 and 18, cross sections. Stage 18 cross section, anterior left. Stage 18 whole embryo, dorsal view, anterior up. Stage 30, lateral view, anterior left. Forebrain (f), eye (eye), otic vesicle (o), branchial arches (b), pronephros (p), posterior dorsal structures of the trunk (t).

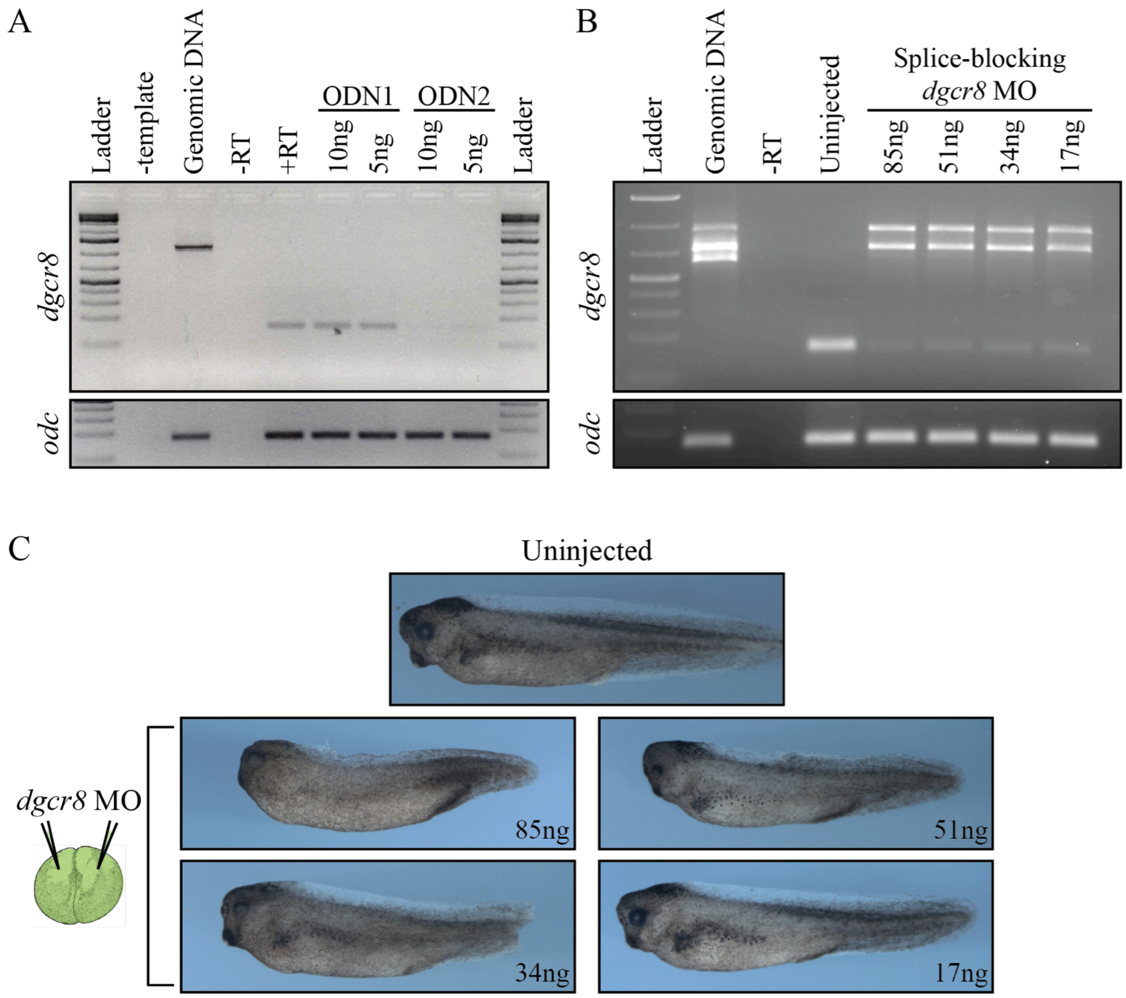


Figure 4.3 *Xenopus laevis dgcr8* depletion. (A) RT-PCR to amplify and visualize maternal *dgcr8* and *odc* transcripts in *Xenopus laevis* oocytes following a total injection of 10ng or 5ng of oligodeoxynucleotide (ODN1, ODN2). (B) RT-PCR to amplify and visualize intron retention of zygotic *dgcr8* transcript following a total injection of 85ng, 51ng, 34ng, or 17ng of splice-blocking morpholino. (C) Brightfield images of embryos, uninjected or following injection of *dgcr8* splice-blocking morpholino. Injections total 85ng, 51ng, 34ng, or 17ng of splice-blocking *dgcr8* morpholino.

Chapter 5: Materials and Methods

Section 5.1: General Xenopus Embryo Culture (Chapter 2, 3 & 4)

Xenopus tropicalis embryos were obtained through natural matings. For next day (daytime) matings, males were housed separately, and females were housed together, in four liter Rubbermaid® containers filled with two liters of water collected from the *X. tropicalis* housing racks. The night before the natural mating, males were boosted with 100 units (U) of human chorionic gonadotropin (HCG: Chorulon®, Merck, NADA NO.140-927, Code No. 133754) and females were primed with 10U HCG. The morning of the natural mating, females were boosted with 200U HCG and paired with males. *X. tropicalis* embryos were collected using a disposable polyethylene transfer pipet (Fisherbrand®, Cat No. 13-711-7M), with the tip cut off to enlarge the opening. Embryos were dejellied cultured as previously described (Khokha et al., 2002).

Xenopus laevis embryos were obtained through *in vitro* fertilizations as previously described (Sive et al., 2000). The night before fertilization, females were boosted with 500U HCG. Eggs were fertilized *in vitro* with sperm from masticated testes.

Xenopus tropicalis embryos were allowed to develop in 1/9X Marc's Modified Ringer (MMR), and *Xenopus laevis* embryos were allowed to develop in 1/3X MMR, until desired stage according to the normal table of development (Nieuwkoop & Faber, 1994).

Section 5.2: Whole-mount RNA in situ Hybridization (Chapter 2, 3 & 4)

Xenopus embryos were allowed to develop until desired stage and then fixed in MEMFA (0.1M MOPS pH7.4, 2mM EGTA, 1mM $MgSO_4$, 3.7% v/v Formaldehyde) as previously described (Sive et al., 2000). RNA probes were labeled with digoxigenin-UTP, and chromogenic reactions were carried out by incubating hybridized embryos in Anti-Digoxigenin-AP Fab fragments, 1:3000 (Roche, 11 093 274 910), and the alkaline phosphatase substrate BM purpled (Roche, 11 442 074 001), as previously described (Sive et al., 2000). *Xenopus tropicalis* embryos were incubated in prehybridization buffer for at least one hour, and *Xenopus laevis* embryos were incubated for at least six hours.

Section 5.3: Western Blotting (Chapter 2)

Xenopus tropicalis embryos were lysed in lysis buffer (20mM Tris–HCl pH 8.0, 50mM NaCl, 2mM EDTA, * add 1x protease inhibitor (Roche cOmplete, Mini, EDTA-free, Product#11836170001), and 1% Triton™ X 100 detergent (Sigma T8787-100mL) fresh) (20uL per embryo) and homogenized by pipietting up and down and freezing at -80°C. To pellet debris, lysates were spun at 5000 rpm (eppendorf Centrifuge 5417C) at 4°, and supernatant was transferred to new tube. To clear embryos of yolk, lysates were spun at 5000 rpm an additional two to three times, each time using a vacuum with a non-filtered p200 tip to briskly suck off the yolk from top of the lysate.

To measure the lysate protein concentrations, Bradford assays were performed.

Standard control: Purified Bovine Serum Albumin (BSA) 100X, 10mg/mL (New England Biolabs Cat#B9001S), was diluted 1:10 in water. 20uL of 1ug/uL BSA was added to 180uL of water. For each well that will contain a standard control, 100uL of water was added. To the first well of the standard control, 100uL of BSA dilution was added to 100uL water and pipetted up and down. Using a new pipette tip, 100uL was drawn out from the first well and transfer to the next well, and pipetted up and down. This was repeat until there was a total of six standards. The excess 100uL was removed from final well. The six dilutions were: 5ug, 2.5ug, 1.25ug, 0.625ug, 0.3125ug, and blank. Experimental samples: To each experimental well, 98uL of water was added. To each of these wells, 2uL of lysate was added. Once the standard and experimental wells were set up, 100uL of 2X Bradford Reagent (Bio-Rad Protein Assay Dye Reagent Concentrate, Cat#500-0006) was added to each well. To measure protein concentrations, a plate reader (Molecular Devices, Spectramax M2) was used.

Lysates were aliquoted for use and 6x loading dye was added. Samples were heated at 80°C for 10 minutes. Lysates were run on 8% polyacrylamide gel and run at 120V for 1 hour and forty-five minutes, eliminating proteins of 10-20 kDa. Proteins were transferred from gels using the semi-dry transfer system (BioRad Trans-Blot® SD Semi-Dry Electrophoretic Transfer Cell #170-3940) to Immobilon®-FL transfer membranes, PVDF (Millipore, IPFL00010), and blocked for one hour at room temperature with 1X Odyssey® Blocking Buffer (PBS) (LI-COR, 927-40000). Anti-TAF15 (TAFII68) antibody (Bethyl Laboratories, A300-309A) was used at 1:3000, anti-FGFR4 (CD334) antibody (Thermo Scientific, PA5-28175) was used at 1:2000, anti-SRSF4 (SRp75) antibody (Millipore, 06-1367) was used at 1:500, and anti-β-actin antibody (GeneTex, clone GT5512, GTX629630) was used at 1:5000, diluted in 5% BSA in TBS-tween (TBS-T), and incubated overnight at 4°C. Fluorescent secondary antibodies, Alexa Fluor® 680 goat anti-Rabbit IgG (Invitrogen, A-21109), Alexa Fluor® 680 goat anti-Mouse IgG (Invitrogen, A-21058), IRDye® 800CW Donkey anti-Rabbit IgG (LI-COR, 925-32213), and IRDye® 800CW Donkey anti-Mouse IgG (LI-COR, 925-32212), were incubated at 1:10,000 for one hour at room temperature in the dark.

Fluorescently labeled proteins were visualized and quantified using a LI-COR imager and software (LI-COR, Odyssey).

Section 5.4: Microinjection of Morpholino Antisense Oligonucleotides: Maternal and/or Zygotic mRNA Depletion (Chapter 2, 3 & 4)

Morpholino antisense and mismatch oligos (MOs) were designed and ordered from GeneTools LLC (Table 5.1). MOs were dissolved in nuclease-free water to 8.5ng/nL (1mM). MOs were injected into either one of two cells, or two of two cells, to deplete target mRNA from half or the whole embryo, respectively. To trace which cells contain MO, each MO was co-injected with the GeneTools fluorescein-conjugated standard control oligo. The optimal doses were determined for depletion and control and are listed in Table 5.1.

Section 5.5: Microinjection of Antisense Oligodeoxynucleotides: Maternal mRNA Depletion (Chapter 4)

Antisense oligodeoxynucleotides (ODNs) were designed and ordered from Eurofins MWG Operon, HPLC purified (Table 5.2). ODNs were resuspended in nuclease-free water to 1ug/uL, aliquoted, and stored at -80°C.

Xenopus laevis ovaries were obtained from the Isacoff lab at U.C. Berkeley. Stage VI oocytes were manually defolliculated using #5 Dumostar® forcepts in oocyte culture medium (OCM) (480 ml Liebovitz L-15 medium (Sigma L-5520), 320 ml sterile deionized water, 0.32 g Bovine serum albumin (BSA) (Sigma A-9418), 4 ml Glutamine from 200 mM stock (Sigma G-6392) (make fresh weekly), 4 ml Penicillin-Streptomycin solution (Sigma P-0781), adjust pH to 7.6-7.8 with 5M NaOH), made fresh daily (Xenbase).

Defolliculated oocytes were injected with 5ng and 10ng of each antisense ODN and cultured in OCM for 24 hours at 18°C. RT-PCR (see below) was performed to determine which oligo depleted maternal *dgcr8*. *Three phosphorothioate links were not added to each end of the ODNs as it was determined that the unmodified oligos were able to sufficiently deplete maternal *dgcr8*.

Section 5.6: RNA-extraction (Chapter 2, 3 & 4)

The following RNA-extraction protocol is adapted from the Trizol® Reagent protocol and optimized for extracting small amounts of RNA from sinlge *Xenopus tropicalis* embryos. This protocol, however, will also work for extracting RNA from *Xenopus laevis* embryos/oocytes.

One *Xenopus tropicalis* embryo was resuspended in 200uL of Trizol® Reagent (Ambion Ref# 15596026) and frozen at -80°C for two hours or overnight (O/N). Homogenized samples were thawed and incubate at room temperature (RT) for five minutes to allow complete dissociation of the nucleoprotein complex. 40uL of chloroform was added to each sample, vortexed, and incubated at RT for 2-3 minutes. Samples were centrifuged at 12,000 x *g* for 15 minutes at 4°C. After spin, samples were transferred to ice to prevent phenol evaporation. 90uL of the upper aqueous phase was removed and place in new tube. RNA was precipitated by adding 5ug of linear acrylamide (Ambion, AM9520) and 100 uL of 100% isopropanol to aqueous phase. Samples were incubated at RT for 10 minutes and centrifuged at 12,000 x *g* for 10 minutes at 4°C. Samples were transferred to ice and supernatant was removed. Pellets were washed by adding 200uL of cold 75% ethanol, vortexed, and centrifuge at 7500 x *g* for five minutes at 4°C. Samples were transfered to ice and supernatant was removed. Pellets were air dryed at RT for 5-10 minutes. RNA pellets were resuspended in 250uL of Milli-Q water and gently pipetted up and down and vortex. A second RNA extraction was performed by adding 250uL of Acid-Phenol:Chloroform, pH 4.5 (with IAA, 125:24:1) (Ambion, Cat#AM9720). Samples were vortexed and centrifuged at 12000 x *g* for 15 minutes at 4°C. Samples were transferred to ice and the supernatant was removed. 200uL of the upper aqueous phase was removed and placed in new tube. RNA was precipitated by adding 20uL 5M NH_4OAC (Ammonium Acetate) (Ambion AM9070G) and 220uL of 100% isopropanol. Samples were incubated for 5-10 minutes at RT. Samples were centrifuged at 12,000 x *g* for 10 minutes at 4°C. Samples were transfered to ice and supernatant was removed. Pellets were washed two times as described in previous step. Pellets were air dryed at RT for 5-10 minutes. RNA pellet were resuspended in 30uL of Milli-Q water and gently pipetted up and down. RNA concentrations were measured using a nanodrop (Nanodrop ND-1000 Spectrophotometer).

Section 5.7: RNA-sequencing Libraries (Chapter 2 & 3)

Each paired-end library for RNA-sequencing (RNA-seq) was prepared using RNA extracted from single *Xenopus tropicalis* embryos. RNA-seq libraries were made strictly following the Low Sample (LS) Protocol from TruSeq RNA Sample Preparation v2 Guide. The one very important modification made to this protocol was that all reagents were used at half volume, except for the Bead Washing Buffer.

The KAPABIOSYSTEMS "KAPA Library Quantification Kits for Illumina sequencing platforms" was used to quantify RNA-seq librarieS.

RNA-seq analysis was performed using the *Xenopus tropicalis* genome version 7.1, and an annotation from Darwin Dichmann. RNA-seq data analysis for differential gene expression was performed using both the Tuxedo Suite (Tophat, Bowtie, Cufflinks, Cuffdiff) (Trapnell et al., 2012) and the Bioconductor package DESeq (Love et al., 2014). RNA-seq data analysis for differential intron-exon usage was performed using the Bioconductor package, DEXseq (Reyes et al., 2014) (www.bioconductor.org).

RNA-seq alignments were visualized using the Integrative Genomics Viewer (IGV) from the Broad Institute (www.broadinstitute.org/igv/).

Section 5.8: Complementary DNA (cDNA) Synthesis (Chapter 2, 3 & 4)

The following cDNA synthesis protocol is an adaptation of the 20uL iScript reverse transcription (RT) reaction protocol from BIO-RAD.

Optimally, 1ug of total RNA was added to each 20uL reverse transcription reaction: 16uL RNA/H_2O + 4uL 5x iScript RT Supermix (BIO-RAD Cat#170-8841). However, total RNA from a single *Xenopus tropicalis* embryo was routinely resuspended in 30uL Milli-Q water, and slightly varying amounts of RNA were yielded from embryo to embryo. To ensure all RT samples contained the same volume and concentration of RNA, the embryo with the lowest RNA yield was made the upper limit of total RNA per sample. The remaining samples were adjusted to this RNA total, and the total volume for each sample was brought up to 30uL with Milli-Q water. For each RT reaction, 7.5uL of 5x iScript RT Supermix was added to 30uL of RNA/H_2O.

For no RT (NRT) samples, the remaining RNA samples (that exceeded the lowest yield), were pooled and the sample volume was brought up to 30uL, and 7.5uL of 5x iScript Supermix no RT was added.

The following RT protocol was run on a thermal cycler: 25°C for 5:00 minutes, 42°C for 30:00 minutes, 85° for 5:00 minutes, 4° forever.

Section 5.9: RT-qPCR (Chapter 2 & 3)

cDNA samples were diluted to a working concentration of 5ng/uL. Master Mix for one reaction, total volume of 15uL: 10uL of 2x SsoAdvanced SYBR Green Supermix (BIO-RAD Cat#172-5261), 0.4uL of [10mM] F+R primer set, 4.6uL of Milli-Q water. 15uL of master mix was added to each well of qPCR plate (Multiplate™ PCR plates 96-well, MLL9651). 5uL of cDNA (25ng) was added to wells containing master mix, for a total volume of 20uL. NRT and no template control (NTC) samples were included for each gene target.

Before using primer set pairs for quantitating transcripts, primer pair efficiency was tested on six standard controls (serial dilutions of 1/5): 25ng = 2.50E+04, 5ng = 5.00E+03, 1ng = 1.00E+03, 0.2ng = 2.00E+02, 0.04ng = 4.00E+01, 0.008ng = 8.00E+00.

For testing primer efficiency as well as for quantitating transcripts, the following protocol was used on the CFX96 Thermal Cycler: Lid: 105°C, Volume: 20uL, 95°C for 2:00, 95°C for 0:10, 60°C for 0:35, Plateread, Goto 2, 39X, 65°C for 0:31, 65°C for 0:05, +0.5°C/cycle, Ramp 0.5°C/s, Plateread, Goto 7, 60X.

Xenopus tropicalis qPCR primer pairs are found in Table 5.3.

Section 5.10: RT-PCR (chapter 4)

The following program was run on a Thermo Cycler to amplify *Xenopus laevis dgcr8, odc, and β-catenin.* 94°C for 3:00, 94°C for 0:45, 55°C for 1:00, 72°C for 1:00, go to 2, 27X, 72°C for 5:00, 16°C forever.

Xenopus laevis PCR primer pairs are found in Table 5.2.

Section 5.11: TAF15 Expression Construct (Chapter 2)

Human *TAF15* (Addgene plasmid pENTR4_TAF15) was purchased from Addgene (Addgene, Inc., 26368) and subcloned into pCS108.

Synthetic *TAF15* mRNA for overexpression experiments was made using the mMesssage mMachine SP6 kit (Ambion, AM1340). RNAs were labeled with ^{32}P-UTPs to quantify RNA after synthesis. RNAs were resuspended in nuclease-free water to a stock concentration of 1ug/uL and a few 5uL aliquots of 0.1ug/uL were made for working stocks. A total of 150-300pg of *TAF15* was injected into embryos at the two-cell stage for rescue and overexpression experiments.

Cloning and qPCR primers are found in Table 5.4.

Section 5.12: Whole-mount Immunohistochemistry (Chapter 2)

Embryos were fixed in MEMFA (0.1M MOPS pH7.4, 2mM EGTA, 1mM $MgSO_4$, 3.7% v/v Formaldehyde) for 2hr at RT or o/n at 4°C in 1 Dram glass vials (True Essence/TAF INC, 13-

425). Following fixation, embryos were dehydrated in Dent's (80% Methanol, 20% DMSO), 3-5 washes for 5-15 minutes each. Embryos were stored o/n at -20.

Embryos were rehydrated by washing for 10 minutes in each of the following solutions: 100% Dent's, 75:25% Dents:PBS, 50:50%, 25:75%, 100% PBS. Embryos were washed in fresh PBST+BSA (1x PBS, 0.1% Triton-X, 2mg/mL BSA, store at 4°)

The following steps were carried out in a total volume of 500uL. Embryos were blocked for 1hr+ at RT in 1/10 CAS-Block™ Histochemical Reagent (CAS block diluted 1:10 in PBST) (Life Technologies, 00-8120). Embryos were incubated in primary antibody diluted in 100% CAS-Block™ + 4% DMSO O/N at 4°C. Primary antibody tor 219.2.13 (sensory neurons) was obtained from the University of Iowa, Developmental Studies Hybridoma Bank (DSHB) and diluted 1:5. Following primary antibody incubation, embryos were washed one time for five minutes with PBST, and for an additional five times for 30-60 minutes. Embryos were incubated in secondary antibody diluted in 100% CAS-Block™ + 4% DMSO O/N at 4°C. Secondary antibody Alexa Fluor 555 goat anti-mouse IgG (Life Technologies, A21127) was diluted 1:250. Following secondary antibody incubation, embryos were washed three to five times in PBST for 20 minutes.

Section 5.13: Non-crosslinking Immunoprecipitation (Chapter 2)

The following protocol was modified from a protocol received by Darwin Dichmann from Michael Sheets.

The following is done the day before one wants to perform an immunoprecipitation (IP). 50uL of sheep α-rabbit IgG Dynabeads M-280 (Invitrogen, Cat# 11203D, 2mL) were washed in 1mL of fresh 0.5% BSA in PBS (washing solution) in 1.5mL screw cap tubes (LSA stockroom #P183) on an inverting rotator for 5-10 minutes at RT. The beads were separated from the washing solution by placing the vials (containing the beads and washing solution) on a magnetic stand (Invitrogen, Dynal® Invitrogen beads separation) and inverting numerous times. Keeping the vials on the stand, the washing solution was removed from the vials. The vials (now containing only beads on the side of the vial) were removed from the stand and washed with 1mL of fresh washing solution. This washing step was repeated for a total of four washes. The beads were resuspended in 1mL of washing solution. 500uL of resuspended beads was put into two new 1.5mL screw cap vials. Both vials were filled to 1mL by adding 500uL of washing solution. To the experimental vial, 5ug of TAF15 antibody (Rabbit anti-TAFII68, Bethyl Laboratories, Cat#A300-309A) was added. To the negative IP control vial, 5ug of purified rabbit IgG (Bethyl Laboratories, Cat#P120-101) was added. The vials containing beads and antibodies were incubated at 4°C O/N on an inverting rotator.

The following is done when one plans to collect embryos for an IP. *Xenopus tropicalis* embryos were developed until desired stage (st.6, 10, and 15) and lysed in 10uL of TNMEN 150 Buffer (150mM NaCl, 1mM EDTA, 2mM $MgCl_2$, 50mM Tris pH 8.0, *Add 0.1% Triton-X 100 and protease inhibitor (cOmplete, Mini, EDTA-free, Roche Product#11836170001) fresh) per embryo (ex: 10 embryos in 100uL buffer).

The following is done when one plans to perform an IP. Lysates were centrifuged at 4°C for 10 minutes at 5000 rpm. During this time, the beads/antibody solutions were divvied up (by the number of samples to IP) into 1.5mL screw cap vials. The lysate supernatant was collected and 10% was reserved for "input sample". The remaining 90% of supernatant was added to the aliquotted beads/antibodies and brought up to a volume of 1mL with TNMEN 150 Buffer. The lysate/beads/anitbodies were incubated for two hours at 4° on an inverted rotator. After incubating, the vials were placed on the magnetic stand and invert until the beads were drawn out of solution. Keeping the vials on the magnetic stand, the solution was drawn off. 10% of this solution was kept as the "supernatant sample". The vials were removed from the magnetic stand and washed four times with 1mL of TNMEN 150 Buffer. These washes were performed the same as before except this time, the beads and buffer were rotated for 5-10 minutes at 4°C on an inverted rotator. The beads were resuspend in 40uL of TNMEN. To uncouple the beads from the protein, 5x sample buffer (10% w/v SDS, 10mM β-mercapto-ethanol, 20% w/v glycerol, 0.2M Tris-HCl, pH 6.8, 0.05% w/v bromophenolblue) (to 1x, ex: 10uL sample buffer to 40uL TNMEN) was added and the samples were incubated at 80°C for 10 minutes. The samples were returned to the magnetic stand to remove magnetic beads from the IP'd solution. The desired amount of IP'd lysate was used for Western Blotting.

Section 5.14: Glutaraldehyde Vibratome Sections (Chapter 3)

Following RNA *in situ* hybridization, embryos were selected for sectioning. Starting from PBS-tween, embryos were equilibrated into an albumin + gelatin solution: 75:25, 50:50, 25:75, 100. Equilibration was considered complete when the embryos sank to the bottom of the 1 Dram glass vial. When possible, to ensure that the embryos were fully equilibrated in 100% albumin + gelatin, the embryos were incubated O/N. Dilute stock glutaraldehyde to 25% (Sigma-Aldrich, G7651-10mL) in water. While gently vortexing 1.875mL of albumin + gelatin in a 15mL conical (so as not to introduce bubbles), 125uL of 25% glutaraldehyde was added and the mixed solution was quickly poured into a Peel-A-Way® disposable embedding mold (Polysciences, 18985). Once cured (becoming a darker brown color after ~10-15 minutes), embryos were positioned onto this first layer of albumin + gelatin + glutaraldehyde and allowed to set, removing any excess liquid albumin + gelatin. The second layer of albumin + gelatin + glutaraldehyde was made just like the first and poured over the embryos. Once both layers were cured, the blocks were peeled out of the embedding molds and cut into prisms sectioning. Prisms were affixed to Heroscape dice (Hasbro) with super glue and mounted in the vibratome. 50-75micron sections were made and mounted on glass slides for imaging.

Table 5.1 *Xenopus tropicalis* and *Xenopus laevis* morpholino antisense oligos.

Organism	MO Name	Sequence	Function	Chapter
Xenopus tropicalis	trnstaf15	5'-AGCTACTGGGATCTGAAGACATGAT-3'	translation-blocking	2 & 3
Xenopus tropicalis	sbtaf15	5'-TTCCAAAACCTACCTTTGTTGCTGC-3'	splice-blocking	2 & 3
Xenopus tropicalis	mismatch	5'-AGCTAGTCGCATCTCAACACATGAT-3'	negative control for MO injection	2 & 3
Xenopus laevis	DGCR8	5’ -AATCATGTTCAGAAACATACCTCAT- 3’	splice-blocking	4
X tropicalis & laevis	Control	5'-CCTCTTACCTCAGTTACAATTTATA-3'	fluorescein-conjugated standard control oligo, tracer	2, 3, & 4

Table 5.2: ***Xenopus laevis*** **maternal** ***dgcr8*** **depletion tools and primers used in Chapter 4.**

Tool	**Name**	**Sequence**
Oligodeoxynucleotide	*dgcr8* ODN1	5' -CAGAAGTGCATCCACATC- 3'
	dgcr8 ODN2	5'-CTCTCCATCTGATTGGTG-3'
Xenopus laevis primers	*dgcr8*	F: 5'-AAGAGCCAGACACCACTGCT-3'
		R: 5'-TTCCAGATAGCTGCGGAAGT-3'
	β-*catenin*	F: 5'-GCCAACGTTTGGTTCAGAAT-3'
		R: 5'-ATGCCTCCAACTTGACAACC-3'
	odc	F: 5'-GGGCTGGATCGTATCGTAGA-3'
		R: 5'-TGCCAGTGTGGTGTTGACAT-3'

Table 5.3 *Xenopus tropicalis* qPCR primers.

Name	Sequence	Chapter
*clk1*_intron3	F: 5'-GAAACTGCAGGTTGGGTGAT-3' R: 5'-TCCTTTCCAGCTGCTGATCT-3'	2
*clk1*_intron3/exon5	F: 5'-ATTGCCTGGATGCAACCTAC-3' R: 5'-AAAGCTCCTTCTCCCAAAGC-3'	2
eef1a1	F: 5'-CCCTGCTGGAAGCTCTTGAC-3' R: 5'-GGACACCAGTCTCCACACGA-3'	2 & 3
*fgfr4*_intron1	F: 5'-AGGGCTAAGCAGTGCCTGTA-3' R: 5'-AATGCAAGAGCAGCTCCAAT-3'	2
*fgfr4*_exon14/17	F: 5'-AGCCAGGAATGTTCTTGTGG-3' R: 5'-TCCCATGTCAACACTCCAAA-3'	2
*ils1*_intron3	F: 5'-CCCTCCTACCCTTTTCCAAG-3' R: 5'-GGCTGAAGTGCGGAATCTAA-3'	2
*ils1*_exon5/6	F: 5'-ACTTTGCCCTGCAGAGTGAC-3' R: 5'-TGCCTCTATAGGGCTGGCTA-3'	2
*pax8*_intron6	F: 5'-CCTCCAAAAACCAGCATCAA-3' R: 5'-CCACTAGGTGGTGCATGAAA-3'	2
*pax8*_exon10/11	F: 5'-AGCTCCACCCCTTCATCTTT-3' R: 5'-CAACCACATCACGACCTGAG-3'	2
*srsf4*_intron4	F: 5'-TCTGATCCCCATTCAGTTGC-3' R: 5'-GTTTTGCCTGCATAGCCAGT-3'	2
*srsf4*_exon6	F: 5'-GAGCAAGGATAGGGACCACA-3' R: 5'-TCTCTTTGCTACGGCTGGAT-3'	2
taf15	F: 5'-GTGGAGGTGGTCACAGAGGT-3' R: 5'-CCTCGATCTCCACCATGTCT-3'	
ventx1.1	F: 5'-TACAAGACCAGCAGCACAGC-3' R: 5'-GGGAGTGTCTGCGGAATAAA-3'	
ventx1.2	F: 5'-CAGAGCAGGTTTCCCTTCAG-3' R: 5'-TGTCCATCCTTTCTCCTTGG-3'	
ventx2.1	F: 5'-AACAGCCAGCTGTCTCCAGT-3' R: 5'-GCTGTGTCCCTGTGTAGCAA-3'	3
ventx2.2	F: 5'-CAAGTATCTCCATATTCCTC-3' R: 5'-TCTTCATCGGAACTGGCTCT-3'	
ventx3.2	F: 5'-TGCAAGGGTTGAAGCTTTCT-3' R: 5'-CAAGGTTTGCGGAAGGAATA-3'	

Table 5.4 *TAF15* cloning and qPCR primers used in Chapter 2.

Name	Sequence
TAF15	F: 5'-ATGTCGGATTCTGGAAGTTA-3' R: 5'-TCAGTATGGTCGGTTGCGCT-3'
	Forward
TAF15-ClaI	5'-GATCGATATCGATGCCGCCACCATGTCGGATTCTGGAAGTTA-3'
	Reverse
TAF15-BamHI	5'-GATCGATGGATCCGCCGCCACCATGTCGGATTCTGGAAGTTA-3'

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Appendix

Appendix I

Stage 10 statistically significant differentially expressed gene transcripts. Gene names are alphabetical. Fold change of M+Z *taf15* depleted over uninjected. Green fold change, increased expression in M+Z *taf15* depleted embryos. Red fold change, decreased expression in M+Z *taf15* depleted embryos. Results generated using the Bioconductor DESeq package. Results generated from the second RNA-seq library: three stage 10 uninjected *Xenopus tropicalis* embryos and three M+Z *taf15* depleted stage 10 equivalent *Xenopus tropicalis* embryos.

Gene Name	baseMean	log2Fold Change	fold change (MO/UC)	lfcSE	stat	pvalue	padj
aco2	370.6378709	-0.848029538	0.55554299	0.186722699	-4.541652103	5.58E-06	0.001711687
acpl2	564.9324263	1.028272384	2.039580407	0.246051637	4.179091817	2.93E-05	0.006067597
afg3l1p	212.8802639	0.706839431	1.632224419	0.206687089	3.419852855	0.00062655	0.059442619
agr2	2210.750099	2.070205501	4.199464873	0.465393656	4.448289048	8.66E-06	0.002363428
alg5	410.3688683	-1.061831255	0.479023635	0.25844666	-4.108512199	3.98E-05	0.007686259
alpl	503.15035	-2.984018401	0.126392398	0.412071069	-7.241513965	4.44E-13	1.66E-09
ankrd39	147.8385089	-1.167124408	0.445308048	0.347742763	-3.356286695	0.000789966	0.068028253
arhgap11a.2	235.3937401	2.068984222	4.19591142	0.400906229	5.160768461	2.46E-07	0.000161958
arhgef40	500.5676895	1.097742296	2.140195067	0.321489184	3.414554359	0.000638864	0.059600728
arhgef5	326.448793	-0.907601791	0.533070485	0.238329713	-3.808177245	0.000139995	0.020479843
arl5c	2369.251298	0.804207135	1.746185873	0.178377095	4.508466382	6.53E-06	0.001874385
arrdc2	121.8837252	0.992828102	1.99008231	0.239126518	4.15189462	3.30E-05	0.006591738
arv1	75.55415406	-1.430297354	0.371054407	0.244530254	-5.849163159	4.94E-09	5.53E-06
atf6b	257.2258891	0.740758966	1.671054708	0.229615291	3.22608726	0.001254951	0.089485193
atg4a	110.3877798	1.080776363	2.115174022	0.281991485	3.832656028	0.000126767	0.019710531
atpaf2	263.730781	-0.981334222	0.506511095	0.223081704	-4.39899016	1.09E-05	0.002767092
bcs1l	239.9654724	-1.496237982	0.354476531	0.469795363	-3.184871752	0.001448182	0.098712103
brd2	3724.592459	1.070340328	2.099928676	0.311588352	3.43511021	0.000592313	0.058166165
c15orf39	1282.752607	-0.644688294	0.639630973	0.17874469	-3.606754947	0.00031005	0.035418492
c19orf53	328.5606781	-1.5234483	0.34785349	0.405367201	-3.758193303	0.000171145	0.022278655
c1orf109	359.2574266	0.853898653	1.807378484	0.262089322	3.25804442	0.001121828	0.084857226
c2orf44	522.238608	1.443010832	2.718876898	0.348302469	4.142981923	3.43E-05	0.006733085
c5	1467.933768	-2.028668511	0.24508116	0.623249879	-3.254984205	0.001133987	0.08517981
calr	17759.60292	-0.741593853	0.598078246	0.195433268	-3.794614191	0.000147873	0.020954945
cct3	1174.72159	-1.140587482	0.453574839	0.278785462	-4.091273179	4.29E-05	0.008004638
cdk1	888.4559612	0.677910743	1.599821275	0.213568003	3.174214923	0.001502424	0.099524475
cdk5	150.3331504	-1.180143916	0.441307473	0.245502055	-4.807063286	1.53E-06	0.000612381
cdk5r1	308.7561328	-1.891706574	0.269488091	0.552359371	-3.424775014	0.000615309	0.058875054
cenpl	716.5841467	0.611276325	1.527610059	0.149120484	4.09921098	4.15E-05	0.007866119

cep85	704.9464597	-0.859839997	0.551013665	0.202767501	-4.240521753	2.23E-05	0.004992988
chd8	2609.971445	-0.697311367	0.616720468	0.171753527	-4.059953689	4.91E-05	0.009007837
creb1	1485.880314	-0.817670301	0.567357386	0.178121594	-4.590517531	4.42E-06	0.001468351
cse1l	790.6753325	-0.567187751	0.674931152	0.176691387	-3.210047539	0.00132713	0.092857642
cyb561	1026.958226	4.384318066	20.88388286	0.854428584	5.131286742	2.88E-07	0.000166966
cyb5b	619.0983429	-0.62577987	0.648069359	0.147878592	-4.231713752	2.32E-05	0.00499805
cygb	1925.549283	-1.577507706	0.335060214	0.416285938	-3.789481124	0.000150962	0.021125284
dbf4b	1058.754753	0.475212187	1.390122659	0.136573238	3.479541044	0.000502273	0.052550944
dbn1	1538.923373	-0.489477206	0.712283163	0.147533076	-3.317745544	0.000907471	0.075814473
degs1	1577.504267	1.428401728	2.691483774	0.288423863	4.952439482	7.33E-07	0.000341862
degs3	982.7310535	-1.981636865	0.253202426	0.423492822	-4.679269071	2.88E-06	0.001007198
dlc	2211.860721	-1.58923222	0.332348277	0.417755753	-3.804213844	0.000142255	0.020479843
dlx3	694.0125822	-1.975806681	0.254227732	0.465056548	-4.248529968	2.15E-05	0.004916156
dmrta2	181.5895336	1.479782778	2.789067361	0.438384646	3.375535139	0.000736723	0.065457239
eif2b3	369.5944653	-1.375269955	0.385480569	0.223242858	-6.160420853	7.26E-10	1.16E-06
elavl3	1416.541003	-0.996753516	0.501126413	0.286145236	-3.483383228	0.000495119	0.052291112
emb	311.0054315	-1.453734712	0.365075128	0.446063188	-3.259033136	0.001117926	0.084857226
fam195a	216.0174871	0.953251649	1.93623176	0.237811697	4.008430446	6.11E-05	0.010691861
fancd2	71.415979	1.237854337	2.358475046	0.366543809	3.377097927	0.00073255	0.065457239
flna	7066.874945	0.839480491	1.789405668	0.215036812	3.903892008	9.47E-05	0.015583774
fos	77.35456488	1.288824958	2.443289741	0.381297317	3.380104974	0.000724581	0.065457239
foxh1	2178.313936	0.891861285	1.855568532	0.240283571	3.711703134	0.000205869	0.025156796
foxi1	647.1129499	-2.742296962	0.14944671	0.565267002	-4.851330349	1.23E-06	0.000508486
foxn3	1921.912054	0.63414601	1.552018775	0.188120103	3.37096355	0.000749058	0.065513287
frat1	1182.990517	0.924128948	1.897538225	0.239992675	3.850654807	0.000117802	0.018606765
fscn1	3606.249049	-1.0663899	0.477512399	0.309143226	-3.449501105	0.000561623	0.056137271
fuk	163.7190078	-1.261754418	0.417036506	0.379835773	-3.321841985	0.000894253	0.075271915
galnt5	317.9308377	-1.269454781	0.41481651	0.389261626	-3.261186553	0.00110947	0.084857226
gapdh	7358.010399	-1.205359578	0.433661244	0.328149409	-3.673203565	0.000239529	0.028226544
gins3	114.7189185	-1.25737957	0.418303052	0.376230483	-3.342045972	0.000831633	0.071069693
gns	1064.064321	-0.769646052	0.586561363	0.223548369	-3.442861403	0.000575594	0.057024578
gps2	138.8272889	-1.226115481	0.427466871	0.305650074	-4.011500688	6.03E-05	0.010691861
hiat1	948.200826	-1.043686389	0.485086391	0.196179228	-5.320065742	1.04E-07	7.74E-05
hmg20a	645.8802663	-1.773333805	0.292531968	0.303120836	-5.850253738	4.91E-09	5.53E-06
hnrnpk	33451.99419	-0.548497484	0.68373184	0.153556564	-3.571957274	0.000354323	0.038888711
hoxb6	323.3858773	2.065171347	4.184836758	0.633612413	3.259360621	0.001116636	0.084857226
ifrd1	923.7003155	2.146589931	4.42779961	0.467795973	4.588731104	4.46E-06	0.001468351
itga5	2469.223216	1.239826089	2.361700612	0.185057485	6.699680869	2.09E-11	5.85E-08
jph1	341.9029465	1.299169483	2.460871767	0.345333055	3.76207682	0.000168508	0.02219353
kcnk5	552.9141563	-1.113636673	0.462127653	0.256819141	-4.33626819	1.45E-05	0.003380006
kiaa1191	671.391176	-0.930995277	0.524496381	0.170032247	-5.475404176	4.37E-08	3.76E-05

kiaa1715	555.4008246	0.781798387	1.719272692	0.213823529	3.656278572	0.000255903	0.029842052
klhl7	1335.418298	0.63220794	1.549935243	0.170502931	3.707900722	0.000208985	0.025156796
lig1	469.8230757	-0.822124007	0.565608612	0.252264417	-3.258977289	0.001118146	0.084857226
lmnb3	1502.219289	0.786312869	1.724661067	0.242497784	3.242556928	0.001184623	0.086196419
loc388630	470.9170862	-0.831725319	0.561856916	0.217789084	-3.818948603	0.000134022	0.020120374
lonrf3	2131.392616	4.014780849	16.16476746	0.657301056	6.107978695	1.01E-09	1.41E-06
march.7	2125.359676	0.718539944	1.645515874	0.206874364	3.473315545	0.000514071	0.05279835
mespa	314.1066159	1.09310498	2.133326791	0.224151105	4.876643272	1.08E-06	0.00046462
mff	662.4262787	-0.50045855	0.706882068	0.135505502	-3.693271069	0.000221388	0.026366347
micu1	274.8206511	-1.115958896	0.461384391	0.25398829	-4.393741519	1.11E-05	0.002771789
mras	257.4901818	-0.775950996	0.584003534	0.163324236	-4.750985001	2.02E-06	0.00075177
mrps15	517.1827869	1.102350577	2.147042244	0.246203695	4.477392489	7.56E-06	0.002114743
mttp.2	68.48372997	-0.996766796	0.5011218	0.268481296	-3.712611687	0.000205131	0.025156796
myt1	1498.137883	-1.978821617	0.253697003	0.510899734	-3.873209328	0.000107411	0.017427126
nav2	4093.185995	-0.684314994	0.622301232	0.208558236	-3.281169843	0.001033775	0.083863102
ndor1	202.8312105	-0.811132996	0.569934094	0.243528193	-3.330756024	0.000866105	0.07345487
ndufaf4	233.3225832	-0.935880981	0.522723172	0.265435126	-3.525836978	0.000422147	0.045882842
nexn	852.6281233	-1.305410071	0.404606087	0.399417807	-3.268282103	0.001082025	0.084857226
nfe2l1	776.4837231	0.760780241	1.694406749	0.211326023	3.60003104	0.000318179	0.035620161
nfil3	221.3986542	1.255345374	2.387242912	0.36613246	3.428664516	0.000606559	0.058538153
ngfr	7088.798274	-0.698940252	0.616024548	0.214285632	-3.261722433	0.001107375	0.084857226
nin	874.3304164	0.768901549	1.703971905	0.219895772	3.49666364	0.000471115	0.05071286
nol6	1167.090487	-1.093998005	0.468461371	0.260840211	-4.19413097	2.74E-05	0.005785907
nr2e1	59.37467316	-1.787241111	0.289725564	0.562092034	-3.179623627	0.001474665	0.098855504
nup35	3222.093867	0.812396743	1.756126465	0.226757994	3.582659775	0.000340113	0.037698715
nusap1	674.1978605	-0.720296717	0.606972594	0.137583541	-5.235340726	1.65E-07	0.000115225
pabpn1l	125.0545964	-1.220301709	0.429192952	0.275606126	-4.427701687	9.52E-06	0.002479627
pcyox1	583.0887724	-0.574079989	0.671714469	0.179681961	-3.194978423	0.001398413	0.096637241
pif1	230.7898358	1.520921921	2.869743754	0.380151628	4.000829689	6.31E-05	0.01087134
pitpnb.2	369.1288969	-1.462252122	0.36292614	0.262707927	-5.566075373	2.61E-08	2.43E-05
plekhm1	332.7420203	0.957474457	1.941907466	0.21095266	4.538811972	5.66E-06	0.001711687
plrg1	3653.682963	-0.61358953	0.653568551	0.189636097	-3.235615691	0.001213807	0.087106204
plxnb3	444.569594	0.819194035	1.76442002	0.247396011	3.311266147	0.000928748	0.077017313
poldip2	450.6502766	0.96528574	1.952450186	0.245654227	3.929448927	8.51E-05	0.014226131
ppl	1917.193688	-2.724152378	0.15133815	0.555719926	-4.902023938	9.49E-07	0.000424757
ppp6r3	2713.561207	-0.914138793	0.53066055	0.178613393	-5.117974521	3.09E-07	0.000166966
pqlc3	162.5102503	-0.770549457	0.586194178	0.235175759	-3.276483336	0.001051085	0.084653944
prc1.2	1024.718563	2.161543918	4.473933826	0.20485526	10.55156659	5.00E-26	2.80E-22
prkcsh	618.1904996	0.743905968	1.674703818	0.20054467	3.709427763	0.000207728	0.025156796
prmt3	376.5295454	-1.230906749	0.426049585	0.387408826	-3.177281122	0.001486629	0.099064326
prnp	171.3653881	1.370499141	2.585600067	0.363788341	3.767298144	0.000165024	0.02219353

psmb7	925.5365347	-1.716699999	0.304243849	0.306337772	-5.603944906	2.10E-08	2.13E-05
ptma	13841.57958	-0.619584191	0.650858489	0.187634271	-3.302084365	0.000959692	0.078998176
pvrl4	201.7988382	-1.512798741	0.350430745	0.414895246	-3.646218545	0.000266128	0.030714425
rab4b	343.171815	-0.751034712	0.594177256	0.216073946	-3.475822632	0.000509289	0.052791577
rad51ap1	535.4263311	0.642563443	1.561100528	0.195153159	3.29261103	0.000992617	0.081112021
rbbp4	2675.743494	0.657376015	1.57721137	0.202569815	3.24518248	0.001173754	0.086196419
rbm20	1327.420482	-1.882053791	0.271297227	0.351915344	-5.348029922	8.89E-08	7.11E-05
rcbtb1	609.3518746	0.963755577	1.950380459	0.253389418	3.803456292	0.000142691	0.020479843
rfng	627.8983314	0.64594029	1.5647588	0.155227967	4.161236554	3.17E-05	0.006442804
rhbdd2	2005.713653	0.567132797	1.481576168	0.174333139	3.253155421	0.001141311	0.08517981
rhou	1137.668732	-0.637580605	0.642790002	0.189941414	-3.356722436	0.000788722	0.068028253
rpn2	1789.194444	-3.683485219	0.077832407	0.294588733	-12.50382246	7.11E-36	7.96E-32
scaf8	2024.841159	-0.80271301	0.57327012	0.212727524	-3.773432769	0.000161017	0.022161383
sdhd	321.7437853	0.710215319	1.636048275	0.191533686	3.708043921	0.000208866	0.025156796
sh3d21	342.3425633	-2.259854139	0.208793088	0.493632104	-4.578012899	4.69E-06	0.001501453
slc13a4	1277.554285	-1.255100193	0.41896447	0.32877291	-3.81752923	0.000134795	0.020120374
slc25a28	1338.320494	1.676566246	3.196662084	0.265893367	6.305408308	2.87E-10	5.36E-07
slco4c1	439.7018704	-1.380654518	0.384044523	0.399509306	-3.455875739	0.000548508	0.055320256
snai1	6113.172798	1.175246862	2.258315201	0.246771406	4.76249206	1.91E-06	0.000738162
snai2	899.7600257	1.135511155	2.196963887	0.356801185	3.182475848	0.001460217	0.098712103
sort1	454.0559589	1.239783062	2.361630178	0.24179422	5.127430525	2.94E-07	0.000166966
sppl3	2204.950824	-0.483343304	0.715318022	0.126305296	-3.826785722	0.000129827	0.019909837
st3gal1	778.2952879	-1.691610081	0.309581232	0.531400268	-3.183306789	0.001456033	0.098712103
stard8	1017.872946	0.66967846	1.590718398	0.152649463	4.387034495	1.15E-05	0.002796476
sun1	679.1721514	0.988479168	1.984092337	0.249133384	3.967670454	7.26E-05	0.01231087
tgds	135.844251	-0.942742634	0.520242932	0.277201041	-3.400934676	0.000671559	0.061623771
tia1	2829.436898	-0.553419132	0.681403314	0.148951643	-3.715428177	0.00020286	0.025156796
tmod3	1688.551665	-0.576898145	0.670403625	0.171022859	-3.373222442	0.000742939	0.065489787
tnfrsf21	175.1339163	-1.417694763	0.374309933	0.38081709	-3.722770848	0.000197048	0.025156796
trim29	4667.029081	1.11404121	2.164511116	0.295390897	3.771413472	0.000162325	0.022161383
tspan3	2245.916178	-0.448633322	0.732736647	0.137683145	-3.258447669	0.001120235	0.084857226
tspan7	510.8588352	0.969981782	1.958815859	0.229229771	4.231482572	2.32E-05	0.00499805
txndc9	535.5085934	-1.109208177	0.46354838	0.340297042	-3.259529295	0.001115973	0.084857226
ubr4	1746.82693	-0.843385345	0.557334225	0.190008911	-4.438662064	9.05E-06	0.002412784
uchl5	240.9477702	-0.885763344	0.541201092	0.220708131	-4.013279174	5.99E-05	0.010691861
vamp7	241.4386207	-0.809366879	0.570632223	0.224720651	-3.601657763	0.000316194	0.035620161
Xetro.A00137	57.02431552	4.65315291	25.16162006	1.355953236	3.431647042	0.000599928	0.058401667
Xetro.A00232	60.89859639	-2.328961297	0.199027364	0.455290979	-5.115324933	3.13E-07	0.000166966
Xetro.A00692	64.29999424	-1.211872396	0.431707961	0.378631949	-3.200660694	0.001371129	0.095340298
Xetro.A00693	690.1157473	-1.110492395	0.463135935	0.295038252	-3.763892944	0.000167289	0.02219353
Xetro.A01936	1017.134248	-1.63941273	0.32098711	0.515249486	-3.181784307	0.001463708	0.098712103

Xetro.A02927	1252.939796	0.437349448	1.354114231	0.13488903	3.242290693	0.00118573	0.086196419
Xetro.A02968	102.3308527	2.610022535	6.105132199	0.410011714	6.365726743	1.94E-10	4.35E-07
Xetro.C00142	927.3791363	-1.641800028	0.320456397	0.323915183	-5.068610904	4.01E-07	0.000203917
Xetro.D00228	533.2993459	-1.838469175	0.279618327	0.387427486	-4.745324585	2.08E-06	0.00075177
Xetro.D00695	406.80633	0.749997165	1.681789525	0.222131141	3.376371092	0.000734488	0.065457239
Xetro.D01561	134.4133178	-0.607073596	0.656527071	0.187171406	-3.243409923	0.001181082	0.086196419
Xetro.E00064	1314.093579	-0.779584442	0.582534564	0.228127017	-3.417326252	0.000632394	0.059492907
Xetro.E01322	384.3239757	2.280762061	4.859345665	0.707729585	3.222646205	0.001270123	0.089993861
Xetro.I00080	284.3466959	-3.193533646	0.109307656	0.634070801	-5.036556863	4.74E-07	0.000230705
Xetro.K00276	1018.641566	-1.778367097	0.291513157	0.394182335	-4.511534224	6.44E-06	0.001874385
Xetro.K00728	628.5526697	-2.454581362	0.182430473	0.702608191	-3.493527965	0.000476683	0.050823493
Xetro.K00823	95.75751854	1.139454965	2.202977812	0.334672829	3.404683214	0.000662408	0.061286471
Xetro.K01092	222.7557623	1.043028115	2.060548062	0.32394129	3.219806016	0.001282774	0.090318561
Xetro.K02408	85.39405429	-1.268312544	0.415145066	0.329412031	-3.8502314	0.000118006	0.018606765
Xetro.K03038	70.48885029	1.03745058	2.052597254	0.320271448	3.239285254	0.001198297	0.086547941
Xetro.K05203	456.8432276	-0.913743061	0.530806131	0.263545156	-3.467121441	0.000526064	0.053538984
zfyve21	367.3480415	-1.366800603	0.387750191	0.314081755	-4.351735122	1.35E-05	0.003217118

Appendix II

Stage 15 statistically significant differentially expressed gene transcripts. Gene names are alphabetical. Fold change of M+Z *taf15* depleted over uninjected. Green fold change, increased expression in M+Z *taf15* depleted embryos. Red fold change, decreased expression in M+Z *taf15* depleted embryos. Results generated using the Bioconductor DESeq package. Results generated from the second RNA-seq library: four stage 15 uninjected *Xenopus tropicalis* embryos and three M+Z *taf15* depleted stage 15 equivalent *Xenopus tropicalis* embryos.

Gene Name	baseMean	log2Fold Change	fold change (MO/UC)	lfcSE	stat	pvalue	padj
10a1.1	1355.75041	1.085957604	2.122784036	0.384747438	2.822520687	0.004764775	0.055263771
42Sp43	680.8241756	1.129296496	2.187520439	0.28227892	4.000640559	6.32E-05	0.00344629
a1cf	146.665538	-0.911905506	0.531482647	0.361589482	-2.521935926	0.011671096	0.094738373
a2m	29.06690813	-1.590197501	0.332125983	0.557239029	-2.853708049	0.004321222	0.052039707
a2ml1	588.7289433	-2.307311303	0.202036617	0.254176398	-9.077598542	1.11E-19	1.60E-15
aamp	840.8216358	-0.595843426	0.661657525	0.232039869	-2.567849341	0.010233162	0.088007629
aars2	60.13242326	-1.024338006	0.491635839	0.297965941	-3.437768765	0.000586528	0.013654493
aasdh	284.1316329	0.537545276	1.451500708	0.201451419	2.668361828	0.007622212	0.073839017
abcb9	499.8728901	-0.832794043	0.561440856	0.315792355	-2.637157077	0.008360411	0.077797881
abcd3	688.0097241	0.576516922	1.491244608	0.130693301	4.411220131	1.03E-05	0.000946517
abce1	5051.995236	0.416710431	1.334880348	0.16139022	2.582005467	0.009822803	0.085341503
abcg2	661.1971709	0.675534976	1.597188928	0.193868315	3.484504289	0.00049305	0.012310911
abcg4	107.0750811	1.969381781	3.916002758	0.742573425	2.652103772	0.007999195	0.07588213
abhd4	557.2414877	1.953614446	3.87343746	0.508132269	3.844696676	0.000120702	0.005240191
abr	1225.119236	-0.530470307	0.692329003	0.198269663	-2.675499112	0.007461807	0.072938029
acad9	278.6111182	-0.796838722	0.575609089	0.283617756	-2.809551611	0.004961056	0.056787009
acadsb	381.6986417	0.985298561	1.979722967	0.356857569	2.761041511	0.005761735	0.062219492
acadvl	250.0779924	-0.982284123	0.506177708	0.262979026	-3.735218505	0.000187552	0.006778608
acap1	56.48545231	2.518640749	5.73041947	0.628000009	4.010574386	6.06E-05	0.003342283
acbd3	1779.14903	-0.800926693	0.573980371	0.179880507	-4.452548563	8.49E-06	0.000823341
acbd4	66.76765198	1.77488133	3.422098603	0.472827141	3.753763644	0.000174199	0.006524344
acmsd	28.28237653	1.808732452	3.503343505	0.695000992	2.602489021	0.009254978	0.082242081
acot11	374.860641	1.191126759	2.283310023	0.384487418	3.097960307	0.001948575	0.030854932
acta1	207.8225558	1.674048339	3.191087878	0.345026892	4.851935832	1.22E-06	0.000245492
acta2	434.811569	-2.69821521	0.154083554	0.623286288	-4.32901423	1.50E-05	0.001221368
acvr1c	31.96825414	-2.134638313	0.227724542	0.731486008	-2.918221659	0.00352034	0.045685419
acy3	1735.440695	0.945943453	1.926448278	0.34800646	2.71817785	0.006564254	0.067209225
adad2	170.4804856	1.455431323	2.742385379	0.372053397	3.911888281	9.16E-05	0.004428314
adam9	970.8726685	-0.385673511	0.765421584	0.134568626	-2.865998732	0.004156959	0.050773929
adamts4	116.5013479	-1.157657781	0.448239663	0.401302842	-2.884748523	0.003917264	0.048652827
adamtsl4	571.4050907	-0.871597334	0.546541392	0.260204542	-3.349662254	0.000809102	0.016806294

adar	1369.138576	1.269069283	2.410060366	0.224902614	5.642750246	1.67E-08	1.05E-05
adcy6	543.6797103	-0.620608686	0.650396462	0.20510206	-3.025853017	0.002479328	0.035953916
add1	5693.227564	-0.336033392	0.792216474	0.113064078	-2.972061494	0.002958074	0.040205568
adh1c	49.00635529	1.850045396	3.605115288	0.483415408	3.82703026	0.000129699	0.005465434
admp	824.8113532	1.459457187	2.750048737	0.399853876	3.649976343	0.000262264	0.008388401
admp2	781.5929672	1.161203099	2.236438521	0.274848939	4.224877503	2.39E-05	0.001702584
aen	848.8338704	1.643041391	3.123235575	0.439495471	3.738471721	0.000185142	0.006725132
ahdc1	1966.477149	-0.366617975	0.775598558	0.146258626	-2.506641726	0.012188418	0.097191376
aimp2	1344.845737	0.652814349	1.572232251	0.235010925	2.777804258	0.005472758	0.060476974
ak5	32.43934963	1.583688127	2.997351185	0.541666825	2.923731075	0.003458634	0.045168449
akap12	6104.512637	1.058533507	2.082813275	0.329867608	3.208964694	0.001332138	0.023572492
akap7	540.8362187	0.94954782	1.931267252	0.221655828	4.283883848	1.84E-05	0.001435219
akirin2	3728.552197	0.546463409	1.460501063	0.190713475	2.865363391	0.004165309	0.050773929
akt1s1	8759.72164	0.656053663	1.575766384	0.208712295	3.143339792	0.001670318	0.027756081
aldh16a1	189.7337606	-0.965299033	0.512172241	0.317043517	-3.044689388	0.002329207	0.034572228
aldh3a2	917.1852953	0.852326227	1.805409654	0.24957439	3.415118938	0.000637542	0.014379001
aldh3b1	252.0329316	2.033775154	4.09474938	0.550553361	3.694056376	0.000220705	0.007615107
aldh7a1	137.0509552	1.271327229	2.413835278	0.393405562	3.231594447	0.001231016	0.022385916
aldh9a1	3003.497649	0.735703977	1.665209826	0.165405994	4.447867687	8.67E-06	0.000829781
aldoc	4628.082094	-0.814738131	0.56851167	0.319033321	-2.553771276	0.010656323	0.089934889
alg1	148.2257405	1.456648603	2.744700255	0.411710727	3.538038985	0.000403111	0.010869491
alg2	457.4899398	0.58938136	1.504601423	0.193263806	3.049620993	0.002291303	0.034207142
alg6	1171.499447	0.533768405	1.447705754	0.187493646	2.846861308	0.004415259	0.052796861
alg8	526.91684	0.586363464	1.501457318	0.206451146	2.840204452	0.004508463	0.053468529
aloxe3	196.164794	1.455456852	2.742433907	0.410350171	3.546865473	0.000389844	0.010694438
alpl	503.15035	-1.441055532	0.368297745	0.368612463	-3.909405342	9.25E-05	0.004443899
alx1	105.710227	0.892832334	1.856817898	0.325497654	2.742976244	0.006088509	0.064437463
ambra1	725.1579323	-0.730901158	0.602527437	0.231835268	-3.15267459	0.00161782	0.027164727
amfr	2961.282114	0.347838375	1.272652352	0.124156859	2.801604181	0.005084922	0.05770229
amh	11.9482183	2.21660288	4.64797684	0.674124081	3.288122977	0.001008578	0.01948109
anapc1	1545.465078	-0.703205049	0.614206187	0.219916779	-3.197596161	0.001385782	0.02425454
anapc2	761.9870589	-0.453125248	0.730458771	0.179380269	-2.526059591	0.011534991	0.093897168
anapc5	397.7306927	-1.102844023	0.465597745	0.207941394	-5.30362908	1.14E-07	4.08E-05
anapc7	864.1065749	-0.566273922	0.675358801	0.215686733	-2.625446239	0.008653547	0.079012149
ankfy1	349.3041385	-0.56692287	0.675055082	0.179118435	-3.165072709	0.001550442	0.026339295
ankrd13a	575.9860824	-0.514530742	0.700020588	0.165383361	-3.111139707	0.001863667	0.030109301
ankrd37	38.47681545	-0.982809394	0.505993447	0.360266622	-2.728005688	0.006371851	0.066081671
ano10	213.7658251	2.100019854	4.287152848	0.469644353	4.471510923	7.77E-06	0.000785216
ano8	177.6837387	-1.064652712	0.478087731	0.415443263	-2.562691004	0.010386444	0.088716044
anp32c	12098.31327	0.530844917	1.444775083	0.165678873	3.204059197	0.001355046	0.023919294
anubl1	230.7460358	1.003979854	2.005524866	0.22430159	4.476026474	7.60E-06	0.000774214

anxa5	399.149895	1.408949865	2.655438037	0.356618144	3.950864224	7.79E-05	0.004020569
ap1g1	1570.134699	-0.461596045	0.726182443	0.162536889	-2.839946353	0.004512112	0.053468529
ap1s2	159.8086721	-0.636781054	0.643146339	0.208427279	-3.055171363	0.00224932	0.033697838
ap3b2	207.8671836	-0.978234639	0.507600488	0.383118226	-2.553349258	0.010669245	0.08999141
apba3	378.5463501	-0.685671173	0.621716524	0.203280836	-3.373024175	0.000743474	0.015937643
apc2	61.56987707	1.693828326	3.235140404	0.632505993	2.677964073	0.007407116	0.072599783
apex2	147.683936	-1.838895507	0.279535708	0.474114916	-3.878586071	0.000105065	0.004761535
api5	6104.483961	0.658481381	1.578420262	0.179767557	3.662960067	0.000249317	0.00815471
aplf	95.23227215	2.370223053	5.170210619	0.584126518	4.057722051	4.96E-05	0.002937405
appl1	1067.489928	1.006309289	2.008765685	0.348473853	2.887761246	0.003879943	0.048272229
arf1	14258.44612	0.691033833	1.614440009	0.172822701	3.9985131	6.37E-05	0.003464335
arfgap2	3334.874128	-0.994175732	0.502022617	0.247149441	-4.022569216	5.76E-05	0.003200932
arfgef1	1029.389893	-0.713666037	0.609768683	0.159360796	-4.478303654	7.52E-06	0.000774214
arfgef2	2159.853445	-0.536196156	0.689586695	0.183783495	-2.917542496	0.003528016	0.045704617
arhgap1	1602.527661	-0.711790252	0.610562017	0.176476308	-4.033347355	5.50E-05	0.003128103
arhgap11a.2	235.3937401	1.959079888	3.888139249	0.403494708	4.85528025	1.20E-06	0.000244785
arhgap18	46.29989088	2.03730631	4.104784007	0.541798888	3.760262995	0.000169735	0.006406935
arhgap31	153.8344356	-0.654558536	0.635269854	0.24022333	-2.724791701	0.006434207	0.066571178
arhgap42	223.7332594	-1.484226855	0.357440037	0.429512041	-3.455611746	0.000549046	0.013141642
arhgef1	3793.819311	-0.677299892	0.625334539	0.154553841	-4.382290921	1.17E-05	0.001016646
arhgef12	916.103619	-0.702372076	0.614560916	0.23739175	-2.958704656	0.00308935	0.041467182
arid4b	242.5891	-0.991871981	0.502824907	0.393142119	-2.522934921	0.011637994	0.094522739
arl6ip4	314.9671467	0.835012016	1.783871896	0.236037471	3.53762482	0.000403743	0.010869491
arpc1a	1505.665834	1.0233814	2.032677586	0.246201553	4.156681329	3.23E-05	0.002161214
arpp19	4216.284763	0.463557055	1.378937487	0.139613112	3.320297422	0.000899216	0.017930986
arrdc2	121.8837252	0.890051618	1.85324243	0.236489351	3.763601255	0.000167484	0.006355156
asap2	895.4317648	-0.688075033	0.620681464	0.186647544	-3.6864939	0.000227365	0.007770719
asb12.2	283.9814891	-1.285346309	0.41027231	0.428381632	-3.000470174	0.002695632	0.037983182
asb4	23.04260222	1.226523462	2.34002422	0.477837259	2.56682257	0.010263511	0.088172923
asnsd1	2048.106436	0.786595168	1.724998572	0.259459866	3.031664131	0.002432097	0.035551891
atat1	281.0667677	-0.91070322	0.531925749	0.345618347	-2.634996748	0.008413809	0.077870523
atf5.2	59.86332594	-1.368440011	0.387309821	0.427554212	-3.200623385	0.001371306	0.024135745
atf6	1295.970726	0.523331645	1.437270537	0.164901868	3.173594402	0.001505639	0.025759796
atg12	279.8764404	0.67794909	1.599863799	0.260463012	2.60286128	0.009244935	0.082242081
atg2a	282.8309187	-0.787590771	0.579310705	0.228410938	-3.448130711	0.000564481	0.013444314
atg3	286.9932695	0.687969017	1.611013984	0.255916715	2.688253546	0.007182684	0.071123326
atl1	49.325603	1.403021157	2.644547993	0.471569994	2.97521296	0.002927852	0.040045372
atl3	220.020285	-0.900246203	0.535795287	0.302566986	-2.975361639	0.002926433	0.040045372
atm	340.0741426	-2.356672631	0.195240921	0.670337482	-3.51565099	0.000438677	0.011406397
atp11a	36.97699308	-1.411753894	0.37585448	0.534348684	-2.642008741	0.008241593	0.077118905
atp1b3	7868.463263	0.570321348	1.484854272	0.159048116	3.585841572	0.000335993	0.009985015

atp5g1	392.6809416	0.58633772	1.501430525	0.22506741	2.605164918	0.009183005	0.082000432
atp8a1	226.6584559	-1.124691287	0.458600144	0.296887962	-3.788268407	0.000151701	0.005943469
atrn	1315.979261	-0.478546773	0.7177002	0.179158596	-2.671079048	0.007560784	0.073507904
avd.2	104.6784352	1.402213068	2.64306713	0.526519085	2.663176148	0.007740688	0.074455841
aven	101.7815669	0.850950573	1.803688961	0.332528263	2.559032318	0.010496398	0.089053069
avpr1a	12.95490023	-1.991291167	0.25151369	0.638754358	-3.117460012	0.001824167	0.029631439
b2m	24.89019465	-1.919725801	0.264304739	0.60325516	-3.182278291	0.001461213	0.025238665
b3gntl1	20.0390638	-1.456074924	0.364483415	0.563226979	-2.585236463	0.009731223	0.084851807
bag6	1352.536006	-0.599468017	0.659997279	0.152936102	-3.919728635	8.86E-05	0.004329712
baiap2	354.8490865	0.61842308	1.535196237	0.241493713	2.560824759	0.010442401	0.088855678
baiap2l1	1033.532926	-0.327392231	0.79697577	0.130812222	-2.502764846	0.012322739	0.097830772
bambi	2042.17596	0.686079816	1.608905751	0.265334721	2.585714429	0.009717741	0.084828775
bard1	1026.504714	1.006422883	2.008923856	0.229047504	4.393948258	1.11E-05	0.000987247
baz1a	1232.462908	-0.569549902	0.673826979	0.224653909	-2.535232547	0.01123727	0.092357711
bbs9	141.3204152	-0.76089868	0.590128615	0.293512065	-2.592393192	0.009531077	0.084044337
bcam	1300.072497	-1.055976606	0.480971526	0.389949854	-2.707980513	0.0067694	0.068293937
bcap29	115.9086274	1.341233797	2.533679071	0.483672471	2.77302075	0.005553858	0.060841287
bcap31	1054.396014	-1.02481475	0.491473403	0.313480209	-3.26915295	0.0010787	0.020438745
bcas3	326.1217049	0.799044352	1.739948195	0.303004739	2.637068831	0.008362586	0.077797881
bcat2	544.8580157	-0.43398397	0.740214874	0.171731721	-2.52710429	0.011500735	0.093776717
bckdhb	102.8067504	0.800672948	1.741913456	0.22966169	3.486314796	0.000489724	0.012249286
bcl10	2025.917959	0.729215683	1.657737622	0.176340511	4.135270339	3.55E-05	0.002333994
bend5	749.2970007	0.710744724	1.636648742	0.228032157	3.116861814	0.001827872	0.029658305
best4	19.70055225	2.916075332	7.54790012	1.115649198	2.613792344	0.008954344	0.080314714
bin1	2031.832668	-0.835105051	0.560542221	0.221012745	-3.778537975	0.000157752	0.006081647
bin3	484.9542799	-0.525002115	0.694958091	0.185159385	-2.835406458	0.004576742	0.053881069
blnk	86.36069778	-1.102791454	0.465614711	0.353306455	-3.121345331	0.001800268	0.029321289
bloc1s2	165.5454787	0.965910586	1.953295995	0.289721968	3.333922491	0.000856305	0.017485316
blvrb	166.1334154	1.478583145	2.786749152	0.441318087	3.350379663	0.000807009	0.016806294
blzf1	941.0849964	0.592061833	1.507399514	0.212904988	2.780873473	0.005421286	0.060075013
bmp2k	144.3286102	-0.830614758	0.56228959	0.296735276	-2.799177671	0.005123294	0.057910445
bmp4	2141.706932	0.787505476	1.726087351	0.257749086	3.055318204	0.002248219	0.033697838
bmp7.2	4010.238366	2.051622811	4.145720373	0.332291396	6.174167713	6.65E-10	9.62E-07
bnip3l	1773.929291	0.449236799	1.365317798	0.117340553	3.828487138	0.000128933	0.005465434
brcc3	486.3776484	0.455056307	1.370836307	0.146730247	3.101312226	0.00192665	0.030672338
brd3	1275.121616	1.26833142	2.408828062	0.389376478	3.257339602	0.001124618	0.021004461
brdt	233.86079	1.59217752	3.01504079	0.499828381	3.185448409	0.001445299	0.025040334
brsk2	79.42012138	-0.989585715	0.503622375	0.31433945	-3.148143559	0.00164311	0.027398429
btbd1	37.04783752	4.286313604	19.51232251	0.962401723	4.453767589	8.44E-06	0.000823341
btbd17	1210.514071	1.194313909	2.288359806	0.476065961	2.508715193	0.012117114	0.096836437
btbd3	1100.331028	0.87681638	1.836318591	0.300596414	2.916922284	0.003535038	0.045752955

btg1	10616.64917	0.718881627	1.645905638	0.272070964	2.642257798	0.008235534	0.077118905
btg4	169.9207289	6.051921027	66.34523866	1.12510205	5.378997421	7.49E-08	2.78E-05
bud31	3817.438218	0.752548242	1.684766018	0.243860984	3.085972304	0.002028877	0.031675462
c10orf26	900.2215139	0.657964567	1.577854929	0.246593297	2.668217567	0.007625486	0.073839017
c10orf35	78.96297366	0.763051876	1.697076826	0.272467549	2.800523877	0.005101973	0.057805038
c10orf46	414.8459349	-0.659624396	0.633043088	0.243979822	-2.703602248	0.006859234	0.069018373
c10orf57	497.4722379	1.120617618	2.174400387	0.312954472	3.580768831	0.000342585	0.01008706
c11orf68	49.83581184	1.6869165	3.219678197	0.492693712	3.423864478	0.000617374	0.014119158
c11orf95	533.4112742	-0.43359102	0.740416515	0.143860591	-3.013966633	0.002578562	0.036926037
c12orf41	2210.390341	0.58663044	1.501735194	0.215995829	2.715934114	0.006608907	0.067456279
c12orf49	326.22449	0.58812882	1.503295703	0.209168726	2.811743565	0.004927377	0.056535784
c12orf51	453.054972	-0.901257182	0.535419957	0.192648769	-4.678240014	2.89E-06	0.00043574
c12orf65	81.90215536	1.2679835	2.408247219	0.479706141	2.643250503	0.008211426	0.077086093
c14orf119	272.5589197	0.504440929	1.418573526	0.200998975	2.509669159	0.012084432	0.096666468
c16orf57	802.5088586	0.72917662	1.657692738	0.258483681	2.820977392	0.004787758	0.055329027
c16orf72	2759.727821	0.462707187	1.378125417	0.141029878	3.280916031	0.001034705	0.019839173
c17orf75	35.62910506	-1.949341356	0.258934417	0.407891928	-4.779063332	1.76E-06	0.000306756
c18orf21	339.8411943	0.508630282	1.422698821	0.199360933	2.551303679	0.010732077	0.090192094
c18orf45	78.00686008	1.485441174	2.800027844	0.508506717	2.921182995	0.003487049	0.045416463
c18orf55	500.3496357	1.484695619	2.798581221	0.281653938	5.271346911	1.35E-07	4.66E-05
c19orf24	983.6672879	0.462060259	1.377507581	0.15907161	2.904731138	0.003675687	0.046695436
c19orf42	2175.912669	0.446763116	1.362978794	0.126114677	3.542514847	0.000396331	0.010810866
c19orf60	122.6723668	1.040899294	2.057509788	0.37306765	2.790108697	0.005269035	0.058867417
c1orf123	98.07665383	0.999775662	1.999689025	0.366949829	2.724556829	0.006438785	0.066571178
c1orf192	18.22859125	-2.206344573	0.216682632	0.753005321	-2.930051769	0.003389055	0.044592538
c1orf35	577.8373825	-0.694109825	0.618090577	0.259787697	-2.671834859	0.007543776	0.073391907
c1orf50	826.9821684	1.164473894	2.241514596	0.337860864	3.446607811	0.000567672	0.013478451
c1orf85	1205.129589	-0.736507041	0.600190737	0.260952391	-2.822380882	0.004766853	0.055263771
c1orf93	1543.498171	1.306354212	2.47315766	0.406805821	3.211247593	0.0013216	0.023414673
c20orf108	23.38456531	1.590731565	3.01202045	0.559202994	2.844640645	0.004446155	0.053034708
c20orf29	267.4475743	0.929493632	1.904607385	0.352728943	2.635149882	0.008410014	0.077870523
c21orf33	25.18707149	-1.5982816	0.33027013	0.601260826	-2.658216752	0.007855535	0.075160472
c22orf23	615.8834983	0.734634059	1.663975347	0.20151571	3.645542374	0.000266828	0.008478107
c22orf25	606.4393777	0.98072779	1.973460701	0.275811526	3.555789718	0.000376845	0.010569452
c22orf28	389.8052383	-0.816099505	0.567975457	0.221412669	-3.685875377	0.000227918	0.007771247
c2cd3	413.9238332	-0.507564477	0.703408914	0.198740796	-2.5539018	0.010652329	0.089934889
c2orf47	585.8336085	0.883908968	1.845368542	0.21903965	4.035383398	5.45E-05	0.003128103
c2orf67	91.18546012	-0.971158646	0.510096234	0.349668124	-2.777372538	0.005480033	0.060476974
c3	6616.146966	-0.657092284	0.634155134	0.17869871	-3.677095851	0.000235904	0.007869936
c3orf52	294.5014978	0.812924884	1.756769466	0.265413191	3.062865418	0.002192286	0.033212342
c3p1	19.89616134	2.196581329	4.583918294	0.819271734	2.681138918	0.007337205	0.072159165

c4orf43	406.6255275	0.711343513	1.637328173	0.157547121	4.515115917	6.33E-06	0.000682739
c4orf49	1178.726066	0.740918037	1.671238968	0.205054754	3.613269254	0.00030236	0.009320309
c5	1467.933768	-1.063527725	0.478460681	0.370615871	-2.86962272	0.004109618	0.050435273
c5orf15	1122.081836	0.585504594	1.500563732	0.20113941	2.910939207	0.003603441	0.046185685
c5orf63	27.31078223	1.768567077	3.40715381	0.612173867	2.888994732	0.003864755	0.048263535
c6orf168	142.3687492	2.026902465	4.075289263	0.573360074	3.535130117	0.000407574	0.010891503
c6orf203	404.3014567	0.763981712	1.698170966	0.222759219	3.429630048	0.000604405	0.013936011
c7orf50	438.9337182	0.700228071	1.624761626	0.237526944	2.947994278	0.00319843	0.042538823
c8orf42	1063.393422	0.467582441	1.38279035	0.17521773	2.668579496	0.007617275	0.073839017
c8orf84	44.02095078	-1.377643332	0.384846936	0.421339403	-3.269675996	0.001076707	0.020438745
c9orf100	393.088956	2.963543116	7.800373018	0.490498839	6.04189629	1.52E-09	1.76E-06
c9orf156	184.3095839	3.192565948	9.142355683	0.782708023	4.078872141	4.53E-05	0.002784032
c9orf46	67.79524376	0.966473212	1.954057895	0.370307659	2.609919586	0.009056351	0.080919446
ca11	26.48964395	1.563287803	2.955265613	0.626064431	2.497007857	0.012524618	0.098537204
ca14	772.1634018	-1.053200261	0.481898007	0.297167267	-3.544132813	0.000393907	0.010785436
ca5b	2313.159784	1.258712729	2.392821418	0.468121548	2.68885877	0.007169675	0.07104317
ca8	67.48523307	-1.109563776	0.463434137	0.391300026	-2.835583189	0.00457421	0.053881069
cabin1	494.1732138	-0.847018631	0.555932399	0.191262606	-4.428563692	9.49E-06	0.000879122
cacna1a	11.12962472	2.580776678	5.982616883	0.885699413	2.91382905	0.003570254	0.045961848
cacna1d	100.2486333	-2.732427967	0.150472529	0.602884267	-4.532259535	5.84E-06	0.000642057
cacna1g	58.46848034	-1.999787255	0.250036869	0.446732815	-4.476472713	7.59E-06	0.000774214
cacnb2	131.8059543	0.899872695	1.865901327	0.340794163	2.640516749	0.00827797	0.077359155
cacng2	81.44909711	1.134417853	2.195299615	0.447066625	2.537469337	0.011165715	0.09195925
cadm4	43.34976558	-2.083174225	0.235994603	0.814403402	-2.557914445	0.0105302	0.089130618
calr	17759.60292	-0.545869101	0.684978637	0.182648139	-2.988637632	0.002802243	0.038991358
caprin2	745.9616655	1.605028393	3.042017374	0.4913643	3.266473356	0.001088961	0.02053364
carm1	3872.649578	-0.384508122	0.766040131	0.148543748	-2.588517705	0.009638999	0.084368437
caskin2	571.3637679	-1.321898333	0.400008252	0.407045222	-3.247546614	0.001164046	0.02160284
casp10	215.4058061	1.923169353	3.792553029	0.502438993	3.827667394	0.000129363	0.005465434
casp9	99.28533167	-0.786822993	0.579619086	0.262917241	-2.992664121	0.002765539	0.038704164
cblb	887.4584546	0.627110661	1.544468729	0.246662516	2.542383294	0.011009936	0.091170982
cbll1	1588.852193	0.920733213	1.893077157	0.197267287	4.667439943	3.05E-06	0.000443859
cbs	461.3235468	-0.71101774	0.610889039	0.254671148	-2.791905351	0.005239868	0.058693448
cbwd2	164.7950005	1.338534604	2.528943147	0.380968268	3.513506809	0.000442233	0.01145695
cc2d1a	215.1675017	-0.984314844	0.505465719	0.393686728	-2.500248991	0.012410605	0.09818911
ccdc12	987.4329838	0.616810765	1.533481503	0.199431622	3.09284335	0.001982488	0.031220939
ccdc165	172.3197492	-1.255867407	0.418741727	0.334155115	-3.75833663	0.000171047	0.006422913
ccdc18	136.1230351	0.648860312	1.567929087	0.21384374	3.034273122	0.00241116	0.035381395
ccdc50	545.9233905	0.584590822	1.499613607	0.201754546	2.897534822	0.00376108	0.047488149
ccdc66	262.5448103	-0.7009359	0.615173004	0.220546912	-3.17817145	0.001482071	0.02549458
ccdc88a	730.4955822	-0.970642058	0.510278917	0.326399605	-2.97378441	0.002941517	0.040156285

ccdc90a	413.5496426	0.868640945	1.825942007	0.211219746	4.112498771	3.91E-05	0.002492715
ccdc99	389.976008	-1.182773749	0.440503764	0.278516232	-4.246695928	2.17E-05	0.001598278
ccl4	98.64572511	2.683484196	6.424054783	0.919269176	2.919149545	0.003509878	0.045631571
ccna2	10323.24314	0.583067519	1.498031041	0.168954296	3.451036949	0.000558437	0.013322319
ccnb1	2532.778862	0.978860679	1.970908335	0.350357116	2.793894104	0.005207753	0.058499211
ccnb2	5873.376397	0.512950025	1.426965075	0.178144734	2.879400431	0.003984321	0.049327295
ccnc	624.4009387	0.55115758	1.465260911	0.209778307	2.627333529	0.008605694	0.078692293
ccndx	459.042093	-1.370520747	0.386751623	0.350349796	-3.911863983	9.16E-05	0.004428314
ccne2	3369.567706	0.684130592	1.606733427	0.222084446	3.080497554	0.002066551	0.031989251
ccng1	2769.469237	2.583259507	5.992921628	1.018159918	2.537184446	0.011174806	0.09195925
ccnl1	1795.32559	0.888856132	1.851707381	0.280315856	3.170909226	0.001519626	0.025937705
ccnt2	2206.828434	0.939815993	1.918283558	0.229956455	4.086930249	4.37E-05	0.00273568
cct7	1464.143881	-0.995210475	0.501662681	0.282210667	-3.526480717	0.000421122	0.011109778
cd36l	9.135876698	-2.706157313	0.153237647	0.981465848	-2.757260805	0.005828784	0.062648415
cd59	2621.192916	0.59723166	1.512810896	0.220505509	2.708465935	0.006759505	0.068241735
cdc123	558.1116426	0.87426711	1.833076646	0.300472759	2.909638502	0.00361847	0.046281321
cdc34	3080.03781	0.377379843	1.298980563	0.098136375	3.845463436	0.000120325	0.005240191
cdc42ep1	10.81838904	-1.941979346	0.260259125	0.725424627	-2.677024286	0.007427925	0.072705154
cdc42se2	555.8040728	0.867404186	1.824377378	0.311350502	2.785941183	0.005337256	0.059491675
cdc5l	4522.140352	0.370472398	1.29277607	0.144592097	2.562189817	0.010401445	0.088716044
cdc6	8687.59763	0.646589495	1.565463091	0.251794114	2.567929348	0.010230801	0.088007629
cdca8	1564.793343	0.701974315	1.626729435	0.256500087	2.736741039	0.006205112	0.065005291
cdcp1	2039.705574	0.603169927	1.519050599	0.192012691	3.141302404	0.001681983	0.027821994
cdh22	74.55906916	-0.861918203	0.5502205	0.292273355	-2.949013952	0.003187896	0.042476876
cdh3	21812.20466	0.359215077	1.282727818	0.138715632	2.589578931	0.009609339	0.084293672
cdhr2	8.66931118	-1.973599994	0.254616886	0.718771944	-2.745794421	0.006036458	0.064074206
cdk14	29.70104524	2.605459439	6.0858528	0.956585323	2.723708359	0.006455348	0.066604576
cdk16	134.1715888	-0.660434003	0.632687938	0.261084285	-2.529581598	0.011419862	0.093433469
cdk5	150.3331504	-0.641584994	0.641008328	0.225871053	-2.840492335	0.004504396	0.053464734
cdkn2aip	1346.724777	0.524832044	1.438766072	0.173197119	3.030258506	0.002443445	0.035645696
cds1	46.05932538	0.867409615	1.824384243	0.319935361	2.7112027	0.006703963	0.067965773
cdx1	1362.859041	0.979611002	1.971933639	0.299165543	3.274478044	0.001058574	0.020216379
cenpl	716.5841467	0.416685172	1.334856977	0.149327492	2.79041164	0.005264107	0.058867417
cep63	148.3341074	0.617715299	1.53444326	0.246362981	2.50733814	0.012164428	0.097160848
cept1	1881.662755	0.85126884	1.804086909	0.200549163	4.244689062	2.19E-05	0.001598278
cer1	332.5527446	1.832482329	3.56149343	0.515709665	3.553321672	0.000380399	0.010593403
cetn4	244.6749445	0.872847147	1.831273339	0.18946166	4.606985635	4.09E-06	0.000527355
cetp	22.34165037	1.764776352	3.398213161	0.587590779	3.003410563	0.00266972	0.03787649
cfb	3319.65064	-1.086488935	0.470906018	0.326207807	-3.330665034	0.000866388	0.017600454
cfhr2	53.6790559	4.970100045	31.343623	1.507777068	3.296309613	0.00097964	0.019112893
cftr	25.4358464	-1.566598135	0.337603523	0.628770543	-2.491525967	0.012719567	0.099559707

chac1	403.3559714	1.205996457	2.306965544	0.352273213	3.423469096	0.000618273	0.014119158
chad	120.5155238	2.471505014	5.546220653	0.696618864	3.547858291	0.000388377	0.010674464
chd3	408.6115532	1.325421335	2.506060658	0.43217219	3.066882518	0.002163039	0.03288228
chd8	2609.971445	-0.576544802	0.670567839	0.1604476	-3.593352598	0.00032645	0.009751018
cherp	2685.70775	-0.403588336	0.755975646	0.114921606	-3.511857791	0.000444986	0.011468735
chmp2b	748.0181055	0.518389201	1.4323551	0.200878567	2.580609807	0.009862599	0.085635788
chmp4b	3741.886259	0.355108301	1.279081596	0.128176228	2.770469266	0.005597558	0.061213237
chordc1	1255.82837	-0.616543777	0.65223159	0.181480553	-3.397299425	0.000680545	0.015066819
chrm4	20.8937272	-1.828363282	0.281583893	0.637927947	-2.866096853	0.004155671	0.050773929
cidea	2083.468766	0.712134554	1.638226179	0.182526324	3.901544379	9.56E-05	0.004522868
cir1	505.0340274	-0.688558303	0.620473585	0.219140694	-3.14208324	0.001677503	0.027821994
cited1	23.67552539	2.750518546	6.729589693	1.022271831	2.690594088	0.007132492	0.070807194
cited4	2971.22905	0.785393761	1.723562675	0.2144544	3.662287929	0.000249973	0.008157686
ckap2	1989.033248	1.489432656	2.807785364	0.35568812	4.1874681	2.82E-05	0.001941944
cks2	1102.478967	0.631622809	1.549306744	0.238759966	2.645430138	0.008158713	0.07689082
cldn12	1561.168018	0.500451264	1.414655987	0.163421913	3.062326563	0.002196237	0.033212342
cldnd1	1053.572747	-1.125112021	0.458466422	0.36047155	-3.121222802	0.001801017	0.029321289
clec16a	763.7757314	-0.845662224	0.556455327	0.21302061	-3.969861052	7.19E-05	0.003805445
clp1	989.8268861	0.393883525	1.313925544	0.158183699	2.490038649	0.01277292	0.099690142
cltc	3359.689448	-0.633662433	0.644538109	0.229015396	-2.766898838	0.005659231	0.061617666
cmc1	167.5394079	1.210022006	2.313411655	0.35343386	3.423616533	0.000617938	0.014119158
cmip	843.9765198	0.76006188	1.693563263	0.282383334	2.691596096	0.007111101	0.070656485
cndp2	1887.10393	-0.816557477	0.567795186	0.311501733	-2.62135774	0.008758031	0.079349224
cnih	3326.042028	0.732679865	1.661722944	0.188734001	3.882076688	0.000103568	0.004738245
cnksr2	81.86865455	1.627670816	3.090137033	0.59933526	2.715793522	0.006611714	0.067456279
cnrip1	187.7881392	1.566774558	2.96241664	0.35265774	4.442762432	8.88E-06	0.000839179
cntd2	258.4984048	1.346426109	2.542814304	0.384161137	3.504847265	0.000456869	0.01166954
cog3	868.0642217	-1.160237302	0.447438932	0.312747527	-3.709820867	0.000207406	0.007247307
col2a1	4933.28399	-0.960584276	0.513848768	0.253536609	-3.788739938	0.000151413	0.005943469
col4a5	946.9478649	-0.523548099	0.695658856	0.172397312	-3.036869274	0.002390491	0.035228674
col4a6	642.1744044	-0.701624837	0.614879308	0.234512785	-2.991840453	0.002773011	0.038733745
col6a2	91.72613945	1.043403987	2.061084976	0.338339692	3.083894711	0.002043099	0.031775781
col6a3	33.04975206	-2.361111333	0.194641152	0.739282349	-3.19378832	0.00140419	0.024517368
commd10	164.4863319	1.941609609	3.841339854	0.423842835	4.580965984	4.63E-06	0.000574424
commd8	125.4686431	0.688041811	1.611095273	0.246449385	2.791817927	0.005241284	0.058693448
copa	4086.236187	-0.767056098	0.587615315	0.165199672	-4.643205928	3.43E-06	0.000464561
copb1	2666.955835	-1.270959994	0.414383943	0.278449943	-4.564411036	5.01E-06	0.000608024
coq3	293.1260318	1.24330554	2.367403369	0.408013063	3.04721994	0.002309686	0.034353021
coro2b	122.4556035	1.845555035	3.593911879	0.618421087	2.984301592	0.002842265	0.039399114
cox5b.2	161.6541952	1.380300243	2.603225419	0.322602668	4.278638648	1.88E-05	0.001456984
cpd	629.1054196	-0.890318697	0.539494929	0.250476939	-3.554493681	0.000378708	0.010569452

cpsf2	1774.871453	-0.374183206	0.771542104	0.104541901	-3.579265368	0.000344561	0.010124644
cpsf4	842.9892548	0.624529003	1.541707422	0.250144539	2.496672545	0.012536466	0.098553394
cpsf7	2735.614494	0.633705421	1.551544872	0.172561768	3.672339635	0.00024034	0.007951018
cpvl	71.91268158	1.260526127	2.395830969	0.360607815	3.495559646	0.000473069	0.011969509
cpxm2	41.44917526	2.081494223	4.232453514	0.747807807	2.783461476	0.005378225	0.059902155
cpz	711.3172918	0.701500271	1.626195008	0.259931073	2.698793424	0.006959136	0.069528838
crbn	110.8387603	-0.8641869	0.549355935	0.33922172	-2.547557685	0.010847992	0.090495912
creb3l1	119.1428949	-1.772662731	0.292668072	0.465307067	-3.809662171	0.000139157	0.005683022
creb3l2	856.1857619	1.339960104	2.531443183	0.357522416	3.747905151	0.000178318	0.006593193
creld2	191.6508292	0.684322287	1.606946933	0.252150148	2.713947595	0.006648668	0.067594028
crispld2	15.04921826	3.422012934	10.71836491	1.111202749	3.079557657	0.002073082	0.032032389
crlf3	720.278117	-0.957112026	0.515086979	0.341850224	-2.799799327	0.005113438	0.057889568
crmp1	64.54593261	-1.571110514	0.336549236	0.312973542	-5.019946739	5.17E-07	0.00012052
crocc	433.4823307	-1.41634594	0.374660051	0.332263019	-4.262725187	2.02E-05	0.001520612
crtc3	428.4718465	0.870483484	1.828275499	0.311144903	2.797678747	0.005147128	0.058089014
crx	1896.38169	1.278280969	2.425497965	0.32275645	3.960512543	7.48E-05	0.003903341
cry-dash	968.8629519	1.528710298	2.885277935	0.39591732	3.861185707	0.000112838	0.005012575
cse1l	790.6753325	-0.42237242	0.746196542	0.165634996	-2.550019203	0.010771699	0.090279318
csgalnact2	292.0597587	0.664822441	1.585373143	0.236669052	2.80908059	0.004968321	0.056789786
csrnp1	930.0168797	1.202764145	2.301802649	0.252805233	4.757671087	1.96E-06	0.000321733
csrp1	45.76104459	2.691800131	6.461191034	0.761248742	3.536032287	0.000406185	0.010891503
csrp3	9.816458404	1.957814533	3.884730544	0.759895631	2.576425567	0.00998277	0.086316328
cst3	2553.443617	0.664274003	1.58477058	0.23191885	2.86425188	0.004179955	0.050866673
ctdsp1	874.5966104	-0.622959013	0.649337749	0.158312518	-3.934995303	8.32E-05	0.004190934
ctif	184.9504035	-1.894036077	0.269053303	0.342282443	-5.533547267	3.14E-08	1.51E-05
ctns	80.50679867	-2.121079435	0.229874854	0.544228741	-3.897404299	9.72E-05	0.004578641
ctsb	8266.695683	0.955083795	1.938692235	0.224399493	4.256176267	2.08E-05	0.001557706
ctsl2	18496.5316	0.542596975	1.45659215	0.195950289	2.769054224	0.005621928	0.061386866
ctu1	450.6066422	0.462769196	1.378184652	0.183095166	2.527479052	0.011488468	0.093776717
cuedc2	644.9570672	-0.904703497	0.53414247	0.236764871	-3.821105272	0.000132855	0.005519206
cxcr4	3366.743579	-0.871386803	0.546621154	0.193106382	-4.512470251	6.41E-06	0.000686193
cxcr7	291.7348826	0.432380517	1.349458413	0.165193152	2.617423988	0.008859622	0.079802837
cxorf38	231.818689	1.08854228	2.126590542	0.304333423	3.576808188	0.000347815	0.010153288
cxorf40a	160.6701191	0.971969659	1.961516755	0.256993015	3.782085899	0.00015552	0.006027742
cxorf57	640.3547873	0.825201621	1.771782633	0.251091018	3.286464117	0.001014537	0.019551139
cyb5d2	327.8420242	1.253817552	2.384716146	0.288712202	4.342793771	1.41E-05	0.001168875
cybrd1	48.30744656	0.952669925	1.93545119	0.374309552	2.545139229	0.010923417	0.090810722
cyp27c1	1322.809868	1.459546099	2.750218226	0.375852454	3.883295384	0.00010305	0.004729516
cyp2e1	32.32397086	2.67027396	6.36550053	0.769302953	3.471030428	0.000518465	0.012747367
cyp2f1	242.2024685	1.790662737	3.459737875	0.605081634	2.959373806	0.003082649	0.041456614
d4s234e	128.2659219	-1.781801906	0.29081994	0.53295935	-3.343222904	0.000828114	0.017005735

dab2	154.504358	-0.632398989	0.645102812	0.193989015	-3.259973196	0.001114227	0.020905852
dagla	584.2699557	-0.730498653	0.602695562	0.248954068	-2.934270808	0.003343324	0.044141032
daglb	132.1423608	-0.85383965	0.553310172	0.216285873	-3.947736573	7.89E-05	0.004058946
dak	33.13297781	0.930394065	1.905796484	0.353065088	2.635191347	0.008408986	0.077870523
dalrd3	182.443922	-0.791402205	0.577782252	0.307402771	-2.574479737	0.010039097	0.086705107
dap3	299.5892125	-0.69785965	0.616486134	0.221529617	-3.15018668	0.001631662	0.027270442
dapp1	13.10862416	2.11171743	4.322054995	0.770936461	2.73915885	0.00615966	0.064858129
dbf4	2482.232061	0.43691742	1.35370879	0.1736809	2.515633099	0.01188188	0.095686603
dbx1	171.7010501	-1.530702927	0.346108691	0.481321099	-3.18021157	0.001471676	0.025389039
dclk1	240.551154	-1.013960665	0.495184937	0.29142284	-3.479345219	0.000502641	0.012474852
dclre1b	74.53435767	1.121349358	2.17550353	0.433948496	2.58406094	0.009764454	0.085038983
dcp2	332.0152404	-0.674056433	0.626741994	0.223208621	-3.019849456	0.002529004	0.036439005
dcst2	66.41084757	1.850123308	3.605309985	0.616735009	2.999867495	0.002700971	0.038021358
dct	350.4087434	1.375634765	2.594820542	0.305807479	4.498368607	6.85E-06	0.000722606
dctd	4285.290341	0.972166556	1.961784479	0.212138141	4.582705183	4.59E-06	0.000574424
dctn1	280.3211057	-1.143240005	0.452741668	0.246444429	-4.638936299	3.50E-06	0.000468791
dctn2	650.4655816	-0.760480143	0.59029984	0.280235461	-2.713718455	0.006653268	0.067594028
dcun1d1	626.8526131	0.531952542	1.445884731	0.166250692	3.199701221	0.001375701	0.024153474
ddah1	185.9271504	-0.826831472	0.563766058	0.309577474	-2.670838612	0.007566202	0.073511139
ddah2	1170.886314	1.049213824	2.069401849	0.326011017	3.218338548	0.001289355	0.023041051
ddc	10.53084333	-1.950957095	0.258644587	0.574146943	-3.398010075	0.000678779	0.015050784
ddhd2	178.6476504	-1.910303304	0.26603661	0.519640835	-3.676199354	0.000236735	0.007869936
ddx11	174.7452644	0.882883546	1.844057378	0.325193852	2.714945377	0.00662867	0.067533958
ddx39b	1463.64982	0.422028599	1.339810161	0.153022611	2.757949282	0.005816522	0.062648415
ddx42	3543.261278	-0.411696569	0.75173883	0.164420053	-2.503931625	0.012282177	0.097723406
dedd	314.9430058	1.391618533	2.623728669	0.378299599	3.678614874	0.000234504	0.007869936
degs1	1577.504267	0.729182047	1.657698973	0.269854523	2.702130165	0.006889678	0.069217569
dennd2c	1191.838871	0.815736093	1.760196012	0.310980295	2.62311184	0.008713067	0.079178308
depdc1	3241.782804	0.33936274	1.265197614	0.129156444	2.6275324	0.008600665	0.078692293
dfna5	72.2005868	-0.929204203	0.525147936	0.360158056	-2.579990052	0.009880316	0.085738133
dhrs3	1449.832691	0.708851489	1.634502393	0.21161663	3.349696519	0.000809001	0.016806294
dhrs7	260.0969509	1.895592906	3.720748577	0.443298531	4.276109153	1.90E-05	0.001462525
dhx16	1261.602577	-0.638234155	0.64249888	0.228573476	-2.792249412	0.005234299	0.058693448
dhx38	1742.717267	-0.432131924	0.741165727	0.172618067	-2.503399166	0.012300673	0.0977469
diablo	955.0968508	1.154955469	2.226774503	0.311954512	3.702320134	0.000213637	0.007424393
dip2a	733.1913492	-1.099096851	0.466808634	0.282485063	-3.890814051	9.99E-05	0.00465928
dip2b	1167.751632	-0.452863504	0.730591309	0.14997172	-3.019659333	0.002530591	0.036439005
dkk2	44.36260473	0.842079814	1.79263257	0.337113894	2.497908952	0.012492828	0.098478085
dlat	1317.174157	0.469096783	1.384242574	0.170899343	2.744871769	0.006053455	0.064160406
dlgap5	3734.08031	0.478093898	1.392902135	0.156379335	3.057270322	0.002233627	0.033532245
dll1	2424.099862	0.453964153	1.369798944	0.175211166	2.590954462	0.009571016	0.084066354

dlx5	1650.335993	0.731919402	1.66084726	0.222113701	3.295246534	0.000983354	0.01915397
dmrta2	181.5895336	-1.268069653	0.415214965	0.332282688	-3.816237501	0.000135502	0.005581064
dnaja2	13291.40064	0.568192068	1.482664386	0.145646874	3.901162131	9.57E-05	0.004522868
dnajb12	1202.409729	0.512803672	1.426820324	0.150279823	3.412325498	0.000644112	0.014459503
dnajc13	443.3042779	-1.007994134	0.497237106	0.330786464	-3.047265366	0.002309337	0.034353021
dnajc5g	179.5124964	-0.933725632	0.52350469	0.250927988	-3.721090022	0.000198365	0.007063445
dnm1	46.91331512	-1.531729916	0.345862399	0.366322042	-4.181375236	2.90E-05	0.001966635
dnm2	1143.440183	-0.652216325	0.63630205	0.183755251	-3.549375168	0.000386147	0.010633525
dnmt1	1991.719757	-0.822545921	0.565443225	0.246858698	-3.3320516	0.000862083	0.017553704
dom3z	240.1435485	-1.222022287	0.428681396	0.300713716	-4.063739772	4.83E-05	0.002909029
dpysl2	479.4322907	-0.735788123	0.600489896	0.234431829	-3.138601648	0.00169756	0.027983617
dtnbp1	111.0679426	0.872664059	1.831040953	0.333991608	2.61283229	0.008979535	0.080431935
dtwd1	405.321895	0.783725489	1.721570771	0.228254968	3.433552818	0.000595726	0.013824097
dtx2	418.0287024	-0.747754829	0.59552962	0.249137018	-3.001379863	0.002687591	0.037980937
dusp14	17.80604253	-1.621153533	0.32507544	0.554802779	-2.922035713	0.003477517	0.04537406
dusp9	31.42480454	-1.002457093	0.499149161	0.37091748	-2.70264182	0.006879083	0.069159182
dync1i1	1054.198329	0.518125965	1.432093775	0.128416332	4.034735742	5.47E-05	0.003128103
dyrk1a.2	1934.528076	0.804762286	1.746857937	0.19626272	4.100433784	4.12E-05	0.002603374
echdc2	84.65916435	0.965105656	1.952206486	0.269368447	3.582845976	0.000339871	0.010038046
eda2r	260.3551347	3.233387347	9.40473535	1.117728026	2.892821216	0.003817986	0.047997058
edem1	1175.348112	0.446675385	1.362895913	0.117561365	3.799508317	0.000144983	0.005806165
ednrb	106.6707237	-1.266347725	0.41571084	0.469640618	-2.696418658	0.007008951	0.069978183
eed	2166.365648	0.627153296	1.544514372	0.238196001	2.632929576	0.00846519	0.077982482
efcab11	64.00276073	1.031113657	2.043601156	0.391986665	2.630481463	0.008526402	0.078363759
efha1	98.89996146	-0.778977704	0.582779606	0.285300052	-2.730380515	0.006326126	0.06592272
efhd2	17.73375755	1.687562522	3.221120254	0.62112138	2.716960929	0.006588438	0.067364389
egfl8	7.361456361	5.175762182	36.14595197	1.374396627	3.765843193	0.000165988	0.006314968
egln2	103.1480818	-1.777401491	0.291708334	0.545518187	-3.258189245	0.001121256	0.020970244
ehd3	60.04016546	-0.621320383	0.650075693	0.235698681	-2.636079174	0.008387016	0.077870523
eif1	11317.22464	0.802533954	1.744161889	0.266283922	3.013828051	0.00257974	0.036926037
eif1ax	8376.674424	0.414870568	1.333179065	0.162808434	2.548213007	0.010827634	0.090484182
eif3g	2099.748655	0.558476645	1.472713344	0.223860648	2.494751311	0.012604543	0.098927191
eif4e1b	330.1399962	0.760673214	1.694281053	0.219067039	3.472330744	0.00051596	0.012729074
eif4ebp2	1119.263525	0.659490512	1.579524716	0.1852796	3.559434028	0.000371655	0.010494169
elac2	467.6159637	-0.58494607	0.666674259	0.234552757	-2.493878463	0.01263558	0.099116973
emilin3	1904.253713	-0.595081134	0.662007224	0.189270908	-3.144070797	0.001666151	0.027718698
eml1	304.768405	1.001566498	2.002172807	0.33084739	3.027276409	0.002467682	0.035890622
en2	136.8944305	-1.57374147	0.33593605	0.558931088	-2.815627014	0.004868215	0.055945773
enoph1	247.2715024	0.837370134	1.78679006	0.237384279	3.527487746	0.000419523	0.011087837
enox1	729.3173592	0.845055966	1.796334429	0.211436382	3.996738678	6.42E-05	0.003477322
eomes	4325.090362	1.043879459	2.061764364	0.365647824	2.854876718	0.004305354	0.051955342

epb41	2377.66191	-0.609296873	0.655516103	0.221838029	-2.746584419	0.006021939	0.064042913
epb41l5	215.110136	-0.638460607	0.642398038	0.207999597	-3.069528098	0.002143972	0.032695579
epc1	843.1912777	0.642654591	1.561199159	0.194091489	3.311091049	0.00092933	0.018279345
epg5	589.2352192	1.862409124	3.63614347	0.493738714	3.772054069	0.000161909	0.006176044
ephx3	106.6126422	0.953596929	1.936695214	0.36417836	2.618488724	0.008832021	0.079739461
erh	9005.347292	0.605609151	1.521621093	0.2280513	2.65558298	0.007917145	0.075400638
ern1	126.8558192	-0.865639191	0.548803204	0.306980076	-2.819854637	0.004804541	0.055478632
erp44	923.7113857	0.492570606	1.406949558	0.168357402	2.925743681	0.003436339	0.045040034
esd	178.0741731	1.296595605	2.456485298	0.305855479	4.239242691	2.24E-05	0.001613107
esr2	17.18840178	3.691021764	12.91541203	1.234712099	2.989378469	0.002795456	0.038934404
esrrgr	35.59343363	2.993240236	7.96260359	0.765569923	3.909819528	9.24E-05	0.004443899
ets2	4272.985947	0.982734246	1.976207239	0.295585081	3.324708544	0.00088511	0.017772273
evx1	377.1761341	0.771287108	1.706791828	0.286405959	2.692985545	0.007081534	0.070450943
ewsr1	11129.45521	-0.664319573	0.63098623	0.167418782	-3.968011017	7.25E-05	0.003810076
exd1	55.30729031	1.066205749	2.093919165	0.395947329	2.692796919	0.007085541	0.070450943
exd3	277.0912731	-1.776512682	0.291888104	0.474574155	-3.743382699	0.000181559	0.00664324
exoc7	118.6953309	-0.77311602	0.585152262	0.294930287	-2.621351733	0.008758185	0.079349224
exosc1	1118.191541	-1.07489213	0.474706553	0.240852391	-4.462866761	8.09E-06	0.000800783
f5	16.09342288	-1.700849412	0.307604942	0.560170056	-3.036309052	0.002394937	0.03525826
fadd	98.89788007	1.407747498	2.653225871	0.401397256	3.507117894	0.000452988	0.011632066
fam114a1	92.30644063	-1.301137965	0.405805981	0.470290276	-2.766669929	0.005663206	0.061617666
fam118b	368.4320725	1.538214913	2.904349178	0.335103311	4.590270714	4.43E-06	0.000566345
fam122a	2450.663669	0.998720309	1.998226758	0.190500739	5.242605947	1.58E-07	4.91E-05
fam149b1	478.9315085	0.571379369	1.485943611	0.158441706	3.606243479	0.000310662	0.009435369
fam171a1	725.935636	0.698766191	1.623116092	0.266390423	2.623090515	0.008713612	0.079178308
fam175a	388.5496175	0.700923971	1.625545537	0.281397185	2.490870588	0.012743053	0.099689562
fam18b1	655.6877265	-0.944945852	0.519449048	0.322161167	-2.93314635	0.003355457	0.044260802
fam195b	1141.057925	0.709861767	1.635647389	0.189659761	3.742816945	0.000181969	0.00664324
fam207a	456.8939751	0.520089966	1.434044672	0.184586972	2.817587606	0.004838591	0.055782706
fam32a	1510.362694	0.724401112	1.652214631	0.225509611	3.212284869	0.001316837	0.023414673
fam46c	2245.203408	1.324889299	2.505136645	0.39810786	3.327965692	0.000874826	0.017619659
fam49a	446.4332164	-0.684152181	0.622371464	0.25833659	-2.648297633	0.008089827	0.076440931
fam54a	1012.150526	0.338394117	1.264348447	0.13122374	2.578756834	0.009915656	0.085993184
fam5b	255.8183601	0.579823448	1.494666325	0.218865142	2.649227019	0.008067612	0.076380789
fam76b	3724.472453	0.612101302	1.528483842	0.217815592	2.810181287	0.00495136	0.05672093
fam98a	302.8911839	1.100022804	2.143580807	0.296067887	3.715441124	0.000202849	0.007143499
fancf	126.6242011	0.848148772	1.800189488	0.247633898	3.425010794	0.000614775	0.014107622
fas	19.61213807	-1.415664806	0.374836979	0.496729659	-2.849970364	0.00437233	0.052498612
fbln5	25.74823941	5.663774847	50.69511558	0.981657266	5.76960518	7.95E-09	6.05E-06
fbp2	62.4734347	4.319080634	19.96056474	0.860124957	5.021457172	5.13E-07	0.00012052
fbrsl1	487.0093605	-0.651839515	0.636468264	0.240223258	-2.713473794	0.006658183	0.067596459

fbxl4	71.43223777	1.039628697	2.055698514	0.407264567	2.552710895	0.010688818	0.090103929
fbxo34	4589.971912	0.856533877	1.810682854	0.287022866	2.984200836	0.002843201	0.039399114
fbxo5	1277.311934	0.526799619	1.440729627	0.15209203	3.463689838	0.00053282	0.01296987
fbxo9	1629.917826	0.82617791	1.772982025	0.236219683	3.49749817	0.000469644	0.011911653
fermt2	2590.926298	-0.823179048	0.565195135	0.264862611	-3.107947345	0.001883916	0.030310381
fgfr4	5681.390736	1.4087299	2.655033197	0.407248256	3.45914287	0.000541897	0.013035292
fkbp4	1269.906762	-0.484913744	0.71453979	0.184130221	-2.63353697	0.008450064	0.077950997
fkbp6	255.4498965	0.966263999	1.953774547	0.249250136	3.876683933	0.00010589	0.004783901
flcn	243.9566455	-0.896968584	0.53701393	0.261600677	-3.428770113	0.000606323	0.013957977
flii	998.3262251	-1.128257605	0.457467892	0.248058003	-4.548362037	5.41E-06	0.000635771
flna	7066.874945	-0.828204258	0.563229866	0.200969042	-4.121053911	3.77E-05	0.002434089
flnc	2657.741067	-0.694591716	0.617884155	0.26718625	-2.599653668	0.009331789	0.082715922
fmn2	294.3004018	0.821917265	1.767753683	0.295759134	2.779008902	0.005452503	0.060311275
fnip1	62.1139805	-1.102740508	0.465631154	0.380981133	-2.894475373	0.003797927	0.047828075
folh1	97.75710046	1.639481326	3.115538027	0.476392031	3.441454139	0.000578597	0.013645628
fos	77.35456488	1.622817928	3.079759998	0.385105323	4.213958703	2.51E-05	0.001767542
foxa4	4808.092291	1.05157651	2.072793663	0.272375036	3.86076685	0.000113032	0.005012575
foxd1	242.8523326	-1.308020056	0.403874774	0.390706726	-3.347830914	0.000814467	0.016821068
foxd4l1.1	870.534652	0.893995929	1.858316105	0.276001108	3.239102686	0.001199064	0.02198837
foxf1	123.6829272	0.606114654	1.522154345	0.240627585	2.518890985	0.01177251	0.095187459
frzb	1419.304417	1.154389095	2.225900486	0.454514489	2.53982903	0.011090667	0.091621584
ftmt	4029.047248	0.807403504	1.750058931	0.323585046	2.49518176	0.012589263	0.098860928
fubp1	18729.09263	0.680303379	1.602476699	0.225325487	3.019202973	0.002534407	0.03645763
fubp3	2330.652352	1.788100123	3.453597905	0.443795428	4.02910893	5.60E-05	0.003128846
fzd5	72.61349795	-1.241869184	0.422824482	0.349687241	-3.551371162	0.00038323	0.010593403
gabarapl1	260.4342253	-0.542891428	0.686393869	0.213293828	-2.545274909	0.010919174	0.090810722
gabbr2	34.63762052	2.346906167	5.087321136	0.805675743	2.912966151	0.003580134	0.04600711
gabpb2	3323.815244	-1.17871795	0.441743879	0.273569452	-4.308660719	1.64E-05	0.00132654
gadd45a	1871.981242	0.946752347	1.927528708	0.259195631	3.652655501	0.000259542	0.00833823
gadd45g	1695.601104	1.08761184	2.125219477	0.302578634	3.59447667	0.000325044	0.00972912
gadl1	49.29604149	1.152377858	2.222799558	0.459844215	2.506017951	0.012209942	0.097309334
galk1	149.496355	0.643524763	1.562141092	0.245778634	2.618310437	0.008836637	0.079739461
galm	55.36795428	2.386490329	5.228837841	0.572870967	4.165842687	3.10E-05	0.002085873
galnt5	317.9308377	-0.911340817	0.531690717	0.287154672	-3.17369315	0.001505127	0.025759796
ganab	410.7705131	-1.083561092	0.471862657	0.355332636	-3.049427449	0.00229278	0.034207142
gata2	4319.360136	0.791825977	1.731264287	0.229019968	3.457453875	0.000545306	0.013095486
gatm	19966.36988	0.812972614	1.756827587	0.213199148	3.813207605	0.000137175	0.005633909
gba2	173.6657945	-1.063810211	0.478367005	0.420170243	-2.531855191	0.011346084	0.093068036
gcat	353.9406173	-0.629719996	0.64630184	0.226944574	-2.774774409	0.005524001	0.060671757
gchfr	38.66805077	-1.086351741	0.470950801	0.405640008	-2.678117838	0.007403717	0.072599783
gdap2	267.5025135	-0.624133134	0.648809508	0.227051763	-2.748858343	0.005980323	0.063709739

gdf3	1151.641922	1.09151004	2.130969641	0.238153676	4.583217269	4.58E-06	0.000574424
gdf9	536.6497385	2.337680766	5.054893742	0.543563668	4.300656769	1.70E-05	0.001352704
gdi1	4602.913342	0.344985831	1.270138508	0.123131505	2.801767365	0.005082351	0.05770229
gdi2	271.0347963	-1.183398713	0.440312982	0.321707521	-3.678492529	0.000234617	0.007869936
gfod1	410.9463817	0.744344999	1.675213529	0.272227728	2.734273262	0.006251814	0.065352473
gfpt1	23983.09644	0.596685373	1.512238168	0.200063916	2.982473726	0.002859292	0.039443495
gfra1	70.99781585	-1.24434203	0.422100362	0.291381476	-4.270491206	1.95E-05	0.001491923
gga1	871.0564558	-0.50492708	0.704695995	0.150215534	-3.361350638	0.000775623	0.016369607
ggcx	433.2684368	-0.871181882	0.546698802	0.279153434	-3.12079944	0.001803608	0.029330444
gigyf2	1174.776019	-0.763111831	0.589224028	0.143979028	-5.300159624	1.16E-07	4.08E-05
gjb2	7048.797128	1.050253295	2.070893404	0.29906198	3.51182486	0.000445041	0.011468735
gjb7	155.7631464	1.566669179	2.962200264	0.426173674	3.676128476	0.0002368	0.007869936
gli1.2	8609.492711	1.028466862	2.039855364	0.290524825	3.540030908	0.00040008	0.010869491
glis1	28.18657329	2.672451199	6.375114258	1.063598646	2.512650057	0.011982813	0.096135145
glis2	328.6656624	-0.765095828	0.588414283	0.241340769	-3.170188903	0.001523399	0.025960135
glod5	144.0600007	1.330814246	2.515446047	0.384323331	3.462746436	0.000534692	0.01296987
glt1d1	118.4779133	0.798783093	1.739633135	0.289623396	2.758006105	0.005815511	0.062648415
glyctk	93.80150828	0.670933568	1.592102884	0.248592948	2.698924378	0.006956398	0.069528838
gmppa	308.6708501	-0.961331326	0.513582758	0.372877518	-2.578142362	0.009933306	0.086094611
gna11	4321.107652	0.493094428	1.407460494	0.180408844	2.73320541	0.00627212	0.065484617
gnai1	3873.884078	0.501254768	1.415444094	0.18181727	2.756915052	0.005834951	0.062648415
gnas	1506.788893	1.012005375	2.016712423	0.163214676	6.200455741	5.63E-10	9.04E-07
gngt1	26.68622576	1.747677432	3.358175043	0.544017401	3.21253958	0.00131567	0.023414673
gnl3	1832.484073	-0.653094714	0.635914754	0.187454617	-3.484015085	0.000493952	0.012312171
gnpda1	160.6830938	1.18244454	2.269610201	0.331003513	3.572302087	0.000353857	0.010153288
golga2	1387.859451	-0.507440974	0.703469132	0.201229869	-2.52169808	0.01167899	0.094740524
golga7b	44.49188616	-1.817877377	0.283637978	0.463298576	-3.923770701	8.72E-05	0.00429251
golph3	993.2221434	0.710321719	1.63616894	0.185673374	3.82565203	0.000130426	0.005465434
gon4l	1497.123317	-0.7611813	0.590013022	0.193936153	-3.924906671	8.68E-05	0.00429251
gorasp2	3760.73582	0.36224684	1.285426251	0.128351942	2.822293414	0.004768153	0.055263771
got2	960.2295699	1.874265941	3.66615032	0.331984717	5.645639234	1.65E-08	1.05E-05
gpat2	96.28521009	2.477309667	5.568580705	0.562472216	4.404323617	1.06E-05	0.000970947
gpc1	26.26127226	-1.176446573	0.442439908	0.415552635	-2.831041062	0.004639676	0.054262162
gphn	119.5380699	0.932486422	1.908562487	0.302708233	3.080479221	0.002066678	0.031989251
gpi	521.089714	1.2321517	2.349170947	0.317540817	3.880293915	0.00010433	0.004758055
gpnmb	1595.107816	2.715537048	6.568377514	0.457931661	5.930005024	3.03E-09	3.06E-06
gpr137c	704.2199306	-0.611919398	0.654325591	0.225069195	-2.71880564	0.006551809	0.067129347
gpr75	127.9227143	-1.300753703	0.405914082	0.384385068	-3.383986039	0.000714416	0.015541102
gpr88	15.76338925	4.502575155	22.66784213	1.102066255	4.08557574	4.40E-05	0.002739829
gpr98	34.43039265	-2.51656413	0.174758662	0.831157066	-3.027784078	0.00246354	0.035890622
gramd3	821.1894893	0.749667923	1.681405763	0.247838276	3.024827056	0.002487753	0.036001452

grhl2	307.3599708	0.652082809	1.571435229	0.228624303	2.852202503	0.004341743	0.052176709
grik5	78.27700413	-1.743736844	0.298595257	0.490527045	-3.554823045	0.000378234	0.010569452
grip1	520.2890223	-0.577340573	0.670198065	0.208024916	-2.775343373	0.005514345	0.060624251
gripap1	34.25068482	-2.150504485	0.225233842	0.647413505	-3.321686168	0.000894753	0.017916122
grk7	82.8989464	2.807587162	7.001126924	1.031780236	2.721109654	0.006506318	0.066900308
gs17	958.4771297	2.050350221	4.142065078	0.425636277	4.817141613	1.46E-06	0.000269918
gsk3b	796.518452	0.459874512	1.375422176	0.168971161	2.721615386	0.00649637	0.066845568
gsn	755.5731461	0.520256105	1.434209825	0.182317829	2.853566807	0.004323144	0.052039707
gss	264.0216425	-0.831982452	0.561756784	0.250693309	-3.318726196	0.00090429	0.017957868
gstcd	165.7315833	0.77429236	1.710350921	0.268073129	2.888362448	0.003872534	0.048263535
gtf2e2	2126.138595	0.485253365	1.399831682	0.185135399	2.621072841	0.008765353	0.079349224
gtf2h4	690.605028	-0.749234918	0.594918968	0.195595908	-3.830524507	0.00012787	0.005437124
gtf3c5	112.6683456	-1.350043778	0.392280145	0.270925756	-4.983076547	6.26E-07	0.00013919
gtf3c6	323.1039038	1.060782776	2.086063069	0.273032291	3.885191647	0.000102249	0.004722737
guca1b	316.8579888	2.840347505	7.161925468	0.343429257	8.270546111	1.33E-16	9.64E-13
gypc	33.5959813	-1.231069682	0.426001471	0.430840052	-2.857370562	0.004271668	0.051681339
gys1	663.5961535	-0.433032939	0.740702987	0.129545409	-3.342711589	0.000829641	0.017012932
h2afy2	486.9793421	0.594398441	1.509842897	0.216663488	2.743417672	0.006080329	0.064398037
h3f3a	22007.72325	0.552349105	1.466471573	0.205096092	2.693123502	0.007078604	0.070450943
h6pd	654.1705118	1.151105862	2.220840621	0.30684457	3.751429789	0.000175829	0.006568372
hace1	722.4893578	-0.409255451	0.75301189	0.154663937	-2.646094865	0.008142698	0.076808064
hadh	1169.314389	1.030990425	2.043426603	0.253910062	4.060455179	4.90E-05	0.002925878
hal.1	1318.630086	1.370180565	2.585029178	0.383299508	3.574699513	0.00035063	0.010153288
has-rs	1322.954716	1.409274982	2.656036518	0.509617333	2.765359202	0.005686015	0.061806551
has2	1217.154136	0.698763515	1.623113081	0.245359915	2.847912285	0.004400705	0.052710021
haus6	928.087257	0.853232908	1.806544644	0.244600843	3.48826642	0.000486163	0.012223416
haus7	624.0855481	0.62283688	1.539900228	0.174502086	3.569223119	0.000358041	0.010209476
hdac2	748.6909151	0.479743443	1.394495658	0.177024591	2.710038424	0.006727541	0.068061628
hdhd1	544.1037819	1.096107866	2.137771812	0.256741741	4.269301365	1.96E-05	0.001492009
hdx	171.6469872	-1.040948554	0.486007825	0.206170023	-5.048981113	4.44E-07	0.000112435
heatr1	2184.932264	-0.735820318	0.600476496	0.211504219	-3.478986486	0.000503314	0.012474852
hebp2	1221.061843	3.960527724	15.56817281	0.806556359	4.910416589	9.09E-07	0.00019322
henmt1	59.42082649	3.158463199	8.928780839	0.514097227	6.143707913	8.06E-10	1.06E-06
hepacam	19.2633388	2.805683151	6.991893213	0.696052751	4.03084845	5.56E-05	0.003128846
herc1	535.5106602	-0.846392601	0.556173688	0.255884009	-3.307719792	0.000940589	0.018475667
herc2	1867.763001	-0.841525238	0.558053275	0.240023546	-3.506011187	0.000454876	0.011650547
herc3	157.5329202	1.072580782	2.103192324	0.379426728	2.826845615	0.004700899	0.05480717
hes6.1	3761.344423	0.972342617	1.962023902	0.252658432	3.848447131	0.000118869	0.005223369
hibadh	1120.164617	0.71113801	1.637094962	0.235192367	3.023644087	0.002497501	0.036106367
hipk3	1310.076438	0.932239329	1.908235633	0.358189724	2.602641188	0.009250872	0.082242081
hist1h2al	22.21217027	2.542143412	5.82453716	0.878151539	2.894880096	0.003793034	0.0478081

hist1h2bk	40.8399887	1.61669516	3.066717256	0.44766539	3.611391896	0.000304558	0.009345914
hist1h3g	3469.952928	0.7203206	1.647548117	0.195528869	3.683960353	0.000229638	0.007811473
hk1	1161.118519	-0.814060236	0.568778866	0.240996592	-3.377891062	0.00073044	0.015761153
hk2	1416.643267	1.171147581	2.25190752	0.324907853	3.604553019	0.000312691	0.009477082
hmgb1	11379.93733	0.404994276	1.324083657	0.149723942	2.704939967	0.006831673	0.068874131
hmgb3	40268.27679	0.440330452	1.356915096	0.155334299	2.834727778	0.004586475	0.05391847
hmgcl	168.3483445	0.691670247	1.615152342	0.245508771	2.817293424	0.004843026	0.055787294
hmgxb4	1924.18087	-0.451155455	0.73145679	0.150674836	-2.994232263	0.002751364	0.038655463
hnrnpa2b1	38610.7473	0.505806547	1.419916947	0.183197882	2.76098469	0.005762738	0.062219492
hnrnpab	46527.79738	0.496186019	1.410479814	0.186773832	2.656614226	0.007892971	0.075319259
hnrnph1	30090.33842	0.932531826	1.908622554	0.219896873	4.240768918	2.23E-05	0.001610187
hnrpdl	9595.230088	0.540774101	1.454752879	0.189911679	2.84750313	0.004406366	0.052734134
hnrpll	588.0496898	-0.429462863	0.742538192	0.165735997	-2.591246754	0.00956289	0.084066354
hoxa4	53.00190307	0.847598048	1.799502427	0.313928246	2.699973832	0.006934493	0.069426569
hoxd4	545.9834894	1.174647557	2.257377277	0.305742942	3.841944961	0.000122063	0.005267665
hs1bp3	192.3077769	0.644929345	1.563662705	0.250623216	2.573302489	0.010073312	0.0869235
hs6st2	32.77562015	2.382458866	5.214246786	0.843166974	2.825607429	0.004719106	0.054886658
hsd17b10	439.0434455	0.977819392	1.969486314	0.274115092	3.567185539	0.000360836	0.010248735
hsdl2	206.8469648	0.552453596	1.466577789	0.216442117	2.552431116	0.010697406	0.090123776
htatsf1	1109.502986	0.609805011	1.52605294	0.173392378	3.516907831	0.000436605	0.011393508
htra2	69.99666017	-1.654506658	0.317646349	0.490440412	-3.373512088	0.000742158	0.015937643
huwe1	4044.555644	-0.651899308	0.636441886	0.166154998	-3.923440853	8.73E-05	0.00429251
id3	13211.34903	0.687495611	1.610485433	0.18636383	3.688997018	0.00022514	0.007731228
ifi30	716.1703664	0.842659599	1.793353132	0.18596441	4.531294999	5.86E-06	0.000642057
ifit5	22.93025835	4.717608359	26.31125865	0.895850549	5.266066271	1.39E-07	4.69E-05
ifngr2.2	439.0711672	0.752999677	1.685293281	0.289747183	2.598816209	0.009354584	0.082855632
ifrd1	923.7003155	1.457026029	2.745418395	0.437821889	3.327896719	0.000875043	0.017619659
ift122	413.2947016	-0.808244114	0.571076485	0.276380796	-2.924385939	0.003451365	0.045168449
igf2	851.1319515	1.077180827	2.109909073	0.318677779	3.380156689	0.000724445	0.015678599
igsf9	1666.312595	-0.948224146	0.518270023	0.203477631	-4.660090353	3.16E-06	0.000450987
ikbip	386.3154134	-0.535396658	0.689968949	0.211809195	-2.527730952	0.011480229	0.093776717
ikbke	7.386998627	-3.1681015	0.111251639	0.798177502	-3.969169127	7.21E-05	0.003805445
ing3	1561.400317	0.783110838	1.720837463	0.244615284	3.201397822	0.001367626	0.024111908
ino80d	368.0595596	0.836840152	1.786133793	0.302479348	2.766602607	0.005664376	0.061617666
inppl1	588.4491328	-1.232420781	0.425602703	0.375298999	-3.283837108	0.001024041	0.01966077
ints1	1318.889994	-0.753049799	0.593347917	0.250687602	-3.00393714	0.002665104	0.03787649
ints5	354.1171052	-0.48456168	0.714714182	0.13705459	-3.535537778	0.000406946	0.010891503
ipo5	2665.151584	-0.349745384	0.784722578	0.139127552	-2.513847033	0.011942222	0.095915946
iqce	251.7554369	-1.034333583	0.488241359	0.375118732	-2.757349857	0.005827197	0.062648415
iqgap3	850.7176854	-0.613229136	0.653731837	0.213817792	-2.867998637	0.004130773	0.050608972
irf2	625.2326804	0.570650664	1.48519325	0.213210438	2.676466825	0.007440293	0.07277694

isl1	956.6350243	1.13409764	2.194812412	0.347310738	3.265368778	0.001093216	0.020578946
itfg2	56.01166844	-1.184834409	0.439875024	0.412280862	-2.873852554	0.004054982	0.049849386
itga2b.1	8.726421027	2.264470276	4.804779671	0.856407335	2.644150957	0.008189612	0.077031376
itga7	63.48061572	-1.424972238	0.372426532	0.465083794	-3.063904302	0.002184688	0.033141691
itgb3bp	272.8089229	1.405742123	2.649540396	0.309541788	4.541364622	5.59E-06	0.000635771
itih3	13.68643586	-3.378714653	0.096140315	0.944868442	-3.575857233	0.000349082	0.010153288
itih5l	23.34355284	1.495803058	2.820210909	0.461191495	3.243344844	0.001181351	0.021812
itm2a	6683.368187	0.842634943	1.793322482	0.216518937	3.891737849	9.95E-05	0.004656593
itsn1	1873.292196	-0.506017569	0.704163538	0.184098117	-2.748629785	0.005984494	0.063709739
ivd	500.0891911	0.678827488	1.600838187	0.256696357	2.644476511	0.008181739	0.077007418
jam2	188.4805169	-0.936252805	0.522588468	0.308695503	-3.032933088	0.002421893	0.035474475
jph3	47.32237102	1.381862458	2.606045834	0.539879827	2.559574164	0.010480049	0.089018843
kbtbd13	11.41201951	5.686573287	51.50259738	1.339589914	4.245010526	2.19E-05	0.001598278
kcmf1	817.1411317	0.771607154	1.707170503	0.169729541	4.546098148	5.46E-06	0.000635771
kcna1	71.01910021	1.415351686	2.667247469	0.413838767	3.420055827	0.000626083	0.014231572
kcnk13	223.8473132	1.879314787	3.679002833	0.517045748	3.634716648	0.000278286	0.00876511
kcnk6	1788.011321	0.615576718	1.53217036	0.231378906	2.660470343	0.00780316	0.07485752
kcnn3	41.30833448	-3.003284212	0.124715768	0.704510376	-4.262938225	2.02E-05	0.001520612
kctd2	166.3483367	-0.477438054	0.718251968	0.186598583	-2.558637086	0.010508338	0.089102077
kdelc2	1248.018252	-0.66930935	0.628807639	0.245722879	-2.723838137	0.006452812	0.066604576
kdelr2	1063.561352	0.832551469	1.780832058	0.229273025	3.631266558	0.000282034	0.008844601
kdm5c	4878.380617	-0.612546377	0.654041291	0.112140627	-5.462305613	4.70E-08	2.12E-05
kiaa0319l	2008.567843	-0.546275881	0.684785529	0.176530478	-3.094513124	0.001971362	0.031113518
kiaa0907	2171.850328	-0.518653998	0.698022769	0.19797288	-2.619823468	0.008797529	0.079491177
kiaa1324l	1851.047389	1.001526619	2.002117463	0.347437553	2.882609003	0.003943967	0.048942424
kiaa1328	27.73714247	-1.780815347	0.291018879	0.630239886	-2.825615116	0.004718993	0.054886658
kiaa1609	316.8564597	0.925326622	1.899114147	0.258758588	3.576022845	0.000348861	0.010153288
kidins220	567.3572568	-1.14955246	0.450765042	0.278057645	-4.134223526	3.56E-05	0.002333994
kif14	228.8621297	1.640530541	3.117804658	0.487073555	3.36813716	0.000756779	0.016111287
kif1b	416.2432274	-0.579477999	0.669205868	0.212474696	-2.727280047	0.006385882	0.066179706
kif1c	875.4728145	-0.478447362	0.717749655	0.140487742	-3.405616419	0.000660149	0.014705344
kif3b	1128.769835	-0.583497945	0.667343779	0.162729339	-3.585696027	0.00033618	0.009985015
kif5a	21.47139982	-1.984842468	0.252640447	0.708142839	-2.802884333	0.005064783	0.057648586
kif5c	15.14537635	-1.369892829	0.38691999	0.445442301	-3.07535415	0.002102527	0.03223355
klf10	546.3555594	1.157754323	2.231098677	0.285390279	4.05674057	4.98E-05	0.002937405
klf17	3589.362386	0.696118925	1.620140494	0.255513859	2.724388131	0.006442075	0.066571178
klf2	543.7850206	1.927871982	3.804935459	0.403630804	4.776325208	1.79E-06	0.000307259
klhdc7a	110.20866	-1.852573285	0.276898034	0.439415879	-4.215990754	2.49E-05	0.001762365
klhdc9	37.71075801	1.064895987	2.092019048	0.388618447	2.74020957	0.006140002	0.064858129
kpna4	7659.450064	0.647412471	1.566356354	0.206138027	3.140674625	0.001685592	0.02784983
kpna7	2732.789487	0.952405581	1.935096592	0.313569891	3.037299211	0.002387084	0.035214357

kras	1761.84497	0.488324201	1.402814454	0.195926396	2.49238597	0.012688807	0.099426601
krcc1	891.0452963	1.225033498	2.337608773	0.360318561	3.399862317	0.000674198	0.014995199
kremen2	143.4906436	0.941308254	1.920268773	0.360165655	2.61354252	0.008960893	0.080314714
krt222	56.78696412	-1.473011147	0.360229654	0.444090896	-3.316913628	0.000910177	0.018049981
krt5.4	9.469999628	2.177714414	4.524362152	0.732929822	2.97124547	0.002965946	0.040238492
l1cam	142.9401154	-0.975821832	0.508450125	0.291540633	-3.347121188	0.000816555	0.016840137
l3mbtl1	154.6125954	1.604730116	3.041388504	0.586326438	2.736922663	0.006201687	0.065005291
lactb2	304.1789065	0.834554903	1.783306772	0.247398078	3.373328158	0.000742654	0.015937643
lage3	101.4592001	0.973376223	1.963430081	0.328087711	2.966817074	0.003008999	0.040655235
lama5	2943.06691	-0.878005167	0.544119272	0.161454982	-5.438080362	5.39E-08	2.30E-05
lamb1	4356.121962	0.86851683	1.825784928	0.297402185	2.920344478	0.003496447	0.045497866
lap3	226.3310166	1.507623362	2.843412407	0.286747755	5.257664043	1.46E-07	4.75E-05
laptm4a	2742.468881	0.669906114	1.590969428	0.228113461	2.936723284	0.003316999	0.043913791
large	44.19391431	-2.068385233	0.238426214	0.585621768	-3.531947318	0.000412512	0.010942531
lats2	1058.772764	-0.596953831	0.66114846	0.217920057	-2.739324861	0.006156551	0.064858129
lca5	274.6451427	1.122219131	2.176815495	0.293744302	3.820394546	0.000133238	0.005519275
lclat1	657.0422341	-1.001218973	0.499577715	0.222726471	-4.495285034	6.95E-06	0.000727845
ldha	2403.456187	0.617076501	1.533763988	0.228548539	2.699980071	0.006934363	0.069426569
ldlr	55.0053683	-1.131151527	0.456551171	0.364095542	-3.106743691	0.001891603	0.030385454
ldlrad2	95.60365419	-1.362740098	0.388843062	0.386812431	-3.522999747	0.000426692	0.011203166
ldlrap1	1416.921949	0.873318484	1.831871725	0.262216203	3.330528295	0.000866814	0.017600454
lepre1	365.3284644	-0.648443448	0.637968259	0.154937756	-4.185186774	2.85E-05	0.001952255
leprel2	820.1734693	0.791743549	1.731165374	0.255762446	3.095620802	0.001964014	0.031031414
lfng	2221.214121	0.751522727	1.683568856	0.274798793	2.734810867	0.006241613	0.065293051
lgr4	1105.262907	-0.562673385	0.6770464	0.219966548	-2.55799525	0.010527753	0.089130618
lhx5	2390.779724	1.321419926	2.499119565	0.329622175	4.008892681	6.10E-05	0.003353372
lim2	30.58793187	1.378857047	2.600622591	0.473207748	2.913851377	0.003569998	0.045961848
lin7b	1325.268392	-0.499838804	0.707185792	0.188729693	-2.648437543	0.008086479	0.076440931
lipe	428.7687629	-0.637011366	0.643043676	0.228981193	-2.781937488	0.005403545	0.060045385
lmnb2	1711.771686	0.987008036	1.982070167	0.341774702	2.887890857	0.003878344	0.048272229
loc100133315	81.4890473	1.784171428	3.444205986	0.409786036	4.35390977	1.34E-05	0.001126691
loh12cr1	90.22338195	-0.790770163	0.578035433	0.28470145	-2.777541746	0.00547718	0.060476974
lonrf1	710.3222298	1.932936217	3.818315242	0.525579066	3.6777268	0.000235322	0.007869936
lonrf3	2131.392616	2.288864885	4.886714721	0.61509599	3.72115072	0.000198317	0.007063445
loxl2	137.1885655	-1.1526169	0.449808585	0.415249567	-2.775720895	0.005507947	0.060599991
lpcat2	140.0068325	1.286128035	2.438726609	0.386317673	3.329198031	0.000870965	0.017610537
lrat	429.5251634	0.579154583	1.493973526	0.217831495	2.658727487	0.007843638	0.075146105
lrch4	108.7943071	-1.217718401	0.429962159	0.354201842	-3.43792227	0.000586196	0.013654493
lrp1	3718.603039	-0.595281723	0.661915187	0.210076496	-2.83364267	0.004602076	0.05396122
lrpprc	2187.883086	-0.778387995	0.583017869	0.195567976	-3.980140352	6.89E-05	0.003674243
lrrc14b	50.36751195	2.297665911	4.916616782	0.585763327	3.922515809	8.76E-05	0.004294422

lrrc16a	549.6162181	-0.499672401	0.707267365	0.163726949	-3.051864124	0.00227425	0.034036062
lrrc19	130.7739405	0.823396134	1.76956669	0.251069616	3.279553086	0.001039716	0.019908849
lrrc20	146.0969044	1.048497701	2.068374897	0.352664205	2.973076615	0.002948308	0.040198583
lrrc48	65.35045285	0.972039936	1.961612308	0.338835461	2.868766847	0.004120754	0.050529046
lrrc8a	3860.25521	-0.344450248	0.787608044	0.101118964	-3.406386237	0.00065829	0.014705344
lrrc8b	37.20958927	-1.093675828	0.468565998	0.385573489	-2.836491253	0.004561223	0.053829876
lrrfip1	931.4034009	-0.616163357	0.652403598	0.180188245	-3.419553569	0.00062724	0.014235488
lrrn1	241.4984879	-1.202875173	0.434408678	0.264849348	-4.541733556	5.58E-06	0.000635771
ltbp1	448.2340638	-0.570443706	0.673409647	0.192274587	-2.966817998	0.00300899	0.040655235
ly6g6c	2808.281992	0.594645663	1.510101647	0.23669123	2.512326558	0.011993805	0.096169957
lyrm5	73.44344381	0.876535185	1.835960709	0.317240868	2.762995797	0.00572735	0.062053179
lysmd1	46.45035612	-1.818062848	0.283601516	0.584819493	-3.108758974	0.001878749	0.030279907
m6pr	1029.35538	-0.50588613	0.704227695	0.201232221	-2.513941985	0.011939007	0.095915946
mab21l1	70.39101241	-1.720719426	0.303397389	0.598667954	-2.874246759	0.004049924	0.049829576
madd	1382.977033	-0.761081644	0.590053779	0.221232006	-3.440196826	0.000581291	0.013653625
mael	198.1037024	0.933562472	1.90998654	0.229816667	4.06220525	4.86E-05	0.002916073
magi1	3019.908807	-0.470466846	0.721731013	0.128934485	-3.648882955	0.000263383	0.008405583
magoh	5920.627424	0.829035282	1.776497037	0.232765403	3.561677427	0.000368493	0.01042525
man1a2	764.0287745	0.761518748	1.695274328	0.294092453	2.589385549	0.009614738	0.084293672
man2a2	448.2535398	-0.821184113	0.565977218	0.275419487	-2.98157593	0.002867689	0.039521624
map3k13	121.6612982	-0.783478812	0.580964207	0.31150628	-2.515130074	0.011898847	0.095700646
map3k7	1506.71982	0.498788601	1.413026577	0.17115769	2.914205022	0.003565956	0.045961848
map4	192.6078989	-0.654961097	0.635092617	0.21403623	-3.060047807	0.002213017	0.033361399
mapk14	996.0391455	0.478885879	1.393666992	0.144476868	3.314619749	0.000917679	0.018099427
mapt	61.77339653	-1.416452122	0.374632477	0.495722028	-2.857351581	0.004271924	0.051681339
march.10	25.70988449	1.617980045	3.069449736	0.594745405	2.720458254	0.00651915	0.066984617
march.2	38.83562875	-1.201961129	0.434683992	0.476678702	-2.521533105	0.011684468	0.094740524
march.8	858.1399357	1.385316597	2.612292775	0.372441139	3.71955848	0.000199571	0.007071576
mark4	667.055923	-0.388824489	0.763751658	0.128621457	-3.023014178	0.002502705	0.036145463
mast2	380.5674601	-1.207548134	0.433003882	0.459311588	-2.62903912	0.008562651	0.078596981
mast4	403.4527194	-0.777127596	0.58352744	0.304266988	-2.554097641	0.01064634	0.089934889
mastl	3100.606998	0.921018891	1.893452056	0.329143878	2.798225801	0.005138418	0.058036019
matn2	73.15086124	-1.589963353	0.332179891	0.524043096	-3.034031679	0.002413091	0.035381395
mb21d2	189.7069492	0.618449374	1.535224217	0.213122809	2.901845071	0.00370972	0.047045102
mcf2l.2	74.82957093	1.938246356	3.83239524	0.506894766	3.823764784	0.000131429	0.005475716
mdh2	331.7550667	1.389988073	2.620765141	0.398074549	3.4917783	0.000479816	0.012084851
mdn1	2721.048724	-0.567063852	0.674989118	0.223193101	-2.540687187	0.011063485	0.091502423
me2	1543.01921	-0.462164283	0.725896476	0.175475653	-2.633780095	0.008444016	0.077950997
me3	223.3157833	-0.801931839	0.573580611	0.187448616	-4.278142218	1.88E-05	0.001456984
med11	243.4554155	0.72998077	1.658616984	0.245600881	2.972223749	0.002956511	0.040205568
med19	1336.376361	0.617901872	1.53464171	0.222875952	2.772402608	0.005564417	0.060896876

med27	368.0870987	-1.454051417	0.364994994	0.345879495	-4.203924893	2.62E-05	0.0018321
med6	694.2961365	0.642828439	1.561387298	0.230218715	2.792251013	0.005234273	0.058693448
metap1d	165.9107513	0.90616004	1.874050773	0.27185639	3.333230606	0.000858438	0.017504136
mettl11a	81.34628867	-1.096945638	0.467505214	0.346685234	-3.164096797	0.00155565	0.026361334
mettl18	326.7503372	0.855128965	1.80892045	0.291880437	2.929723461	0.003392638	0.044592538
mettl19	668.668987	-0.554752899	0.680773649	0.179625768	-3.088381498	0.002012499	0.031556078
mettl22	111.1881752	1.829972679	3.555303395	0.652952346	2.802612914	0.005069047	0.057648586
mgc69493	1277.919998	-1.557139241	0.339824261	0.518447312	-3.003466706	0.002669228	0.03787649
mgst3	145.9528643	1.284113804	2.435324136	0.511357182	2.511187579	0.012032574	0.096427341
mier3	2668.420332	0.518728835	1.43269234	0.200771654	2.583675661	0.009775367	0.085082773
mix1	2404.113558	1.787804862	3.452891168	0.533912266	3.348499325	0.000812505	0.016821068
mixer	4340.206985	2.089302568	4.255423062	0.433320798	4.821606943	1.42E-06	0.000267373
mkl1	1225.777072	-0.472640491	0.720644431	0.138766937	-3.406002197	0.000659216	0.014705344
mlana	390.6169931	1.902648353	3.738989328	0.374219416	5.084312235	3.69E-07	9.70E-05
mll	1992.832889	0.90123305	1.867661563	0.360203533	2.502010577	0.012349024	0.097976048
mll4	2155.980912	-0.96887601	0.510903948	0.327212825	-2.960996436	0.003066455	0.041315693
mllt10	1458.2108	-0.357071198	0.780747961	0.132222062	-2.700541751	0.006922665	0.069426569
mmab	86.83643376	0.716024228	1.642648987	0.25921548	2.762274182	0.005740025	0.062087658
mmadhc	255.7756139	-0.749137078	0.594959315	0.286261971	-2.616963316	0.008871588	0.079829026
mmp21	206.4767646	1.647014506	3.131848674	0.621828146	2.648665094	0.008081037	0.076440931
mmp3	1048.095728	-1.210469724	0.432127897	0.406531653	-2.977553444	0.00290559	0.039853996
mms22l	467.1548041	-0.769153943	0.586761475	0.287736036	-2.673123441	0.007514859	0.073235959
mnat1	470.2711581	0.731363177	1.66020705	0.225726136	3.240046497	0.001195102	0.02198837
mogat1	311.9811978	1.442976122	2.718811485	0.421247137	3.425485883	0.000613701	0.014105362
mon1a	261.6669684	1.59654818	3.024188738	0.304628877	5.240961381	1.60E-07	4.91E-05
morn4	156.420261	-0.709993142	0.611323045	0.269524517	-2.634243263	0.008432505	0.077896947
mosc1	79.68376338	1.666384171	3.174180504	0.541432781	3.077730477	0.002085835	0.032148095
mov10	654.8467087	0.782807144	1.720475257	0.277431203	2.821626177	0.004778084	0.055263771
mpg	126.0432884	1.148161436	2.216312685	0.450400349	2.549201925	0.010796976	0.090383259
mpp7	228.0144846	-1.634284582	0.322130109	0.351188584	-4.653581174	3.26E-06	0.000450987
mpzl3	650.52236	0.620321799	1.537218026	0.179118579	3.463190709	0.00053381	0.01296987
mreg	724.3039091	1.173026248	2.254841848	0.272717491	4.30125052	1.70E-05	0.001352704
mrpl18	630.5632894	0.607394012	1.523504765	0.205846058	2.950719664	0.003170345	0.04231202
mrps11	354.76739	0.698187263	1.622464895	0.250601785	2.786042658	0.005335585	0.059491675
mrps27	1188.763944	0.576046062	1.490757982	0.231197004	2.491581001	0.012717596	0.099559707
mrps9	194.1751059	1.329797842	2.513674495	0.411790197	3.229309125	0.001240897	0.022452623
mrto4	679.8185861	-1.107575099	0.464073396	0.327148594	-3.385541371	0.00071038	0.015490141
mrvi1	14.76147909	1.594138216	3.019141168	0.516662449	3.085453989	0.002032417	0.031696492
msh2	842.9658237	0.941112717	1.920008525	0.242022207	3.888538692	0.00010085	0.004688047
msln	7400.708304	-0.949794498	0.5177062	0.273436125	-3.473551632	0.000513619	0.012692963
msra.2	63.07664902	0.834022073	1.782648265	0.271807286	3.068431623	0.002151856	0.032746713

mst1r	1328.333008	1.214056097	2.319889513	0.294479435	4.122719465	3.74E-05	0.002427386
mt4	248.5729433	1.572406912	2.974004667	0.271107709	5.799934334	6.63E-09	5.64E-06
mtch2	2070.919743	0.582901589	1.497858757	0.187829431	3.103355987	0.001913393	0.030599477
mthfs	135.8202372	1.21747348	2.325391263	0.308085613	3.951737534	7.76E-05	0.00402028
mtif3	177.883342	1.116916767	2.168829688	0.314466832	3.551779245	0.000382636	0.010593403
mtx2	228.3980746	0.604297998	1.520238839	0.239503225	2.523130945	0.011631508	0.094522739
mus81	194.9248288	0.510969646	1.425007632	0.176873114	2.888905128	0.003865857	0.048263535
myadm	725.4195502	-0.77551226	0.584181161	0.241477168	-3.211534519	0.001320281	0.023414673
myf5	650.8769837	0.919895582	1.891978353	0.328251439	2.802411424	0.005072214	0.057648586
myh10	624.3632486	-0.897110768	0.536961007	0.19743255	-4.543884816	5.52E-06	0.000635771
mylip	3031.415586	1.078629372	2.112028601	0.313105896	3.444934714	0.000571197	0.013515221
mylk3	9.038193797	3.405983377	10.599934	1.049710275	3.244688995	0.00117579	0.021764905
myo10.2	1459.640176	-1.676635426	0.312811309	0.286279326	-5.856641666	4.72E-09	4.27E-06
myo1a	619.8099005	-1.618967306	0.325568425	0.44238877	-3.659603084	0.000252606	0.00820658
mzt2b	934.22969	1.92242868	3.790606449	0.365808273	5.255290334	1.48E-07	4.75E-05
naa16	106.7931627	1.028093045	2.039326885	0.373841839	2.750074867	0.005958165	0.063616833
naa38	1384.830543	0.798032153	1.73872787	0.257307985	3.101466716	0.001925645	0.030672338
naa40	2351.247079	0.623961575	1.541101171	0.22945498	2.719320252	0.006541624	0.067120125
nae1	409.3902512	0.84748881	1.799366177	0.237117389	3.57413184	0.000351392	0.010153288
naglu	620.4677716	-0.6378216	0.642682636	0.255394966	-2.497393003	0.012511021	0.098514073
nagpa	756.446774	0.956381195	1.940436463	0.302761722	3.158857691	0.001583888	0.026687961
nanos2	432.3678687	1.771181389	3.41333352	0.544340721	3.253810196	0.001138683	0.021213846
nap1l4	43.17008433	-0.867229999	0.548198392	0.335583829	-2.584242519	0.009759314	0.085038983
nat6	142.3140694	-1.184799395	0.439885699	0.379386701	-3.122933384	0.001790583	0.029250231
nat8l	16.9278883	-1.742786036	0.298792111	0.613220007	-2.842024095	0.00448281	0.053296044
ncald	917.09632	-0.95896668	0.514425235	0.215663221	-4.446593505	8.72E-06	0.000829781
ncapd2	3918.854064	-0.696282567	0.617160414	0.179824122	-3.872019833	0.000107937	0.004846111
nck2	189.1604747	-0.796845108	0.575606541	0.226440944	-3.518997471	0.000433181	0.011324585
ncstn	972.1382777	-0.699301832	0.615870175	0.247074986	-2.830322258	0.004650114	0.054302665
nde1	489.5281898	-0.73142809	0.602307409	0.223810924	-3.268062508	0.001082864	0.020490801
ndrg2	2422.874783	-0.669512261	0.628719205	0.242995631	-2.755244023	0.005864838	0.062899078
ndufa13	543.5376838	0.555805514	1.469989158	0.186009298	2.988052324	0.002807615	0.039028546
nedd1	639.7592049	0.588737693	1.503930286	0.177617849	3.314631355	0.000917641	0.018099427
nek2	3230.372149	0.634502975	1.552402837	0.229712157	2.762165411	0.005741938	0.062087658
nek8	127.1322905	-1.016609852	0.494276475	0.327282581	-3.106214357	0.001894993	0.030406118
nenf	850.7772452	0.561342064	1.475641291	0.211356575	2.655900643	0.007909691	0.075379308
neo1	4072.919036	-0.554407558	0.680936627	0.200599904	-2.763747878	0.005714167	0.062019306
neurl4	943.1444439	-0.758830483	0.590975209	0.181750864	-4.175113491	2.98E-05	0.002012073
nfatc1	97.9756537	-0.874541786	0.545427072	0.324559531	-2.694549694	0.007048382	0.070274795
nfu1	536.8265163	0.745013873	1.675990386	0.239470579	3.111087284	0.001863998	0.030109301
nfx1	482.9154498	0.775102617	1.711311771	0.174525133	4.441209153	8.95E-06	0.000839771

nfyb	2515.282337	0.542010151	1.455999793	0.201660112	2.687741	0.007193717	0.071135135
nhlrc2	156.2334967	-1.549407392	0.341650373	0.421694576	-3.67424074	0.000238558	0.007910159
nhlrc3	64.69388144	1.215011226	2.321425893	0.413366971	2.939304084	0.003289502	0.04366972
nid1	21.49430454	-1.611666452	0.327220162	0.629006105	-2.562242939	0.010399854	0.088716044
nim1	14.22860947	2.06250027	4.177095912	0.798784074	2.582049814	0.009821541	0.085341503
nipsnap1	701.6709762	1.280584637	2.429374048	0.40298115	3.177778013	0.001484083	0.02549458
nit1	16.28198027	1.710047811	3.271716658	0.60436065	2.829515473	0.004661855	0.054395829
nkap	1372.063391	0.593104022	1.508488839	0.234388765	2.530428551	0.011392329	0.093260981
nkiras2	255.9067974	-0.931623065	0.524268196	0.319573486	-2.915207627	0.00355452	0.045961848
nlgn3	105.1152728	-1.018087728	0.493770404	0.386412368	-2.634718277	0.008420714	0.077870523
nmnat1	155.8624776	1.296642552	2.456565236	0.30943847	4.190308172	2.79E-05	0.001926972
nodal	138.9673364	2.122019667	4.353029108	0.717718433	2.956618598	0.003110326	0.041635699
nol6	1167.090487	-0.698240128	0.616323571	0.241734319	-2.888460896	0.003871322	0.048263535
nol7	1248.951583	0.488454714	1.402941366	0.177680784	2.749057623	0.005976688	0.063709739
nosip	2199.297171	-1.202047822	0.434657872	0.301140316	-3.991653583	6.56E-05	0.003539493
notch2	444.1972853	-0.802012257	0.573548639	0.315667842	-2.540684069	0.011063584	0.091502423
npm2	583.775454	1.382576127	2.607335307	0.45349588	3.04870714	0.002298284	0.03425391
nr1d1	209.3972764	-0.596078995	0.661549496	0.22556276	-2.642630348	0.008226479	0.077118905
nr1h2	106.9445267	-0.987995701	0.50417773	0.241935578	-4.083713971	4.43E-05	0.00275003
nrp1	1220.790815	-0.803785615	0.572844067	0.24396492	-3.294677021	0.000985349	0.01915397
nsa2	2424.535056	0.469794478	1.384912164	0.170413413	2.756792847	0.005837132	0.062648415
nsrp1	1077.064667	-0.453596096	0.730220413	0.134354185	-3.376121827	0.000735154	0.015839218
nsun5	381.3822046	-0.644687029	0.639631534	0.257166855	-2.50688227	0.012180127	0.097178863
nsun6	328.7073941	0.867000583	1.823867068	0.239357981	3.622192079	0.000292117	0.009082014
nsun7	403.0852594	0.714779645	1.641232519	0.272326703	2.624713758	0.008672184	0.079012149
nt5dc3	294.8389794	-0.868001259	0.547905405	0.279908374	-3.101019259	0.001928557	0.030672338
ntan1	428.7245987	1.618548079	3.070658513	0.362638673	4.46325282	8.07E-06	0.000800783
ntf4	21.58266921	-1.373932116	0.385838198	0.497249113	-2.763065998	0.005726119	0.062053179
ntng2	72.45897142	-2.257386271	0.209150555	0.354984069	-6.359119939	2.03E-10	4.19E-07
nucb2	285.6695329	-0.705058307	0.613417696	0.245629829	-2.87040996	0.004099399	0.050352604
nudt12	216.7678188	1.7422153	3.345484825	0.437254729	3.984440155	6.76E-05	0.003621714
nudt19	166.2122861	-2.953864039	0.129061979	0.729162139	-4.051038695	5.10E-05	0.002996641
nudt5	588.326088	1.764123361	3.396675414	0.338849152	5.206220376	1.93E-07	5.46E-05
nup155	985.8699526	-1.02694261	0.490749053	0.336699373	-3.050028282	0.002288198	0.034207142
nup210	2179.391593	-0.526304454	0.694331027	0.189157642	-2.782358922	0.005396532	0.060013589
nup35	3222.093867	0.757925001	1.691056662	0.214430905	3.534588457	0.000408411	0.010893715
nup37	854.8615647	1.21945822	2.328592545	0.464615078	2.624663465	0.008673465	0.079012149
obsl1	52.55289308	-1.59438586	0.33116317	0.414482868	-3.846686997	0.000119726	0.005240191
ociad1	385.086516	1.085688251	2.122387746	0.315695757	3.439033397	0.000583795	0.013653625
ocln	5510.212117	0.544478518	1.458493056	0.133413485	4.081135558	4.48E-05	0.002768837
oct.25	11580.23239	1.659184299	3.158378991	0.343196205	4.834506546	1.33E-06	0.000260766

oct.60	1044.934853	1.481108578	2.791631621	0.446150982	3.319747434	0.000900989	0.017941599
odz2	272.4185557	-0.772596917	0.585362846	0.23848635	-3.239585483	0.001197036	0.02198837
odz4	726.9152074	-1.216327915	0.430376761	0.315743172	-3.852269893	0.000117028	0.005158149
ogdh	2695.991896	-0.496475229	0.708836486	0.148347242	-3.346710208	0.000817767	0.016841097
ogfod2	366.9965475	0.78683214	1.725281938	0.288340123	2.728833333	0.006355882	0.066081671
olig3	97.83595471	1.689865774	3.226266857	0.497924415	3.393819873	0.00068925	0.015170529
orc2	355.5479436	0.72279905	1.650380923	0.200326362	3.608107498	0.000308439	0.00940738
orc3	379.0157954	1.060718967	2.085970806	0.234587104	4.521642266	6.14E-06	0.000666997
ormdl1	106.1603017	0.661917547	1.582184175	0.245583753	2.695282323	0.007032901	0.070168844
otop2	34.14140279	2.359882132	5.133284184	0.899029699	2.624921218	0.008666902	0.079012149
p2ry10	38.28404858	1.878084416	3.675866613	0.568135217	3.305699697	0.000947396	0.018584124
pabpn1l	125.0545964	-1.279318031	0.411990213	0.482309761	-2.652482147	0.007990235	0.07588213
paqr4	99.37557481	-0.724584782	0.605171192	0.273937011	-2.645078074	0.008167207	0.076920725
paqr8	38.68160554	-1.223108209	0.428358847	0.386969893	-3.160732224	0.001573731	0.026578773
parp11	137.6213254	1.252719172	2.38290126	0.345080999	3.630217763	0.000283182	0.008861396
parp3	262.9553999	1.766892571	3.403201493	0.664655428	2.658358749	0.007852226	0.075160472
patl2	504.8272228	1.162771747	2.238871531	0.386221467	3.010634695	0.002607023	0.037206051
pbx2	8600.086745	0.58770407	1.502853177	0.186225401	3.155874906	0.001600175	0.026930997
pcbd1	38.45453466	1.343755531	2.538111644	0.502714295	2.673000437	0.007517615	0.073235959
pcdh8.2	9602.508763	0.834639983	1.783411943	0.262765647	3.176366439	0.001491324	0.025575418
pcid2	1136.949171	0.424820038	1.34240504	0.150448683	2.823687321	0.004747467	0.055172136
pcm1	2619.571081	-0.73949124	0.598950532	0.250632485	-2.950500372	0.003172597	0.04231202
pcmt1	312.5943616	0.927411407	1.901860471	0.310065061	2.991021966	0.002780455	0.038762813
pcsk7	388.0089629	-0.852293826	0.553903352	0.250066144	-3.408273553	0.000653753	0.014653194
pcyox1	583.0887724	0.642830033	1.561389023	0.186698935	3.443137115	0.000575008	0.013583148
pdcd2l	449.2432598	0.944152521	1.924058309	0.297009479	3.178863261	0.001478538	0.025477029
pde4dip	450.4394138	-0.715962851	0.608798686	0.246638194	-2.902887177	0.003697398	0.046930013
pde8b	59.08358446	1.211147048	2.315216402	0.395848279	3.059624383	0.002216147	0.033373795
pdha1	589.767691	-0.658047274	0.633735494	0.20795143	-3.164427744	0.001553882	0.026361334
pdia3	5083.328252	0.937725035	1.915505323	0.15536294	6.03570602	1.58E-09	1.76E-06
pdk1	1909.8121	1.11165763	2.160937925	0.348764158	3.187419362	0.001435485	0.02491333
pdk3	275.7373313	-1.093656551	0.468572259	0.375743412	-2.910647306	0.003606809	0.046185685
pebp1	246.1420685	0.695235552	1.619148773	0.215561834	3.225225632	0.001258734	0.022663192
perp	3169.49198	0.560528939	1.474809832	0.212903232	2.63278737	0.008468735	0.077982482
pex2	168.0995005	0.593227881	1.508618351	0.218427359	2.715904658	0.006609495	0.067456279
pex5	404.2587932	-0.832421503	0.561585853	0.17442886	-4.772269356	1.82E-06	0.000309234
pfas	717.920755	-1.088400786	0.47028239	0.371185093	-2.932231938	0.003365353	0.044350875
pfdn1	541.8325954	0.848771107	1.800966202	0.293072089	2.89611716	0.003778113	0.04766159
pfkfb1	1702.565747	0.819214769	1.764445378	0.314654756	2.603535319	0.009226776	0.082242081
pfkp	1552.769394	-1.116639384	0.461166818	0.391841979	-2.84971862	0.004375792	0.052498612
pfn2	1871.284822	-0.481575091	0.716195277	0.183790607	-2.620237777	0.008786848	0.079486239

pgap1	57.49596709	1.739299969	3.338731251	0.55511593	3.133219342	0.001729002	0.028372508
pgk1	670.1594645	0.554461259	1.468620108	0.217623175	2.54780429	0.010840327	0.090484182
pgp	451.2831786	1.38850826	2.618078327	0.480725528	2.888359739	0.003872567	0.048263535
phactr1	158.1316487	-1.146382832	0.45175647	0.303873462	-3.772566461	0.000161577	0.006176044
phf21a	704.3144593	-1.234360447	0.425030876	0.277580869	-4.446849858	8.71E-06	0.000829781
phgdh	263.3547832	-1.30409705	0.404974493	0.32828679	-3.972432305	7.11E-05	0.003781274
phr	203.6472758	0.75361379	1.686010814	0.280519872	2.686489858	0.007220714	0.071247675
pi4ka	357.2015392	-1.016988059	0.494146916	0.220338026	-4.615581229	3.92E-06	0.000510549
pi4kb	409.3442447	-0.577402768	0.670169173	0.221083431	-2.611696255	0.009009426	0.080649704
picalm.1	1554.24816	-0.402472985	0.756560319	0.1231719	-3.267571447	0.001084745	0.02049955
pigs	359.6859649	-0.930782557	0.524573721	0.291061896	-3.1978853	0.001384393	0.02425454
pigv	208.2111734	0.889958427	1.853122723	0.265401924	3.35324783	0.000798692	0.016734325
pim3	710.7707761	1.056292387	2.07958029	0.240946338	4.383932096	1.17E-05	0.001015091
pip4k2c	1777.38669	0.404843813	1.323945572	0.162050741	2.498253388	0.012480695	0.098478085
pitpnm2	311.9678658	-1.016435481	0.494336219	0.271079503	-3.749584427	0.000177128	0.006582873
piwil1	87.09402175	1.530742667	2.889345379	0.542435897	2.821978918	0.004772831	0.055263771
piwil3	95.6233556	1.8331838	3.56322553	0.466609869	3.928729167	8.54E-05	0.00427088
pkdcc.1	1000.421046	0.48550759	1.400078374	0.188586333	2.574457981	0.010039728	0.086705107
pkn1	413.2682405	0.821743333	1.767540575	0.293946021	2.795558623	0.00518101	0.058291561
pla2g12a	482.0259626	1.137883913	2.200580142	0.258937506	4.394434519	1.11E-05	0.000987247
pla2g12b	425.0786583	4.955813794	31.03477528	1.262354049	3.925850913	8.64E-05	0.00429251
plcd4	15.08313465	3.596084362	12.09286654	1.234124701	2.91387439	0.003569735	0.045961848
plcg1	1787.751957	-0.886039961	0.541097334	0.270824567	-3.271638062	0.001069264	0.020378342
pld3	701.9565033	0.937616186	1.915360806	0.24616422	3.808905232	0.000139583	0.005684388
pld6	157.9348624	1.206345413	2.307523617	0.333507369	3.617147704	0.000297867	0.009240919
plec	4045.602376	-1.300139721	0.406086868	0.330878443	-3.929357592	8.52E-05	0.00427088
plin2	1474.284592	0.454298851	1.370116767	0.140659563	3.22977578	0.001238873	0.0224441
plod3	1178.193785	-0.754274564	0.592844413	0.294422114	-2.56188149	0.010410684	0.088719207
plscr4	11.99515648	3.568452422	11.86345582	1.328204309	2.686674329	0.007216728	0.071247675
pmm1	73.55147881	-1.091708429	0.469205416	0.313830272	-3.478658768	0.00050393	0.012474852
pmp22	1526.282091	-0.611201501	0.65465127	0.167293463	-3.653469107	0.000258721	0.008330353
pms1	179.9313377	1.537828319	2.903571013	0.502480158	3.060475711	0.002209857	0.033348539
pnhd	995.809322	1.095193544	2.136417406	0.354060178	3.093241237	0.001979831	0.031213109
pnpla3	182.9770674	0.917980398	1.88946841	0.329885901	2.782720921	0.005390515	0.059992824
pofut2	609.4656817	0.607686563	1.523813734	0.224225982	2.71015231	0.006725232	0.068061628
pogz	3306.484304	-0.499170493	0.707513463	0.128693393	-3.878757745	0.000104991	0.004761535
pold3	297.2019048	-0.821924434	0.56568686	0.232603174	-3.533590788	0.000409955	0.010914776
pole	629.7658918	-0.48401328	0.714985912	0.190033596	-2.546987952	0.010865718	0.090591518
poli	402.1322452	0.970449551	1.959451075	0.326433903	2.972882239	0.002950176	0.040198583
polk	169.7076172	1.192309962	2.285183411	0.461145782	2.585538044	0.009722714	0.084828775
polr1a	1190.002071	-0.729209825	0.603234219	0.179756247	-4.056659158	4.98E-05	0.002937405

polr3b	491.88823	-1.059625869	0.479756458	0.362420957	-2.923743363	0.003458498	0.045168449
polr3e	783.7855305	-0.430521257	0.741993649	0.163412005	-2.634575446	0.008424258	0.077870523
polr3g	174.0812432	0.870792652	1.82866734	0.3285522	2.650393611	0.008039804	0.0761674
polrmt	416.2056546	-0.721871484	0.606310418	0.256250913	-2.817049412	0.004846707	0.055787294
pon2	250.653438	1.119562897	2.172811314	0.32964589	3.396259234	0.000683136	0.015101072
pop4	967.7044942	0.808343821	1.751199953	0.268702613	3.008321396	0.002626952	0.037453491
post	66.20577059	1.165328909	2.242843426	0.463263858	2.515475549	0.011887192	0.095686603
ppap2c	3670.168222	0.495594693	1.409901811	0.138245118	3.584898338	0.00033721	0.009989832
ppapdc3	44.84394725	-1.420431687	0.373600506	0.564776906	-2.515031461	0.011902176	0.095700646
ppat	1537.630894	-0.730052869	0.60288182	0.23848261	-3.061241533	0.002204212	0.033298113
ppef2	7.200371512	2.185314351	4.548258812	0.874832676	2.497979799	0.012490331	0.098478085
ppif	482.2633569	0.64795252	1.566942804	0.191160337	3.389576148	0.000700008	0.015287025
ppme1	380.3677195	-0.820471508	0.566256846	0.309282427	-2.65282291	0.007982174	0.07587001
ppp1r10	2526.493844	1.422635332	2.680747488	0.411249156	3.459302735	0.000541576	0.013035292
ppp1r13b	513.2895564	-0.947729927	0.518447595	0.301659586	-3.141719914	0.001679586	0.027821994
ppp1r14c	1743.439302	0.842061162	1.792609394	0.226332662	3.720457994	0.000198862	0.007063748
ppp1r16b	209.8692978	-1.307046597	0.404147381	0.300003285	-4.356774276	1.32E-05	0.001126691
ppp1r3c.2	4904.290772	1.285413035	2.437518274	0.383327708	3.353300604	0.000798539	0.016734325
ppp1r8	2364.148783	0.407999856	1.326845008	0.141891479	2.875435919	0.0040347	0.049721566
ppp1r9b	88.09451638	-0.890924835	0.539268311	0.318535335	-2.796941929	0.00515888	0.058176236
ppp2r2d	1243.492206	0.616241107	1.532876117	0.230367353	2.675036628	0.007472109	0.072989375
ppp3cb	274.0630414	-0.802388065	0.573399255	0.203504127	-3.942858932	8.05E-05	0.004113145
ppp4r1l	1795.500963	-0.350594429	0.784260895	0.106526179	-3.29115745	0.000997761	0.019335957
pqlc3	162.5102503	0.636659428	1.55472501	0.232424215	2.73921299	0.006158646	0.064858129
prcp	1500.225216	-0.358487132	0.779982072	0.138347033	-2.591216614	0.009563727	0.084066354
prdm13	24.71199587	-2.017999646	0.246900276	0.653861271	-3.086281046	0.002026772	0.031675462
prdm6	23.40776451	1.618453895	3.070458055	0.517070568	3.130044513	0.001747798	0.028648433
prdx2	161.4429798	-1.468218713	0.361428277	0.437541962	-3.355606638	0.000791911	0.016664716
prdx6	2892.118339	0.619573724	1.536421144	0.204367	3.031672058	0.002432033	0.035551891
preb	119.8580484	-1.421484251	0.373328033	0.452513864	-3.141305413	0.001681965	0.027821994
prep	1094.759811	1.017388711	2.024251731	0.247864978	4.10460857	4.05E-05	0.00256802
prex1	524.8242483	-0.605369971	0.657302797	0.205983507	-2.938924476	0.003293533	0.043683128
prkar1a	768.0922696	-0.898314528	0.536513163	0.2087971	-4.302332393	1.69E-05	0.001352704
prkar2b	35.43542886	1.622068311	3.078160187	0.610398372	2.657392919	0.00787476	0.075253736
prkcb	569.3315678	-2.101797678	0.232967776	0.322174889	-6.523778698	6.86E-11	1.98E-07
prkd1	1246.209884	0.3764806	1.29817115	0.131610911	2.86055765	0.004228967	0.051290411
prmt10	394.3877345	0.788611326	1.727410933	0.214929126	3.669169188	0.00024334	0.007995378
prmt2	109.9545964	-0.807892759	0.571215582	0.318067201	-2.540006505	0.011085041	0.091621584
prmt3	376.5295454	-1.021401205	0.49263765	0.362660367	-2.816412539	0.004856326	0.055853548
prosapip1	11.3683622	-2.592438309	0.165805261	0.712085813	-3.640626258	0.000271976	0.008622703
prph2	8.336278982	3.123335482	8.714002229	1.032223459	3.025832687	0.002479495	0.035953916

prrc1	1195.275913	-0.514286148	0.700139279	0.183457953	-2.803291657	0.00505839	0.057627382
prrc2a	862.453212	-0.391929627	0.762109589	0.118074444	-3.319343413	0.000902294	0.017942866
prune	135.7534383	-0.643140001	0.64031779	0.220684251	-2.914299496	0.003564877	0.045961848
prx	78.68832341	-1.199400229	0.435456276	0.467679407	-2.56457781	0.010330141	0.088473255
psmc3ip	296.8176216	0.851148876	1.8039369	0.334327077	2.545856839	0.010900988	0.09078087
psmd13	1208.368513	-1.013996059	0.495172789	0.388427026	-2.61051881	0.0090405	0.080827773
psme1	180.4919156	0.826108635	1.772896893	0.313821339	2.632417022	0.008477973	0.078017858
psme2	102.4158951	1.049568374	2.069910479	0.291813424	3.596710391	0.000322267	0.009666002
ptbp2	652.9304373	0.627384842	1.54476228	0.210523499	2.980117871	0.002881375	0.039596993
ptdss1	468.8209088	-1.066254975	0.47755706	0.21888696	-4.871258547	1.11E-06	0.000232338
pter	71.12863399	2.025003927	4.069929846	0.52024135	3.892431709	9.92E-05	0.004656593
ptgis	23.66101798	1.868377242	3.651216565	0.543195798	3.439601796	0.000582571	0.013653625
ptgs2	1381.874296	1.429203779	2.692980491	0.376920692	3.791789118	0.000149566	0.005893093
pth1r	39.21250412	-1.54183025	0.343449467	0.605136345	-2.547905545	0.010837181	0.090484182
ptk2	1529.479832	-0.465287386	0.724326776	0.181586529	-2.562345285	0.01039679	0.088716044
ptk2b	915.9153714	-0.929376884	0.525085083	0.339807627	-2.735008895	0.006237859	0.065293051
ptpn23	1486.661981	-0.6681698	0.629304516	0.197043427	-3.390977362	0.000696439	0.01525517
ptprg	989.0740493	-0.882295277	0.54250364	0.235304517	-3.749589213	0.000177124	0.006582873
ptprn	64.56326573	-1.059030339	0.479954537	0.380839191	-2.780780877	0.005422833	0.060075013
ptprn2	573.7079179	-0.535112723	0.690104754	0.211346672	-2.53191932	0.011344009	0.093068036
ptprs	1517.278198	-0.77924734	0.582670696	0.277463671	-2.808466196	0.004977811	0.056798904
ptpru	740.4692554	-0.670727773	0.628189715	0.252901873	-2.652126556	0.007998655	0.07588213
ptrf	39.42274978	-2.441053796	0.184149094	0.752541043	-3.243748388	0.001179679	0.021808977
puf60	2824.587786	-0.505658101	0.704339013	0.194299536	-2.60246685	0.009255576	0.082242081
pvrl2	4627.837445	-0.424656537	0.745016077	0.133962199	-3.16997288	0.001524532	0.025960135
pygl	462.2202959	1.13571845	2.197279582	0.442467054	2.566786478	0.01026458	0.088172923
qrsl1	107.1862611	0.73937844	1.669456428	0.292075098	2.531466891	0.011358654	0.093068036
qser1	986.5926182	0.693488903	1.617189681	0.262451936	2.642346301	0.008233382	0.077118905
qsox1	506.9924561	1.293309318	2.450896087	0.366080047	3.53285935	0.000411091	0.010924898
qsox2	2653.233374	-0.475503616	0.719215683	0.149092895	-3.189311031	0.001426123	0.024780609
rab12	280.8673108	1.463486733	2.75774055	0.258520621	5.6610058	1.50E-08	1.04E-05
rab14	2792.964715	-0.421376497	0.746711836	0.162284975	-2.596521931	0.009417289	0.083218675
rab15	207.8887126	0.895234174	1.859911756	0.308116701	2.905503566	0.003666627	0.046621304
rab20	135.1021397	1.151021429	2.220710652	0.43131223	2.668650109	0.007615674	0.073839017
rab25	1494.883854	-1.124481211	0.458666927	0.438261105	-2.565779165	0.010294435	0.088324416
rab2b	2420.714736	0.528667208	1.442595879	0.152746805	3.461068844	0.000538035	0.013007316
rab31	102.7469196	1.121379819	2.175549464	0.376470822	2.978663291	0.002895087	0.039747651
rab3gap1	450.9799549	-1.092289985	0.469016315	0.288985679	-3.779737415	0.000156994	0.006068609
rab3gap2	259.7315306	-1.03696732	0.487350855	0.226409928	-4.580043508	4.65E-06	0.000574424
rab3ip	613.8660021	0.450974602	1.366963387	0.174058168	2.590941908	0.009571365	0.084066354
rabggta	313.2393148	-0.800089169	0.57431368	0.303352496	-2.637489984	0.008352209	0.077797881

raf1	2078.502241	0.461491442	1.376964573	0.18469531	2.498663558	0.01246626	0.098429668
ralbp1	2872.837853	0.733868709	1.663092842	0.222622598	3.296469969	0.000979081	0.019112893
ralgapa1	1026.168098	-0.742948298	0.597517015	0.27877675	-2.665029623	0.007698154	0.074244306
ranbp1	5591.153036	0.596089798	1.511614013	0.205474254	2.90104374	0.00371922	0.04712424
rarg	5295.254357	0.482127025	1.396801511	0.184189102	2.617565426	0.008855951	0.079802837
rasip1	21.186549	1.560974674	2.950531119	0.597049439	2.614481434	0.008936302	0.080293421
rasl11a	70.04486413	2.116213278	4.335544757	0.615337956	3.439107337	0.000583636	0.013653625
rbl2	180.2253015	1.132531204	2.192430642	0.409147433	2.768027151	0.005639676	0.061534183
rbm14	5008.578671	0.696948042	1.621071856	0.150115958	4.642731192	3.44E-06	0.000464561
rbm23	267.8943687	-1.612684152	0.326989417	0.594268019	-2.713732023	0.006652996	0.067594028
rbm24	3333.212345	1.004651708	2.006459043	0.258555586	3.88563141	0.000102064	0.004722737
rbm46	9.237734715	-1.756281333	0.296010174	0.665470349	-2.639157906	0.008311226	0.077619762
rbms1	1231.227575	0.867153468	1.824060357	0.328759385	2.637653881	0.008348174	0.077797881
rbpms2	608.4703338	0.903535384	1.870644463	0.252535291	3.577857899	0.000346422	0.010138094
rcan1	4000.767822	0.612495365	1.528901396	0.218681577	2.800854898	0.005096743	0.05779107
rcc2	4189.966476	-0.568233746	0.674441985	0.222784918	-2.550593415	0.01075397	0.090232237
rcn1	629.9141992	-0.637600361	0.6427812	0.243533608	-2.618120618	0.008841555	0.079739461
rcor2	2134.083221	-0.64594203	0.63907536	0.232267314	-2.781028542	0.005418697	0.060075013
rcor3	222.8489431	0.803011077	1.744738807	0.223956977	3.585559549	0.000336356	0.009985015
rdh10	2838.785947	0.618025646	1.534773378	0.169795247	3.639828899	0.000272819	0.008623433
recql4	279.2993788	-1.682375218	0.311569255	0.545561527	-3.083749741	0.002044095	0.031775781
reep1	26.43445104	-1.70687977	0.30632186	0.508837498	-3.354469307	0.000795174	0.016709051
reep6	504.9047012	3.059434515	8.336457851	0.463304464	6.603507522	4.02E-11	1.94E-07
rexo2	1610.537438	0.587789892	1.50294258	0.207081087	2.838452802	0.004533282	0.053587623
rfc4	449.9069408	0.963848521	1.950506115	0.326485985	2.952189575	0.003155291	0.04215901
rfc5	377.6521641	0.767742549	1.702603557	0.2978306	2.577782635	0.009943653	0.086132645
rffl	1657.444401	0.467312272	1.382531423	0.185685214	2.516690814	0.011846273	0.095570076
rfng	627.8983314	0.356462723	1.28028298	0.14201271	2.510076203	0.012070511	0.096624241
rfx7	1258.667196	0.69506619	1.618958708	0.230287265	3.018257178	0.002542331	0.036498979
rfxank	316.3897999	1.295679243	2.454925499	0.378559307	3.422658538	0.000620119	0.014119158
rgs16	274.2957925	2.070212072	4.199484	0.578593653	3.578006881	0.000346224	0.010138094
rgs7bp	192.5902797	1.195974094	2.290994657	0.469367876	2.548052721	0.01083261	0.090484182
rhof	618.4513439	0.641320213	1.559755842	0.196605524	3.261964363	0.001106431	0.020800606
rhou	1137.668732	0.447893578	1.36404721	0.177716048	2.520276485	0.011726269	0.095026157
rimkla	8.638371281	2.972807535	7.850625116	1.050157948	2.83081944	0.004642892	0.054262162
riok3	1203.68453	1.18494418	2.273545978	0.397219747	2.98309485	0.002853495	0.039438799
ripk4	2555.00719	0.882695118	1.843816544	0.335935225	2.627575358	0.008599579	0.078692293
ripply2.2	777.4698172	0.795002135	1.735079942	0.315514201	2.519703177	0.011745383	0.095127735
rmi1	268.1602173	0.81357389	1.757559938	0.27849708	2.921301327	0.003485725	0.045416463
rmnd5a	2587.924606	0.38386899	1.304836451	0.152099051	2.523809238	0.011609091	0.094394051
rnf138	181.7674742	1.639825064	3.116280428	0.499253666	3.284552874	0.001021443	0.019636976

rnf151	14.60650906	3.119412244	8.690337723	0.751095333	4.15315088	3.28E-05	0.002184728
rnf180	71.48717368	1.912035757	3.763397703	0.574302162	3.329320142	0.000870583	0.017610537
rnf20	655.6720299	-0.800547071	0.574131425	0.28869909	-2.772946288	0.005555129	0.060841287
rnf220.2	58.52191198	0.741630371	1.67206435	0.291519552	2.544015889	0.01095861	0.090894219
rnpep	813.0234528	1.269565502	2.410889457	0.256291826	4.953593418	7.29E-07	0.000157204
rnps1	6340.661085	0.590035946	1.505284253	0.18649566	3.163805244	0.00155721	0.026361334
rp9	515.5750498	0.88699708	1.849322813	0.220162165	4.028835193	5.61E-05	0.003128846
rpap1	690.9542879	-0.405920957	0.754754335	0.151858233	-2.673025676	0.00751705	0.073235959
rpf2	2109.52663	0.439742115	1.356361853	0.161179178	2.728281162	0.006366532	0.066081671
rpl22l1	8087.270548	0.582827815	1.497782164	0.208559013	2.794546287	0.00519726	0.05842674
rpp38	554.0022953	0.54536641	1.459390947	0.152227551	3.582573632	0.000340226	0.010038046
rrm2.2	9204.974519	0.871600245	1.829691279	0.342571339	2.54428829	0.010950067	0.090891619
rrp12	1873.776463	-0.797899934	0.575185841	0.265431505	-3.006048339	0.002646669	0.037660331
rsf1	2091.711815	0.838591293	1.788303116	0.295354693	2.83926856	0.004521708	0.053494548
rspo3	318.5457454	0.872841786	1.831266536	0.291600429	2.993280182	0.002759962	0.038663544
rsrc1	1087.443914	0.495179378	1.409495994	0.185280377	2.672594834	0.00752671	0.07327518
rtel1	257.5163856	-1.107600159	0.464065336	0.348561846	-3.177628796	0.001484847	0.02549458
rtn4ip1	104.765867	0.733879852	1.663105688	0.28619679	2.564249073	0.010339931	0.088504671
rttn	279.0382592	-0.950063047	0.517609841	0.339848761	-2.795546592	0.005181203	0.058291561
rufy2	37.81290596	1.201155546	2.299237577	0.435303637	2.759351046	0.005791628	0.062484754
rundc3b	113.4885922	-0.819292528	0.566719784	0.297452664	-2.754362723	0.005880655	0.062975285
samd4b	1066.946447	-0.536005952	0.689677616	0.140874124	-3.804857386	0.000141886	0.005729734
sap130	1250.208751	-0.956711247	0.515230089	0.311330704	-3.072974284	0.002119368	0.032388685
sar1a	3132.768737	0.454297307	1.3701153	0.152987911	2.969498078	0.002982867	0.040377626
sars2	95.51885595	-0.831603847	0.561904225	0.333957596	-2.490148017	0.01276899	0.099690142
sart3	1580.875813	-0.488467067	0.712782061	0.166836969	-2.92781073	0.003413578	0.044822973
sass6.2	407.6889087	-0.459783205	0.727095512	0.180716314	-2.544226335	0.010952009	0.090891619
sbf1	2299.151323	-0.439510778	0.737384616	0.163433928	-2.689226056	0.00716179	0.071013718
sbf2	588.4033817	-0.798310263	0.57502227	0.260124957	-3.068949146	0.002148132	0.032724487
scarb1	569.0583025	0.52792057	1.441849486	0.212024013	2.489909346	0.012777568	0.099690142
scfd1	577.7564111	-0.509624001	0.702405477	0.174633382	-2.91825076	0.003520012	0.045685419
scn1a	54.95588251	-1.260114762	0.417510747	0.470253879	-2.679647776	0.007369966	0.072340525
sco2	381.5327834	-0.54425736	0.685744305	0.168660512	-3.226940041	0.001251217	0.022611051
scrib	781.7823565	-1.04798034	0.483644756	0.218543299	-4.79529843	1.62E-06	0.000293536
sdf2l1	243.9686654	1.001030702	2.001429366	0.333403816	3.00245724	0.002678096	0.037925941
sdhd	321.7437853	0.634988296	1.552925152	0.176389625	3.59991862	0.000318317	0.009587304
sdr16c5	392.3064895	1.799584381	3.481199228	0.362986575	4.95771608	7.13E-07	0.000156238
sec23a	411.2177242	-1.412442656	0.375675085	0.293564583	-4.811352379	1.50E-06	0.00027434
sec24a	4260.735947	-0.707727884	0.612283672	0.18892061	-3.746165559	0.000179558	0.006605271
sec24c	697.0728214	-0.916721787	0.529711308	0.345317235	-2.654723521	0.007937343	0.075543235
sec31b	534.6323336	-0.645519889	0.639262385	0.210012809	-3.073716757	0.0021141	0.032342381

sema3f	1638.83303	-0.640357293	0.641554044	0.24691146	-2.593469303	0.009501302	0.083858562
sema5b	281.0666894	-1.403382189	0.378041838	0.507717374	-2.764101172	0.005707984	0.061998739
senp5	1089.280839	0.439709584	1.356331269	0.135322425	3.249347495	0.001156701	0.021494118
senp6	712.5921489	0.820115011	1.765546735	0.176264834	4.652743221	3.28E-06	0.000450987
sept.11	554.8684738	0.779671217	1.716739591	0.226217413	3.446557032	0.000567779	0.013478451
sept.5	341.2135179	-0.788363999	0.5790003	0.275118145	-2.865547089	0.004162894	0.050773929
serpinf2	3710.000235	0.867432825	1.824413593	0.340018033	2.551137707	0.010737189	0.090192094
sesn2	1663.47625	0.532777346	1.446711594	0.149855692	3.555269337	0.000377592	0.010569452
setdb1	1434.147991	-0.559657033	0.678463434	0.150223413	-3.725498059	0.00019493	0.00699281
sftpb	143.0104216	1.667160982	3.175890084	0.47598236	3.502568837	0.000460795	0.011728361
sfxn4	123.6796262	1.652844768	3.144530803	0.508103917	3.252966005	0.001142072	0.021249587
sgk1	1225.076613	0.487730362	1.40223715	0.194994425	2.501252859	0.012375478	0.098087879
sh2d4a	360.9942624	0.437115664	1.353894819	0.160102596	2.730222214	0.006329165	0.06592272
sh3bp4	2921.55978	0.644296023	1.56297643	0.207235669	3.109001576	0.001877207	0.030279907
sh3bp5l	402.6046132	0.798422919	1.739198883	0.262523169	3.041342678	0.002355256	0.034887231
sh3glb2	124.9208312	-0.99209172	0.502748327	0.279511952	-3.549371371	0.000386152	0.010633525
shc1	996.892642	-0.839787128	0.558726004	0.239545527	-3.50575166	0.00045532	0.011650547
she	99.4247174	1.134814011	2.195902519	0.430252775	2.637551872	0.008350685	0.077797881
sigmar1	70.55612174	-1.144404839	0.452376271	0.324855062	-3.5228167	0.000426987	0.011203166
sil1	167.7325231	0.896324315	1.861317689	0.31020096	2.88949562	0.003858604	0.048263535
six3	422.4210449	-1.106543043	0.464405498	0.278963986	-3.966616117	7.29E-05	0.003818548
ska1	391.1734577	-0.879776455	0.543451632	0.238090066	-3.695141385	0.000219764	0.007600801
slc16a6	63.34040559	1.351544613	2.551851917	0.475339256	2.843326312	0.004464534	0.053166196
slc1a6	183.2870617	1.427144325	2.689138992	0.415029273	3.438659437	0.000584602	0.013653625
slc20a2	156.2273086	-0.937216689	0.522239437	0.34523712	-2.71470428	0.006633497	0.067535544
slc22a13	48.49146549	7.258738636	153.1433208	1.538722622	4.717379554	2.39E-06	0.000386065
slc22a4	1448.353935	-1.431368636	0.37077898	0.414697108	-3.451600232	0.000557273	0.013316515
slc24a1	8.874312124	3.164935284	8.968926293	1.045370139	3.027573838	0.002465255	0.035890622
slc24a3	219.015734	-1.363209656	0.388716525	0.534392753	-2.550950864	0.010742947	0.090192094
slc24a5	303.4688788	0.826230723	1.77304693	0.315014996	2.622829815	0.008720282	0.079189143
slc24a6	828.6016754	0.547786424	1.461841022	0.216751219	2.527258794	0.011495676	0.093776717
slc25a17	2057.99807	0.816606325	1.76125808	0.3206568	2.546667727	0.010875693	0.09062242
slc25a47	27.39406193	1.428286786	2.691269348	0.444592045	3.212578366	0.001315493	0.023414673
slc28a2	7.792773914	2.361372377	5.138589398	0.850543363	2.776310392	0.005497969	0.060536285
slc2a11	24.12916133	-1.978035751	0.253835235	0.664553535	-2.976488193	0.002915703	0.039954805
slc2a9	221.396191	1.693011216	3.233308612	0.353748843	4.78591309	1.70E-06	0.000303796
slc35f3	112.9101491	5.862382314	58.17721436	1.808801835	3.24103072	0.001190983	0.021961796
slc38a6	579.2028919	-1.131340379	0.456491411	0.257778454	-4.388808926	1.14E-05	0.000998612
slc38a8	2060.241339	0.450688775	1.366692591	0.173300527	2.600619756	0.009305553	0.082537369
slc39a9	1712.517695	-0.64956166	0.637473971	0.246872405	-2.631163492	0.008509309	0.078256412
slc6a20	10.41964976	2.802035753	6.97423875	0.809509243	3.461400566	0.000537373	0.013007316

slc6a3	98.37221667	-1.660711959	0.316283027	0.547058686	-3.035710796	0.002399694	0.035292348
slc7a2.1	481.5521127	1.111096672	2.160097859	0.369612	3.006116343	0.002646077	0.037660331
slc7a9	141.0488572	3.038666668	8.217312698	0.602189127	5.046033762	4.51E-07	0.000112435
slc9a1	1590.831082	-0.615912451	0.65251707	0.176977648	-3.480170854	0.000501094	0.012468705
slc9a3	403.32218	-1.154599883	0.449190748	0.374689542	-3.081484145	0.002059714	0.031949884
slc9a8	350.4805425	0.581658615	1.496568812	0.227999157	2.551143707	0.010737004	0.090192094
sltm	5478.18836	0.527742223	1.441671254	0.1739218	3.034365002	0.002410426	0.035381395
slx4	823.1430185	-0.684826913	0.622080456	0.209340445	-3.271355004	0.001070335	0.020378342
smad7	1053.619605	0.660654874	1.580800024	0.236267436	2.796216375	0.005170477	0.058261565
smarca4	6410.900808	-0.692613654	0.61873191	0.216475651	-3.199499109	0.001376666	0.024153474
smc1b	17.69253266	2.828429225	7.103003642	1.04103241	2.716946367	0.006588728	0.067364389
smcr7l	2196.063584	0.839808592	1.789812665	0.250771925	3.348893984	0.000811348	0.016821068
smg9	461.4695854	-0.675459185	0.6261329	0.194587216	-3.471241331	0.000518058	0.012747367
smn2	729.2320251	-0.939894137	0.521271129	0.353873358	-2.656018359	0.007906931	0.075379308
smpd3	78.14772939	-1.398264534	0.379385242	0.418167104	-3.343793715	0.000826412	0.016994926
smtnl2	875.024399	-1.230469516	0.426178726	0.365830815	-3.363493357	0.000769627	0.01631451
smu1	3991.296821	0.713837536	1.640161111	0.197759583	3.609622986	0.000306642	0.009372365
snai1	6113.172798	0.928991972	1.903945222	0.230493135	4.030453976	5.57E-05	0.003128846
snap29	635.3212707	0.501192397	1.415382902	0.148143931	3.383144981	0.000716608	0.015555556
snap91	155.8850653	-0.68754967	0.620907529	0.264340513	-2.600999978	0.009295246	0.082537369
sncg	170.1218669	0.980011832	1.972481586	0.362490675	2.703550461	0.006860303	0.069018373
snrpa1	4424.637216	0.558529659	1.472767462	0.196937235	2.836079524	0.004567107	0.053855359
sntb1	21.15770538	-2.482371385	0.178950021	0.82059075	-3.025102811	0.002485486	0.036001452
snw1	6746.611129	0.453558792	1.369414119	0.171904596	2.638433196	0.008329011	0.077735643
snx14	123.190737	0.755535532	1.688258162	0.303132444	2.492427145	0.012687336	0.099426601
sostdc1	89.4106674	-1.070842452	0.476040937	0.372440927	-2.875200806	0.004037706	0.049721566
sox17b.1	4290.832179	0.693422417	1.617115155	0.273043682	2.5396025	0.011097852	0.091628582
sox3	698.9547458	-0.769031322	0.586811349	0.228139496	-3.370882004	0.000749279	0.016024161
sp3	3893.699309	0.609776462	1.526022741	0.189372575	3.219982942	0.001281982	0.022966069
spata5l1	103.7316672	-1.22335077	0.428286833	0.360615144	-3.392399873	0.000692832	0.015222309
spcs3	1207.51039	0.663457057	1.583873435	0.162001868	4.095366707	4.22E-05	0.002649407
speg	172.3664242	-1.484347603	0.357410122	0.519799497	-2.855615698	0.004295347	0.051877887
spns1	723.2165055	-0.764462695	0.588672568	0.242569988	-3.151513931	0.001624264	0.027209718
spred3	38.39730739	1.714738388	3.282371171	0.480068403	3.571862629	0.000354451	0.010153288
spry1	1790.442076	0.560581197	1.474863254	0.186736934	3.001983507	0.002682267	0.037942794
spryd7	1198.043311	0.701958671	1.626711795	0.202295712	3.469963168	0.00052053	0.012776398
sptbn4	334.1659421	-0.613119368	0.653781578	0.236886286	-2.588243412	0.009646679	0.084368437
srbd1	567.8863754	-0.830854461	0.562196174	0.225775437	-3.680003782	0.00023323	0.007869936
srebf1	125.234425	-1.02273588	0.492182109	0.273522201	-3.739132972	0.000184656	0.006724364
srgap2	848.1900169	0.749148471	1.68080047	0.248714562	3.01208126	0.002594631	0.037065795
srgap3	200.2035058	-1.007998136	0.497235727	0.398205177	-2.531353672	0.011362322	0.093068036

srm	2311.302942	-1.346278731	0.393305228	0.321865584	-4.182735899	2.88E-05	0.001964119
srp14	3756.324003	0.726504692	1.654625467	0.204503306	3.552532758	0.000381542	0.010593403
srp19	2042.859497	0.557563825	1.471781826	0.21280592	2.620057864	0.008791485	0.079486239
srp54	4288.697924	0.479729056	1.394481752	0.142679877	3.362275497	0.00077303	0.016359888
srp72	4470.875019	0.548034658	1.462092572	0.193511284	2.832055309	0.004624985	0.054184283
srp9	1434.917943	0.550961492	1.46506177	0.192133309	2.867600079	0.00413598	0.050629855
srpk2	414.9337884	-0.654917779	0.635111686	0.258452488	-2.533996808	0.011276976	0.092631387
srpk3	725.5720256	-0.889662482	0.539740375	0.19498045	-4.562829148	5.05E-06	0.000608024
srsf10	4958.687215	0.532445743	1.446379107	0.171720513	3.100653107	0.001930944	0.03067654
srsf11	5579.979611	0.551174504	1.4652781	0.170635623	3.230125658	0.001237358	0.0224441
srsf12	1502.866231	0.709095677	1.634779069	0.174050987	4.074068695	4.62E-05	0.002821489
srsf4	4250.16524	-0.816574165	0.567788618	0.2357771	-3.463331103	0.000533531	0.01296987
ssr1	5430.600437	0.462945934	1.378353498	0.16487938	2.807785515	0.004988344	0.056874201
st3gal2.2	794.6270767	0.632483166	1.550230956	0.192318799	3.288722524	0.001006432	0.019477893
st3gal4	406.4474611	0.982708561	1.976172056	0.277957911	3.535458144	0.000407069	0.010891503
st6galnac1	17.10892874	2.656619245	6.305537021	0.787664351	3.372780858	0.000744132	0.015937643
st8sia5	8.392690106	4.038595926	16.43381956	1.131907116	3.567957006	0.000359776	0.01023873
stam2	1113.584179	-0.503430015	0.705427628	0.134726036	-3.736694325	0.000186455	0.006755853
stim1	890.2354901	-0.874225805	0.545546545	0.307895247	-2.839361155	0.004520396	0.053494548
stk11ip	912.9783744	-0.790685968	0.578069168	0.191272708	-4.133814891	3.57E-05	0.002333994
stk31	256.9920892	0.854013808	1.807522754	0.332577323	2.56786542	0.010232687	0.088007629
stoml1	410.5718587	0.723714407	1.651428384	0.287424581	2.517928023	0.011804744	0.095394738
stoml3	269.369011	-1.073554919	0.475146755	0.397341752	-2.701842715	0.006895637	0.069229326
stox1	1320.584331	0.56360047	1.477953081	0.202663649	2.78096478	0.005419762	0.060075013
strc	11.96234647	4.912188734	30.11037423	1.099992375	4.465657076	7.98E-06	0.000800783
stx1a	96.47706319	-0.773214883	0.585112165	0.306231713	-2.524934058	0.011572	0.094145416
stx1b	61.84291301	-1.705969884	0.306515113	0.554672139	-3.075636516	0.002100537	0.03223355
sufu	1209.427072	-0.542783808	0.686445074	0.202325896	-2.682720394	0.007302602	0.071867742
sult2b1	56.1124303	3.530006576	11.55148622	0.739997013	4.77029841	1.84E-06	0.000309234
sult6b1	92.50681916	1.25030312	2.378914003	0.481134944	2.598653734	0.009359013	0.082855632
sumo1	1205.081885	0.481814758	1.396499211	0.166660272	2.890999477	0.003840188	0.048192354
suox	639.9744359	0.720356955	1.647589635	0.288279767	2.498812047	0.012461038	0.098429668
suv420h1	958.7619153	0.520548287	1.434500317	0.198291119	2.625171973	0.008660521	0.079012149
svep1	12.95523549	-1.482322719	0.357912114	0.520782889	-2.846335297	0.00442256	0.052840455
sycp2l	223.3645461	1.374725654	2.593185937	0.363108253	3.785993966	0.000153095	0.005949731
syn2	383.92499	-1.122992766	0.459140383	0.348489834	-3.222454883	0.001270972	0.02282539
syngap1	212.775387	-0.722991371	0.605839954	0.278923373	-2.592078832	0.009539791	0.084044337
sys1	883.8357202	0.569398482	1.483904742	0.169968117	3.350031136	0.000808025	0.016806294
syt13	102.2191302	2.451090704	5.468293597	0.756614752	3.239549187	0.001197188	0.02198837
szl	478.7507381	1.001612627	2.002236826	0.325339781	3.078666323	0.002079294	0.032081491
szt2	407.0626742	-0.74435312	0.596935467	0.244889056	-3.039552408	0.0023693	0.035023483

t	3227.408328	0.914195904	1.88451843	0.237766181	3.844936658	0.000120584	0.005240191
taf1	1326.548578	-0.436629866	0.738858567	0.149657303	-2.917531313	0.003528142	0.045704617
taf12	649.7401844	0.623712306	1.540834922	0.237381315	2.627470095	0.00860224	0.078692293
taf1a	399.6169576	-0.460095469	0.726938152	0.180972314	-2.542352805	0.011010897	0.091170982
taf4	1573.272139	0.576430661	1.491155447	0.210300614	2.740984207	0.006125545	0.064782009
taf4b	423.5874123	1.121424392	2.175616681	0.385442369	2.909447645	0.00362068	0.046281321
tamm41	21.67648862	-1.572870431	0.336138936	0.467849124	-3.361918088	0.000774031	0.016359888
tasp1	111.1309616	0.869639368	1.827206094	0.323752807	2.68612148	0.00722868	0.071247675
tax1bp3	2051.293892	-0.380986159	0.767912502	0.130203556	-2.926081064	0.003432615	0.045032044
taz	1651.921297	0.976216355	1.967299154	0.299471544	3.259796709	0.001114921	0.020905852
tbc1d23	709.8173939	-0.771424385	0.585838786	0.219910848	-3.507896008	0.000451666	0.011618735
tbx2	952.9257866	0.560403954	1.47468207	0.218360705	2.566413925	0.010275612	0.088215279
tcta	128.0795684	1.133222247	2.193481056	0.337197897	3.360703779	0.000777442	0.016384071
tdgf1	1593.780711	3.483027526	11.18138911	0.643001136	5.416829504	6.07E-08	2.44E-05
tdgf1p2	224.872841	0.857716717	1.81216801	0.237287862	3.614667473	0.000300733	0.009289962
tdgf1p3	444.9310804	3.076553359	8.435966459	0.659346234	4.666066477	3.07E-06	0.000443859
tdrd12	147.8765232	1.498769733	2.826016195	0.483222865	3.101611788	0.001924702	0.030672338
tdrd5	215.0852027	1.082377535	2.117522846	0.29624847	3.653613925	0.000258575	0.008330353
tdrkh	132.1838452	-1.107381711	0.464135608	0.331960276	-3.335886222	0.00085028	0.017386834
tecpr2	197.4439308	-0.6138351	0.653457313	0.21822041	-2.812913328	0.004909488	0.056375275
tef	2764.10863	0.641489591	1.559938975	0.208565271	3.075725836	0.002099908	0.03223355
tes	528.5125928	0.788537664	1.727322737	0.239344557	3.294571118	0.00098572	0.01915397
tex2.2	218.5093898	-0.685141183	0.62194496	0.232865502	-2.942218477	0.003258699	0.043300566
tfap2b	433.5695838	-1.546036333	0.342449621	0.446842857	-3.459910589	0.000540355	0.013035292
tfap4	2661.959058	0.643401159	1.56200726	0.244040398	2.636453495	0.008377768	0.077850012
tgif2	3352.358131	0.662993983	1.583365128	0.1417174	4.678282155	2.89E-06	0.00043574
th	72.23718629	-1.970204846	0.255216791	0.4787226	-4.115545927	3.86E-05	0.002470894
thap5	87.38195152	0.987585404	1.982863552	0.316333013	3.121980198	0.00179639	0.029311979
thbs3	48.71067537	-1.047074243	0.483948608	0.321327968	-3.258584215	0.001119696	0.0209682
thoc7	1671.332867	0.546087689	1.460120756	0.200508419	2.723515003	0.006459128	0.066604576
thsd7b	18.07755036	-1.644052602	0.319956437	0.657473966	-2.500559242	0.012399739	0.098172525
thumpd3	891.9602145	0.394985784	1.314929803	0.142438952	2.773018038	0.005553904	0.060841287
thyn1	298.1135183	1.061215225	2.086688461	0.299878176	3.53882113	0.000401918	0.010869491
tk2	998.5208758	1.059779616	2.084613055	0.285409191	3.713193723	0.00020466	0.007181483
tktl2	759.4250552	-1.284936791	0.410388784	0.354143272	-3.628296487	0.000285298	0.008908307
tlk2	2483.806692	0.588885995	1.504084891	0.184487967	3.1920022	0.001412903	0.024639725
tln2	843.6504406	-0.579155499	0.669355479	0.198945349	-2.911128623	0.003601257	0.046185685
tm6sf2	198.6536216	1.294767492	2.453374532	0.33468288	3.868639751	0.000109444	0.00489856
tmbim1	414.1945826	-1.747746589	0.297766511	0.385283352	-4.53626293	5.73E-06	0.000636773
tmbim4	786.7767936	0.552675781	1.466803671	0.159354633	3.468212815	0.000523932	0.012838115
tmc5	77.82651056	-1.266760903	0.415591801	0.488996944	-2.590529283	0.009582847	0.0841161

tmco7	466.1191032	-0.774847972	0.584450209	0.216985937	-3.570959394	0.000355676	0.010162072
tmed2	4050.068336	0.424810351	1.342396027	0.146121332	2.907243889	0.003646288	0.046527733
tmem132a	423.3889111	-0.587465893	0.665510857	0.234636303	-2.503729752	0.012289186	0.097725393
tmem135	95.27613816	-1.319339393	0.400718385	0.272857626	-4.835266697	1.33E-06	0.000260766
tmem163	96.13884719	-1.903555234	0.267283886	0.658371038	-2.891310711	0.003836386	0.048186477
tmem177	43.28035177	-1.572342577	0.336261945	0.487331145	-3.226435644	0.001253424	0.022622663
tmem185a	724.2144936	0.521668015	1.435614117	0.206469859	2.526606147	0.011517058	0.093856881
tmem186	21.72638469	-1.398542704	0.379312099	0.529019127	-2.643652436	0.008201683	0.077086093
tmem198	464.3729558	-1.107583015	0.46407085	0.420324952	-2.635063682	0.00841215	0.077870523
tmem209	1891.440981	-0.514552966	0.700009804	0.1873735	-2.746135217	0.00603019	0.064054712
tmem214	253.8280363	-0.457063877	0.728467303	0.166829438	-2.739707589	0.006149387	0.064858129
tmem57	439.3235318	-0.793904595	0.576780943	0.317953086	-2.496923701	0.012527591	0.098537204
tmprss4	395.3462355	0.588084406	1.503249424	0.219465893	2.679616395	0.007370657	0.072340525
tmtc2	213.7640281	-0.850174927	0.554717472	0.318931949	-2.665693828	0.007682963	0.074244306
tnfrsf1a	46.00318468	-2.846729326	0.139010973	0.595130695	-4.78336834	1.72E-06	0.000303918
tnik	433.3020396	1.07595761	2.108120903	0.355556721	3.026120857	0.002477133	0.035953916
tns1	126.5616472	-1.922985729	0.263708188	0.561842776	-3.422640301	0.000620161	0.014119158
tomm40l	34.45231087	-2.226510975	0.213674852	0.472568598	-4.711508517	2.46E-06	0.000390641
top1.1	7455.966997	0.597004206	1.512572407	0.21008936	2.841667975	0.00448782	0.053311765
tp53i11	1323.670632	-0.870720845	0.546873536	0.307213336	-2.834254709	0.004593271	0.053943877
tp53inp1	3080.659852	1.695549842	3.239003085	0.459422879	3.690608198	0.000223719	0.00770071
tpcn1	164.7261177	-1.128071947	0.457526767	0.336712003	-3.350257598	0.000807364	0.016806294
tpk1	496.3114208	0.56923089	1.483732373	0.222085377	2.563117387	0.010373697	0.088716044
tpmt	627.8137342	0.564262883	1.478631838	0.196921243	2.865424142	0.00416451	0.050773929
tprkb	203.3652352	0.815970409	1.760481918	0.314390119	2.595407298	0.009447889	0.083438072
tra2a	11791.95514	0.495983385	1.410281718	0.198134764	2.503262807	0.012305413	0.0977469
tra2b	2594.141664	0.766227922	1.700817	0.241789447	3.168988274	0.001529706	0.026017594
tradd	89.76744379	-1.022957695	0.492106441	0.404561208	-2.528561006	0.011453118	0.093652561
tram2	1614.78506	-0.405641457	0.754900571	0.134559784	-3.014581658	0.002573339	0.036907506
trappc8	910.9585591	-0.445857782	0.734147685	0.174709624	-2.551993258	0.010710859	0.090184561
trdn	83.98911596	-1.492431919	0.355412932	0.586525392	-2.544530789	0.010942466	0.090891619
treh	76.98417821	1.900052357	3.732267411	0.754720494	2.517557656	0.011817163	0.095441744
trim14	131.6271272	-0.911267777	0.531717636	0.319048671	-2.856203017	0.004287409	0.05182531
trim3	213.1547467	-1.517705051	0.349241026	0.232553126	-6.526272405	6.74E-11	1.98E-07
trim39	38.98566467	3.055692574	8.314863469	0.895133151	3.413673787	0.000640933	0.014410519
trim72	142.006242	-1.0666148	0.477437966	0.329862829	-3.233510136	0.00122279	0.022264326
trip13	609.5221305	0.739990835	1.670165229	0.252582856	2.929695411	0.003392944	0.044592538
trpt1	30.75234122	-1.159742664	0.447592366	0.45274801	-2.561563253	0.010420226	0.088719207
tsnax	1030.590437	0.469492444	1.384622257	0.176247956	2.663817814	0.007725939	0.07442809
tspan1	496.695837	1.074104873	2.105415352	0.21156301	5.076997512	3.83E-07	9.90E-05
tspan15	1013.067159	0.791833508	1.731273324	0.292134288	2.710512052	0.006717941	0.068059754

tspan3	2245.916178	0.346583811	1.271546138	0.130632529	2.653120279	0.007975145	0.07585307
tspan32	15.6845434	-1.601446994	0.329546284	0.556707005	-2.876642432	0.004019308	0.049621802
ttc17	460.1440712	-0.731733806	0.60217979	0.187514521	-3.902278085	9.53E-05	0.004522868
ttc21b	217.3774363	-0.958660001	0.5145346	0.350936613	-2.731718394	0.006300497	0.065718818
ttc35	1253.359173	-0.63341041	0.644650713	0.155484254	-4.073791351	4.63E-05	0.002821489
ttc9b	9.486265053	2.314411237	4.974016305	0.830622846	2.786356343	0.005330424	0.059491675
ttl	359.1176062	-0.710502911	0.611107075	0.207008815	-3.432235047	0.000598628	0.013869186
ttr	8.031611184	-1.85059009	0.277278932	0.683187609	-2.708758277	0.006753552	0.068241735
ttyh2	877.5303639	0.669513207	1.5905362	0.243391572	2.750765783	0.005945614	0.063576729
tuba4a	2058.898242	1.300401761	2.46297462	0.226048876	5.752745971	8.78E-09	6.35E-06
tulp4	1127.104906	-0.863783864	0.549509427	0.215218737	-4.013516087	5.98E-05	0.003313529
twf1	1154.452955	0.60458465	1.520540928	0.204067522	2.962669629	0.003049837	0.041130126
txnip	166.6365189	1.415937589	2.668330905	0.401931221	3.522835538	0.000426956	0.011203166
tyrp1	610.9455622	1.541665366	2.911303742	0.353976321	4.355278231	1.33E-05	0.001126691
uba1	2345.879363	-0.738135891	0.599513484	0.205218459	-3.596829917	0.000322119	0.009666002
uba2	1766.83631	0.535810338	1.44975623	0.167968035	3.189954195	0.001422953	0.02475528
uba5	285.3482714	0.608255216	1.524414479	0.209260935	2.90668306	0.003652831	0.046527733
ubac2	219.5309867	0.953509262	1.936577532	0.250695776	3.803451646	0.000142694	0.005746309
ubap2	3696.218868	-0.778899409	0.582811234	0.192695253	-4.042130764	5.30E-05	0.003087717
ube2a	2304.484373	0.387700272	1.308306235	0.115720788	3.35030792	0.000807218	0.016806294
ube2g2	888.9006364	0.551806263	1.465919888	0.155807475	3.541590429	0.000397723	0.010828388
ube3c	462.7465314	-0.482645085	0.715664298	0.145030469	-3.327887502	0.000875072	0.017619659
ubfd1	673.9974052	0.486034997	1.400590296	0.175918909	2.762835436	0.005730165	0.062053179
ubl7	713.2786148	-0.881100942	0.542952938	0.272376574	-3.234863151	0.00121701	0.022190159
ubn1	398.0745004	-0.606943325	0.656586356	0.23818744	-2.548175187	0.010828808	0.090484182
ubr1	261.2294184	-1.038794822	0.486733905	0.250905948	-4.140176153	3.47E-05	0.002301443
ubr4	1746.82693	-0.643261975	0.640263657	0.176327831	-3.648102344	0.000264184	0.008412586
uchl1	358.1088794	1.31003857	2.479481688	0.386015067	3.393749838	0.000689426	0.015170529
uchl3	146.5731248	1.556806334	2.942018532	0.417783271	3.72634914	0.000194273	0.00699281
uchl5	240.9477702	-1.19189836	0.437726502	0.220759437	-5.399082266	6.70E-08	2.62E-05
uck1	89.14169698	-0.842781712	0.557567466	0.336863275	-2.50185097	0.012354592	0.097976048
ugdh	2120.849156	-0.710973684	0.610907694	0.225830705	-3.148259595	0.001642458	0.027398429
ugt1a1	84.81799925	-1.92202948	0.263883037	0.500072281	-3.843503338	0.00012129	0.005249984
ulk2	239.6362185	0.894820313	1.859378286	0.278636164	3.211429201	0.001320765	0.023414673
unc93b1	38.7774305	1.358322177	2.563868338	0.443516965	3.062616057	0.002194114	0.033212342
unk	239.4677779	0.698106731	1.62237433	0.277795728	2.513021838	0.011970192	0.096087214
uqcrc2	484.4128796	1.117472173	2.169664802	0.303564165	3.681172882	0.000232164	0.00786207
uqcrfs1	8332.969366	0.633157589	1.550955818	0.205799762	3.076571049	0.002093964	0.03223355
urb1	952.7150042	-0.53937701	0.688067969	0.169440452	-3.18328359	0.001456149	0.025181278
urod	99.80620448	0.9813147	1.974263698	0.33170045	2.958436444	0.00309204	0.041467182
usp12	365.3503474	-1.013421964	0.495369873	0.365004673	-2.776462986	0.005495389	0.060536285

usp13	529.4000015	-1.076172634	0.474285401	0.280819766	-3.832253861	0.000126975	0.005419324
usp24	1854.229442	-0.814885976	0.568453413	0.23313958	-3.495270845	0.000473581	0.011969509
usp25	3006.997643	-0.8396739	0.558769856	0.244772916	-3.430419975	0.000602648	0.013917696
usp30	167.8492062	0.688385981	1.611479662	0.254545918	2.704368574	0.006843434	0.068944612
usp40	201.448161	0.673899459	1.595379295	0.23250796	2.898393065	0.003750802	0.047399775
usp5	1018.837379	-0.590936483	0.663911809	0.181436205	-3.256993186	0.001125991	0.021004461
usp54	1518.478751	-0.721974043	0.606267317	0.233183592	-3.096161429	0.001960436	0.031008778
uspl1	1555.709005	-0.502348275	0.705956759	0.201127663	-2.497658784	0.012501646	0.098493897
vamp3	1421.855317	0.549988908	1.464074439	0.199671551	2.754468051	0.005878763	0.062975285
vav2	397.0669651	-0.766633416	0.5877875	0.200384612	-3.825809808	0.000130343	0.005465434
vax2	83.95831291	-1.553416183	0.340702353	0.571350342	-2.718850534	0.00655092	0.067129347
vdac2	2104.532139	0.462566137	1.377990686	0.173281126	2.669454817	0.007597449	0.073765162
vdac3	509.5743259	-0.869879103	0.547192703	0.338242992	-2.571757947	0.010118361	0.087227872
vegt	12006.9323	1.564514407	2.9577793	0.312823381	5.001270698	5.70E-07	0.000130695
velo1	515.2255045	1.436977447	2.707530232	0.330082155	4.353393319	1.34E-05	0.001126691
ventx1.2	857.7526775	1.167256778	2.245842535	0.352054619	3.315555928	0.00091461	0.018099427
ventx2.1	2422.147508	1.450408203	2.732853652	0.304742012	4.759462586	1.94E-06	0.000321733
ventx2.2	1989.452351	1.028811162	2.040342235	0.41150609	2.500111634	0.012415418	0.09818911
ventx3.1	274.9623137	2.342337917	5.071237767	0.395498833	5.922490083	3.17E-09	3.06E-06
ventx3.2	533.790991	1.752032607	3.368327944	0.408046318	4.293710127	1.76E-05	0.00138058
vezf1	2138.748694	0.870030785	1.827701901	0.270157232	3.220460836	0.001279847	0.022956259
vill	1294.212573	-0.97434707	0.508970142	0.366050241	-2.661785081	0.007772749	0.074697752
vps16	153.7327062	-0.801666303	0.573686191	0.311102216	-2.576858217	0.009970284	0.086311612
vrk3	886.0198306	1.070119891	2.099607842	0.273186531	3.917176622	8.96E-05	0.004361054
vsig8	816.7239304	-1.005180031	0.498207957	0.306758409	-3.276780693	0.001049979	0.020078763
vta1	581.568588	0.763344765	1.697421392	0.179916916	4.242762612	2.21E-05	0.001603964
vti1a	458.9101647	-1.61656815	0.326110286	0.470636014	-3.43485858	0.000592863	0.013779779
wac	2732.966805	0.711774382	1.637817243	0.232688088	3.058920589	0.00222136	0.033417487
wasl	1071.611951	0.779670381	1.716738597	0.198040939	3.936915181	8.25E-05	0.004179433
wbp1	246.4550486	-0.979845452	0.507034053	0.215274737	-4.55160445	5.32E-06	0.000635771
wbp2nl	978.665753	0.497901154	1.412157647	0.181359816	2.745377467	0.006044133	0.064108611
wdfy4	13.79052108	1.635192063	3.106289006	0.639984714	2.555048625	0.010617296	0.089762722
wdhd1	812.2432036	-0.693603829	0.618307397	0.239143506	-2.900366565	0.003727265	0.047143543
wdr24	334.6588285	-0.877318819	0.544378193	0.227720611	-3.8526105	0.000116865	0.005158149
wdr3	2517.013868	-0.455951121	0.729029389	0.173520208	-2.627654297	0.008597584	0.078692293
wdr33	2223.014007	-0.349331248	0.784947871	0.103007694	-3.391312184	0.000695588	0.01525517
wdr37	153.983712	-0.796239303	0.575848296	0.222854423	-3.572912274	0.000353033	0.010153288
wdr43	3375.263254	-0.475523004	0.719206017	0.142023433	-3.34820103	0.00081338	0.016821068
wdr59	223.0795147	-0.629519339	0.646391737	0.204753783	-3.074518712	0.002108425	0.032289724
wdr6	104.7361349	-1.098290694	0.467069553	0.313524468	-3.503046195	0.00045997	0.01172801
wdr76	607.9743408	1.588867846	3.008131938	0.358105836	4.436866663	9.13E-06	0.000851357

wdr81	207.6192267	-0.784461941	0.580568442	0.305867939	-2.564707967	0.010326268	0.088473255
wdr85	66.61223201	3.02851449	8.15969083	0.712137993	4.252707368	2.11E-05	0.001572132
wdr89	499.6416407	0.585366	1.500419586	0.176167771	3.322775773	0.000891265	0.017871043
wdr91	234.6102344	-0.799836418	0.574414305	0.267210088	-2.993286753	0.002759903	0.038663544
whamm	585.1570185	0.825581626	1.772249381	0.293669579	2.811260294	0.004934785	0.056575877
whsc2	1480.077177	0.803243133	1.74501947	0.278325932	2.885980217	0.003901967	0.048504501
wnk4	81.36300998	-1.037321336	0.487231281	0.40661752	-2.551098475	0.010738398	0.090192094
wnt3a	111.3004068	1.110513883	2.159225445	0.420314289	2.642103569	0.008239286	0.077118905
wnt8a	1047.000145	0.852017373	1.805023191	0.276213239	3.084636256	0.002038012	0.031749509
wrap53	528.5760045	-0.420874883	0.746971506	0.162649043	-2.587625945	0.009663986	0.084418275
wtap	2958.478531	0.504628084	1.418757564	0.177540604	2.842324919	0.004478582	0.053289599
wwox	304.9877235	1.100512286	2.144308212	0.370298221	2.971962119	0.002959032	0.040205568
xbp1	4141.63915	0.483140953	1.39778353	0.169271549	2.854236023	0.004314047	0.052016826
Xetro.A00060	112.3434967	2.328051782	5.021268187	0.659628287	3.529338916	0.000416599	0.011030724
Xetro.A00137	57.02431552	7.306538238	158.3022815	1.307869435	5.586596062	2.32E-08	1.37E-05
Xetro.A00203	513.2227762	-1.377422339	0.384905892	0.438054426	-3.144409139	0.001664226	0.027718563
Xetro.A00297	347.5821733	-0.892443098	0.538701095	0.245211867	-3.639477606	0.000273192	0.008623433
Xetro.A00451	36.45250284	2.635322053	6.213137806	1.018270395	2.588037585	0.009652445	0.084368437
Xetro.A00781	101.699314	1.139370282	2.202848507	0.439645848	2.59156384	0.009554081	0.084066354
Xetro.A00995	58.21861238	1.651314998	3.14119825	0.498325564	3.313727244	0.000920613	0.018132557
Xetro.A01325	45.73865566	1.836536486	3.571515757	0.537906509	3.414229903	0.000639626	0.014403536
Xetro.A01576	94.50191268	1.204243876	2.304164752	0.328918361	3.661224234	0.000251013	0.008173185
Xetro.A01736	58.70920456	-0.924550191	0.526844754	0.360920197	-2.561647142	0.01041771	0.088719207
Xetro.A01754	40.73803484	1.405714092	2.649488916	0.49091721	2.86344431	0.004190625	0.050953626
Xetro.A01761	8.678204682	2.224087854	4.672154083	0.835028508	2.663487334	0.007733532	0.074436536
Xetro.A01984	68.09367234	1.40632121	2.650604113	0.299134061	4.701307524	2.59E-06	0.000401844
Xetro.A02275	175.8018814	0.615688751	1.532289346	0.234291415	2.627875853	0.008591987	0.078692293
Xetro.A02396	33.71561749	2.564131394	5.913988321	0.750122859	3.418281904	0.000630178	0.014279754
Xetro.A02427	19.21824656	2.990485587	7.947414483	0.804657517	3.71647008	0.000202026	0.007141035
Xetro.A02433	84.30284954	1.366194489	2.577896763	0.401955129	3.398873134	0.000676641	0.015026418
Xetro.A02589	74.51238788	-0.801067196	0.573924475	0.243769848	-3.286161944	0.001015626	0.019551139
Xetro.A02620	12.066219	3.633407005	12.40979179	0.898355005	4.044511341	5.24E-05	0.003068886
Xetro.A02756	725.5018586	-0.63081278	0.645812478	0.223787971	-2.818796639	0.004820405	0.055617391
Xetro.A02912	3343.029819	1.014974644	2.020867376	0.261941289	3.874817327	0.000106705	0.004805701
Xetro.A03025	987.8589479	1.399180336	2.637516896	0.409469272	3.417058204	0.000633017	0.014321648
Xetro.A03148	42.49453778	1.853125194	3.612819539	0.523718219	3.538401236	0.000402558	0.010869491
Xetro.A03373	11.15800469	-2.356642027	0.195245063	0.905372804	-2.602952083	0.009242487	0.082242081
Xetro.A03511	28.81829407	-1.760302096	0.295186348	0.496850549	-3.542920699	0.000395722	0.010810866
Xetro.B00081	19645.87778	0.929760662	1.904959943	0.303364604	3.064829084	0.002177944	0.033074096
Xetro.B00147	736.8993703	0.912639918	1.88248702	0.240692046	3.79173276	0.0001496	0.005893093
Xetro.B00151	9.083117465	5.488504367	44.89566882	1.429678509	3.838978016	0.000123547	0.005315851

Xetro.B00166	278.6942928	-1.112181463	0.462594025	0.442079085	-2.515797515	0.011876339	0.095686603
Xetro.B00579	43.0815582	2.088196286	4.252161187	0.531624453	3.927953789	8.57E-05	0.00427088
Xetro.B00587	711.702062	-0.578509719	0.669655164	0.194059886	-2.981088628	0.002872257	0.039546869
Xetro.B00597	2296.342273	-0.691211293	0.619333636	0.203608011	-3.394813844	0.000686753	0.01515784
Xetro.B00793	8.856150186	3.606824408	12.18322699	1.357299708	2.657352968	0.007875694	0.075253736
Xetro.B00894	30.82928129	1.779142489	3.432221091	0.660673607	2.692921995	0.007082884	0.070450943
Xetro.B00930	11.47550064	-4.613216353	0.040858602	0.902415903	-5.112073423	3.19E-07	8.53E-05
Xetro.B01186	188.1032044	2.470372789	5.541869695	0.871804012	2.833633197	0.004602212	0.05396122
Xetro.B01263	30.57061586	-1.979189407	0.253632336	0.693682631	-2.853162698	0.004328645	0.052062584
Xetro.B01277	46.86074248	2.108933185	4.313721943	0.52225392	4.038137591	5.39E-05	0.003115614
Xetro.B01444	409.6775814	-0.852443375	0.553845938	0.320270351	-2.661636869	0.007776172	0.074697752
Xetro.B01714	49.1346649	2.632683351	6.201784305	0.695333384	3.786217391	0.000152958	0.005949731
Xetro.B01772	265.96989	-1.063459003	0.478483472	0.280308506	-3.793887734	0.000148307	0.005890304
Xetro.B01790	303.6716609	0.962506967	1.948693193	0.339279034	2.836918494	0.004555124	0.053801818
Xetro.B01800	2320.793872	0.974232199	1.964595363	0.201895368	4.825431163	1.40E-06	0.000265744
Xetro.B01886	60.05964816	-1.390009321	0.381562337	0.449689295	-3.091043828	0.001994542	0.031376597
Xetro.B02112	69.87251749	1.494282433	2.817239925	0.545758036	2.737994376	0.006181513	0.06496105
Xetro.B02229	257.8517257	2.672085006	6.373496297	0.969038148	2.757461108	0.005825214	0.062648415
Xetro.B02275	63.50844539	1.609044551	3.050497506	0.446726533	3.601855791	0.000315954	0.009535995
Xetro.B02333	17.10151232	4.5189046	22.92587036	1.181635809	3.824278653	0.000131156	0.005475716
Xetro.B02569	39.2151662	2.260638923	4.792036586	0.712714025	3.171873773	0.001514588	0.025882272
Xetro.C00029	473.1349289	-0.869972809	0.547157163	0.193101857	-4.505253463	6.63E-06	0.000704712
Xetro.C00061	11.87532107	3.638178813	12.45090594	1.207628958	3.01266278	0.002589665	0.037031442
Xetro.C00128	128.2747418	1.474968545	2.779775832	0.428806322	3.439708021	0.000582342	0.013653625
Xetro.C00152	187.1481461	2.528614185	5.770171444	0.709647525	3.563197355	0.000366365	0.010385371
Xetro.C00156	148.7676584	1.80330841	3.490196854	0.589677786	3.05812505	0.002227266	0.033471503
Xetro.C00180	60.74406925	4.02365683	16.26452551	0.879855029	4.573090677	4.81E-06	0.000588794
Xetro.C00250	136.1032528	-0.74124633	0.59822233	0.280420718	-2.643336536	0.008209339	0.077086093
Xetro.C00432	19.71975964	3.525765643	11.51757944	0.813354913	4.334842744	1.46E-05	0.00119816
Xetro.C00468	72.93948636	1.838787155	3.577091829	0.418687118	4.391792998	1.12E-05	0.000991007
Xetro.C00635	8.56281315	2.974939293	7.862233948	1.138087455	2.613981272	0.008949394	0.080314714
Xetro.C00656	665.4873951	0.914278782	1.884626692	0.271326972	3.369656823	0.000752619	0.016071796
Xetro.C00878	21.69197727	1.285506016	2.437675376	0.495084902	2.596536493	0.00941689	0.083218675
Xetro.C00894	173.6933259	-1.56430951	0.338139507	0.355312768	-4.402626784	1.07E-05	0.00097242
Xetro.C00896	130.7260063	-2.050886176	0.241335796	0.32127844	-6.383516358	1.73E-10	4.17E-07
Xetro.C00924	41.04008306	-1.319772756	0.400598033	0.361397361	-3.651860518	0.000260347	0.008345545
Xetro.C00978	14.46666442	4.323454843	20.02117642	1.150355375	3.758364535	0.000171028	0.006422913
Xetro.C01384	219.5978637	1.073583116	2.104654056	0.314240533	3.416437425	0.000634462	0.014331912
Xetro.C02021	94.06828943	0.596498502	1.512042302	0.218247217	2.733132223	0.006273514	0.065484617
Xetro.C02059	411.7655464	-1.151440377	0.450175555	0.453490755	-2.539060308	0.011115066	0.091718328
Xetro.C02064	105.793409	1.632999336	3.101571398	0.520061936	3.140009341	0.001689424	0.02788129

Xetro.C02067	758.8346211	-0.759924507	0.590527231	0.29692507	-2.559314058	0.010487895	0.089033171
Xetro.C02121	578.7545729	0.521464723	1.435411837	0.195656262	2.665208447	0.007694062	0.074244306
Xetro.D00009	64.81493073	-1.794737561	0.288224012	0.482122239	-3.722577832	0.000197199	0.007056701
Xetro.D00019	35.09614658	-1.76380139	0.294471233	0.562167742	-3.137500177	0.001703952	0.028056982
Xetro.D00061	79.18018579	-0.954737991	0.51593528	0.372179033	-2.565265387	0.010309692	0.088402855
Xetro.D00143	1725.901927	-0.399885191	0.757918596	0.1443558	-2.770135946	0.00560329	0.061229602
Xetro.D00311	1002.718808	-0.809996379	0.570383289	0.320648503	-2.526119322	0.01153303	0.093897168
Xetro.D00427	51.52339292	-1.09156593	0.469251763	0.423652704	-2.576558393	0.009978935	0.086316328
Xetro.D00462	364.2621064	1.241567593	2.364553187	0.364462101	3.406575302	0.000657834	0.014705344
Xetro.D00468	31.09662474	1.534442045	2.896763784	0.573141395	2.677248682	0.007422952	0.072705154
Xetro.D00578	1179.965657	-0.83258955	0.561520442	0.269727257	-3.086783142	0.002023351	0.031667553
Xetro.D00630	91.69510664	1.420274623	2.676364519	0.559567086	2.538166843	0.011143485	0.091900374
Xetro.D00642	549.5645203	1.08915079	2.127487699	0.378300878	2.879059643	0.003988629	0.049327295
Xetro.D00711	1164.33759	-0.456719996	0.728640961	0.170367253	-2.680796852	0.007344709	0.072183858
Xetro.D00795	14.00821621	3.297703226	9.833487901	0.860364768	3.832912909	0.000126635	0.005419324
Xetro.D00932	21.18486966	3.609233106	12.20358489	0.956438668	3.773616885	0.000160898	0.006176044
Xetro.D01004	19.53670658	2.325861433	5.013650511	0.76400756	3.044291125	0.002332293	0.034582527
Xetro.D01070	1458.650523	1.302795879	2.46706526	0.52323046	2.489908327	0.012777605	0.099690142
Xetro.D01078	208.5767899	-1.323305578	0.399618263	0.237960287	-5.561035388	2.68E-08	1.38E-05
Xetro.D01082	115.0118207	1.51355992	2.855136895	0.510595779	2.964301669	0.003033707	0.040950799
Xetro.D01297	1764.995044	1.334359022	2.521634227	0.408515367	3.26636188	0.001089389	0.02053364
Xetro.D01325	1005.085342	0.680982563	1.603231281	0.227659932	2.991227125	0.002778587	0.038762813
Xetro.D01369	23.00446376	1.622242549	3.078531965	0.633767891	2.559679295	0.01047688	0.089018843
Xetro.D01489	28.64289814	1.947128323	3.856062201	0.749523872	2.597820291	0.009381758	0.083006166
Xetro.D01493	193.2958157	0.639483209	1.557771047	0.249565582	2.562385422	0.010395588	0.088716044
Xetro.D01496	472.5520935	0.904926044	1.872448506	0.250541163	3.611885698	0.000303979	0.009345914
Xetro.D01568	24.0579061	2.957844759	7.76962387	0.854133902	3.46297548	0.000534237	0.01296987
Xetro.D01792	58.7719993	0.911418796	1.880894326	0.363790287	2.505341207	0.012233332	0.097388367
Xetro.D01999	223.7121323	-1.022748653	0.492177751	0.307603195	-3.324896065	0.000884515	0.017772273
Xetro.D02301	47.40704297	-1.386939017	0.382375232	0.445176247	-3.115482972	0.00183644	0.029763908
Xetro.D02390	1135.786058	-0.672402523	0.627460905	0.258556125	-2.600605663	0.009305936	0.082537369
Xetro.D02419	1694.781494	1.467920116	2.766228084	0.395117363	3.715149611	0.000203083	0.007143499
Xetro.D02440	1057.190922	2.125849713	4.36460082	0.746950075	2.846039897	0.004426665	0.052845825
Xetro.D02510	454.5630077	-1.095599039	0.467941783	0.217555445	-5.035953197	4.75E-07	0.000115892
Xetro.E00103	67.15053782	-1.102006036	0.465868266	0.431270813	-2.555252993	0.010611064	0.089762526
Xetro.E00110	297.1581457	-1.050064201	0.482946673	0.386750513	-2.715094529	0.006625686	0.067533958
Xetro.E00428	215.8588983	-0.695265372	0.617595706	0.255414687	-2.722104122	0.00648677	0.066835744
Xetro.E00445	311.4958218	0.778740489	1.715632426	0.241519585	3.224336812	0.001262648	0.022704107
Xetro.E00483	235.4507542	-1.526759567	0.347056014	0.382970451	-3.986624977	6.70E-05	0.00360188
Xetro.E00539	43.00560629	1.886999616	3.698652128	0.614616882	3.070204662	0.002139121	0.032656047
Xetro.E00745	221.1096296	1.23713656	2.357301938	0.465634756	2.656881908	0.007886706	0.075309191

Xetro.E01126	13.59044779	1.520732587	2.869367165	0.603729374	2.518897793	0.011772282	0.095187459
Xetro.E01224	63.77914956	-1.34047757	0.394889915	0.532698478	-2.516390838	0.011856362	0.09559812
Xetro.E01322	384.3239757	3.667529102	12.70680221	0.660169851	5.555432585	2.77E-08	1.38E-05
Xetro.E01370	66.50079841	2.420886656	5.355000301	0.626503902	3.864120638	0.00011149	0.00497473
Xetro.E01543	33.14896783	1.905044305	3.745204004	0.578313982	3.294134962	0.000987251	0.019157967
Xetro.E01589	122.0633089	1.266208827	2.405286633	0.428699584	2.953604051	0.003140867	0.042005102
Xetro.E01629	111.793697	1.616660434	3.066643441	0.423262554	3.819521521	0.000133711	0.00552302
Xetro.E01725	7.987738276	-2.595453946	0.165459044	0.947965659	-2.7379198	0.006182915	0.06496105
Xetro.F00255	309.3457164	-1.190422396	0.438174552	0.353455759	-3.367953036	0.000757285	0.016111287
Xetro.F00318	15.7098982	2.764131064	6.7933871	1.067991901	2.588157328	0.00964909	0.084368437
Xetro.F00355	137.0913665	1.295472082	2.454573014	0.248273221	5.217929172	1.81E-07	5.45E-05
Xetro.F00383	748.8767654	1.757898175	3.382050436	0.379767611	4.628878614	3.68E-06	0.000483194
Xetro.F00431	831.3463521	0.551629167	1.465739953	0.148939746	3.703706915	0.000212472	0.007401696
Xetro.F00502	548.608106	1.096263697	2.138002733	0.309856892	3.53796777	0.000403219	0.010869491
Xetro.F00631	7.829736464	4.260308797	19.16376069	1.335432375	3.19020931	0.001421698	0.02475528
Xetro.F00789	99.32682446	2.138284054	4.402381142	0.781313434	2.736781373	0.006204351	0.065005291
Xetro.F00822	112.3789051	1.186837823	2.276532133	0.384929121	3.08326328	0.002047439	0.031793587
Xetro.F00964	2661.472198	-0.481555658	0.716204924	0.164678124	-2.924223612	0.003453166	0.045168449
Xetro.F01139	56.07227819	-1.793441752	0.288483008	0.608284132	-2.948361889	0.003194628	0.042527389
Xetro.F01399	9.091663511	4.088632495	17.01378821	1.227846447	3.329921674	0.000868704	0.017610537
Xetro.F01588	27.92753564	-1.685093318	0.310982797	0.466667869	-3.610904953	0.00030513	0.009345914
Xetro.F01705	230.5969679	1.8099053	3.506192729	0.459776033	3.936493356	8.27E-05	0.004179433
Xetro.F01743	24.88624055	3.380660343	10.41550109	0.716824975	4.716158704	2.40E-06	0.000386065
Xetro.F01749	27.22286238	3.986108702	15.8466799	1.495605047	2.665214797	0.007693916	0.074244306
Xetro.F01783	191.0453461	0.853332881	1.806669836	0.263795852	3.234822972	0.001217182	0.022190159
Xetro.F01803	1119.120829	-1.108244153	0.463858231	0.353621346	-3.133985451	0.001724494	0.028330694
Xetro.F01896	619.9527058	-0.367300035	0.775231966	0.144308576	-2.545240521	0.010920249	0.090810722
Xetro.F01937	340.2853479	2.844104395	7.180599981	0.988885633	2.876070093	0.004026603	0.049669452
Xetro.F01941	298.5788443	2.790856826	6.920406703	0.865325736	3.225209548	0.001258805	0.022663192
Xetro.F01953	453.5751158	1.178682678	2.263699847	0.331805025	3.552335228	0.000381828	0.010593403
Xetro.F01955	142.5834309	1.640156942	3.116997379	0.406607265	4.033762017	5.49E-05	0.003128103
Xetro.F01960	24.81043589	3.137182808	8.798043948	1.079249542	2.906818753	0.003651247	0.046527733
Xetro.F01963	354.6488454	1.893813955	3.716163443	0.379859754	4.985560947	6.18E-07	0.00013919
Xetro.F01980	15.57142501	-3.395574787	0.095023306	0.939219963	-3.615313685	0.000299984	0.009286662
Xetro.G00081	653.7465379	-0.562032532	0.677347215	0.157252704	-3.574072283	0.000351472	0.010153288
Xetro.G00086	32.02854124	-2.379852799	0.192129	0.78530315	-3.030489307	0.002441578	0.035645696
Xetro.G00105	17.70832706	2.455566133	5.485283297	0.867361012	2.831077371	0.00463915	0.054262162
Xetro.G00233	190.4050425	1.669487396	3.181015487	0.367116054	4.547573929	5.43E-06	0.000635771
Xetro.G00725	15.41515919	1.983457064	3.954395211	0.662941562	2.991903325	0.00277244	0.038733745
Xetro.G00786	10.97354385	-3.289491291	0.102273814	0.995280631	-3.305089228	0.000949462	0.018599414
Xetro.G00872	12.65684342	2.842067449	7.170468822	1.117721458	2.542733191	0.010998918	0.091170982

Xetro.G00992	192.0919553	0.917121111	1.888343354	0.308677115	2.971134129	0.002967022	0.040238492
Xetro.G01045	799.8812432	3.542683005	11.65343209	0.795498457	4.45341279	8.45E-06	0.000823341
Xetro.G01065	39.89947255	1.558198708	2.944859302	0.520036351	2.996326516	0.002732537	0.038428291
Xetro.G01204	7.81675572	3.015410014	8.085909264	1.197882667	2.517283284	0.01182637	0.095462775
Xetro.G01213	8.668380648	-1.743747897	0.29859297	0.633971297	-2.750515527	0.005950157	0.063578287
Xetro.G01248	38.92915373	1.400563132	2.640046118	0.460956616	3.038383838	0.002378508	0.035123685
Xetro.G01387	43.94918704	2.00791004	4.021991522	0.649964713	3.089260081	0.002006557	0.031523148
Xetro.G01392	184.7511578	-1.312628695	0.402586669	0.500630809	-2.621949493	0.008742839	0.079344142
Xetro.G01400	39.63048326	-1.061694137	0.479069165	0.406587841	-2.611229431	0.009021735	0.080709911
Xetro.G01440	16.23097894	4.351885118	20.41963422	1.05389812	4.129322404	3.64E-05	0.002369345
Xetro.G01452	10.9989867	2.914535196	7.539846727	1.125998267	2.588401139	0.009642262	0.084368437
Xetro.G01462	18.25785296	1.711252242	3.274449184	0.652376463	2.623105429	0.008713231	0.079178308
Xetro.G01467	145.3705056	-1.037595859	0.487138577	0.256764852	-4.041035406	5.32E-05	0.003089718
Xetro.G01483	952.7704639	0.609008484	1.525210622	0.189517253	3.213472519	0.001311403	0.023406123
Xetro.G01503	122.0849061	-0.905524474	0.533838598	0.282940044	-3.200411163	0.001372317	0.024135745
Xetro.G01539	1251.434211	1.411689048	2.660484591	0.383494593	3.681118519	0.000232213	0.00786207
Xetro.G01805	2768.242261	0.604022435	1.519948493	0.221373618	2.728520417	0.006361915	0.066081671
Xetro.G01814	137.7184711	-0.636061615	0.643467142	0.204995569	-3.102806657	0.001916948	0.030622455
Xetro.G01838	61.21965805	1.494342165	2.81735657	0.544102155	2.746436773	0.00602465	0.064042913
Xetro.G01853	1051.89891	0.974101554	1.964417465	0.231847218	4.201480446	2.65E-05	0.001843095
Xetro.G01861	7182.345263	-0.81263436	0.569341291	0.248428124	-3.271104516	0.001071283	0.020378342
Xetro.G01862	3384.190169	-1.375212628	0.385495887	0.381776415	-3.602141399	0.000315607	0.009535995
Xetro.G01863	608.7244372	-1.476194014	0.359435793	0.400321679	-3.687519545	0.000226451	0.007757815
Xetro.G01877	55.61456707	-1.358185761	0.390072511	0.429931024	-3.159078279	0.00158269	0.026687961
Xetro.G01898	466.3328604	-1.480270769	0.358421536	0.477586333	-3.099483103	0.001938586	0.030764152
Xetro.G02084	36.26116161	-3.206331614	0.108342289	0.92466604	-3.467556367	0.000525214	0.012847737
Xetro.G02276	18.82245256	-1.188142737	0.438867476	0.47507881	-2.500938185	0.01238648	0.09812128
Xetro.H00041	205.5868116	-0.830337242	0.562397762	0.301528116	-2.753763901	0.005891425	0.063043918
Xetro.H00312	148.4972755	0.625327143	1.542560574	0.249101	2.510335737	0.012061642	0.096606739
Xetro.H00345	339.3162018	-1.063398716	0.478503467	0.318326707	-3.34058906	0.000836009	0.01711923
Xetro.H00500	172.1249769	1.751978864	3.368202469	0.516740005	3.390445576	0.000697791	0.015261673
Xetro.H00538	128.5552372	1.632251868	3.099964874	0.621832857	2.624904506	0.008667327	0.079012149
Xetro.H00570	2335.237385	-0.653880103	0.635568662	0.242163098	-2.700164094	0.006930528	0.069426569
Xetro.H00600	23.77040696	1.646561555	3.13086555	0.645759767	2.549805112	0.010778315	0.090279318
Xetro.H00830	2869.590819	0.949044477	1.930593567	0.269921495	3.516001859	0.000438098	0.011406397
Xetro.H00862	10.16736454	-1.842454058	0.278847055	0.594547665	-3.098917324	0.001942292	0.030789164
Xetro.H01054	62.08469372	1.571091908	2.971295125	0.425080928	3.695983061	0.000219038	0.007593828
Xetro.H01074	721.2595185	1.749368738	3.362114221	0.604580891	2.89352304	0.003809463	0.047931604
Xetro.H01110	11.84143667	1.776953296	3.427016875	0.653340558	2.719796397	0.006532212	0.06707116
Xetro.H01138	39.5956572	4.941470372	30.72775311	1.057887037	4.671075642	3.00E-06	0.000443859
Xetro.H01183	100.9369952	1.308158785	2.476253107	0.356674873	3.667650522	0.000244789	0.008024764

Xetro.H01350	9.274910573	2.747854048	6.717172357	0.772474332	3.557210816	0.000374813	0.010562723
Xetro.H01400	723.9693088	-0.857387312	0.551951225	0.249910508	-3.43077735	0.000601854	0.013917696
Xetro.H01671	54.18712727	-1.450607484	0.365867334	0.486263593	-2.983171073	0.002852785	0.039438799
Xetro.H01750	67.67306248	2.225146175	4.675582704	0.827862959	2.687819464	0.007192027	0.071135135
Xetro.H01824	136.2568762	0.670485668	1.591608676	0.268279305	2.499207566	0.012447138	0.098386155
Xetro.H01916	206.4965131	0.815379922	1.75976151	0.321318837	2.537603861	0.011161424	0.09195925
Xetro.H01983	32.08292589	-1.341256128	0.394676868	0.451511734	-2.970589745	0.002972285	0.0402721
Xetro.H02065	247.9380291	1.454551118	2.740712728	0.503568649	2.888486249	0.00387101	0.048263535
Xetro.H02285	18.4967988	3.23554871	9.418835546	1.032319266	3.134251987	0.001722928	0.028330694
Xetro.I00014	698.8365146	-0.55448806	0.680898632	0.160936795	-3.445377787	0.000570262	0.013515204
Xetro.I00080	284.3466959	-3.550559232	0.085344428	0.637691756	-5.567829908	2.58E-08	1.38E-05
Xetro.I00082	33.04011074	-1.709583544	0.305748316	0.40401529	-4.231482284	2.32E-05	0.001661526
Xetro.I00174	431.266033	-1.204752888	0.433843648	0.193361175	-6.230583204	4.65E-10	8.40E-07
Xetro.I00214	206.1185457	1.221012249	2.331102188	0.409691995	2.980317564	0.002879497	0.039596993
Xetro.I00337	2004.616431	-0.805534868	0.572149921	0.25782852	-3.124304745	0.001782258	0.029147171
Xetro.I00344	1409.446874	0.432074278	1.349171995	0.172173315	2.509531036	0.012089159	0.096666468
Xetro.I00463	789.2312217	1.175885307	2.259314808	0.285493284	4.118784484	3.81E-05	0.002447256
Xetro.I00806	45.85158406	1.748649495	3.360438485	0.657170034	2.660878316	0.007793712	0.074816528
Xetro.I00909	3807.755081	-0.688139953	0.620653535	0.176112321	-3.907392437	9.33E-05	0.004466234
Xetro.I00911	885.5023229	4.821385374	28.27363312	0.833723576	5.782954344	7.34E-09	5.90E-06
Xetro.I00912	872.9069666	1.882059461	3.686008661	0.694079481	2.711590695	0.006696122	0.06793392
Xetro.I00996	379.1211297	3.477507273	11.13868697	0.636436037	5.464032625	4.65E-08	2.12E-05
Xetro.I01096	98.10326777	0.986907779	1.981932432	0.375373901	2.629132654	0.008560296	0.078596981
Xetro.I01219	11.95822062	1.488134046	2.805259137	0.586585232	2.536944276	0.011182475	0.091959638
Xetro.I01431	42.54766105	-1.726009526	0.302286923	0.555379225	-3.10780355	0.001884833	0.030310381
Xetro.I01591	198.394432	2.930971936	7.626240013	0.695676191	4.213126699	2.52E-05	0.001767542
Xetro.I01731	34.49607244	-2.596991296	0.165282823	0.892183328	-2.910826975	0.003604736	0.046185685
Xetro.I01914	40.45837051	1.321388733	2.499065532	0.408361439	3.235831321	0.00121289	0.022167833
Xetro.I01918	1461.231632	0.787649888	1.726260139	0.315615627	2.495598509	0.012574484	0.098798537
Xetro.I02033	15.12856809	1.673829668	3.190604239	0.584357144	2.864394977	0.004178067	0.050866673
Xetro.I02078	357.5729899	-0.585388024	0.666470062	0.22478543	-2.604208043	0.009208684	0.082178979
Xetro.I02123	22.87231454	4.633054939	24.8135275	1.216860894	3.807382553	0.000140445	0.005703425
Xetro.J00051	57.54153458	-0.992482026	0.502612332	0.348312352	-2.84940233	0.004380145	0.052507263
Xetro.J00053	271.7722386	0.598663575	1.514313149	0.216363285	2.766936986	0.005658569	0.061617666
Xetro.J00056	13.54824493	-3.874731655	0.068169412	1.173675414	-3.301365614	0.000962154	0.018822547
Xetro.J00110	248.7523117	-1.24374234	0.422275854	0.28560295	-4.354795152	1.33E-05	0.001126691
Xetro.J00143	85.56722142	4.23296427	18.80395555	0.779204464	5.432417893	5.56E-08	2.30E-05
Xetro.J00165	202.1676453	-1.698517139	0.308102621	0.601966844	-2.821612449	0.004778288	0.055263771
Xetro.J00314	331.6391626	-0.843808118	0.557170925	0.1939467	-4.350721714	1.36E-05	0.001133915
Xetro.J00372	7.601961304	5.178015178	36.20244368	1.363393458	3.79788765	0.000145934	0.005828105
Xetro.J00380	11.36533399	2.447460858	5.454552567	0.82284057	2.974404699	0.002935576	0.040113068

Xetro.J00454	1068.660188	1.969746477	3.916992801	0.519348537	3.792725571	0.000149003	0.005893093
Xetro.J00576	9.634111318	3.761865569	13.56545534	1.132792458	3.320878015	0.000897347	0.017918443
Xetro.J00643	75.04458821	1.656988148	3.153574789	0.492014689	3.367761544	0.000757811	0.016111287
Xetro.J00710	8.78265886	2.453893792	5.478928559	0.962348917	2.5499003	0.010775373	0.090279318
Xetro.J00713	16.92229317	1.794729391	3.469503906	0.646843885	2.774594355	0.00552706	0.060671757
Xetro.K00081	70.02584967	-1.202829599	0.4344224	0.338297013	-3.555543065	0.000377199	0.010569452
Xetro.K00266	15.0137136	2.785877265	6.896561621	1.056695384	2.636405256	0.00837896	0.077850012
Xetro.K00289	60.75164588	2.34279023	5.072827947	0.61703926	3.796825229	0.000146561	0.005837005
Xetro.K00374	202.2713029	-0.749828081	0.594674418	0.249861387	-3.000976226	0.002691156	0.037983182
Xetro.K00442	7.002307704	-4.07499595	0.059334049	1.404968181	-2.900418674	0.003726645	0.047143543
Xetro.K00474	205.301697	3.072371816	8.411550843	1.080545526	2.843352494	0.004464167	0.053166196
Xetro.K00477	121.7104906	0.585886565	1.500961077	0.228872022	2.559887228	0.010470613	0.089018843
Xetro.K00630	467.5475617	0.801046377	1.742364394	0.268448202	2.983988608	0.002845174	0.039399114
Xetro.K00666	187.2940121	0.921962372	1.894690724	0.226531842	4.069901889	4.70E-05	0.002856955
Xetro.K00668	601.4951846	0.66067641	1.580823622	0.233759476	2.826308566	0.004708788	0.054854914
Xetro.K00670	104.4506976	1.346199638	2.54241517	0.532634847	2.527434406	0.011489928	0.093776717
Xetro.K00742	499.6777914	-0.878899174	0.543782198	0.261071386	-3.366509007	0.000761261	0.016160866
Xetro.K00743	421.9469787	-0.702561552	0.614480208	0.265516839	-2.646015047	0.008144619	0.076808064
Xetro.K00758	86.10588506	1.384974158	2.611672793	0.387762871	3.5717039	0.000354666	0.010153288
Xetro.K00772	310.0851478	0.867871496	1.824968416	0.271687725	3.194371389	0.001401357	0.024497484
Xetro.K00778	667.0937556	0.794911641	1.734971112	0.265529737	2.993682177	0.002756329	0.038663544
Xetro.K00789	103.7565338	1.192673861	2.285759888	0.26280628	4.538224353	5.67E-06	0.000635771
Xetro.K00795	403.6178259	0.899950317	1.866001721	0.288048182	3.124304794	0.001782257	0.029147171
Xetro.K00842	316.1869773	1.047379642	2.066772571	0.375375721	2.790216801	0.005267276	0.058867417
Xetro.K00859	8.345640229	5.108168301	34.49148409	1.340139776	3.811668299	0.000138032	0.005653057
Xetro.K00872	44.12546302	-2.459616749	0.181794852	0.624591804	-3.937958736	8.22E-05	0.004179433
Xetro.K00987	13.27008451	1.616086411	3.065423521	0.581387728	2.779705062	0.005440829	0.060228227
Xetro.K01079	65.26684695	0.915329412	1.885999655	0.340819217	2.685674305	0.007238361	0.071284049
Xetro.K01089	60.10990489	-1.349091805	0.39253908	0.363670029	-3.709659029	0.000207539	0.007247307
Xetro.K01093	251.578673	2.269986059	4.823184704	0.487575498	4.655660651	3.23E-06	0.000450987
Xetro.K01094	23.07615558	4.786662754	27.60127016	1.125795202	4.251805963	2.12E-05	0.001572132
Xetro.K01097	15.90627535	3.117412206	8.678298472	1.083121055	2.878175242	0.003999829	0.049423525
Xetro.K01137	117.2764991	0.825172879	1.771747336	0.318325903	2.592226623	0.009535693	0.084044337
Xetro.K01225	1450.236111	-0.415145727	0.749943739	0.110739539	-3.748848267	0.000177649	0.006585294
Xetro.K01241	13.30945228	-8.055727069	0.00375824	1.444322225	-5.57751375	2.44E-08	1.37E-05
Xetro.K01288	12859.09421	-0.531475662	0.691846716	0.164092768	-3.238873151	0.001200029	0.02198837
Xetro.K01308	69.07838669	-2.24082509	0.211565297	0.401927359	-5.575199202	2.47E-08	1.37E-05
Xetro.K01593	131.9235026	-1.413796539	0.375322702	0.447121275	-3.161997917	0.001566907	0.026494471
Xetro.K01601	39.01747488	-2.025470344	0.245625058	0.766789146	-2.641495847	0.008254082	0.07718581
Xetro.K01603	85.49647041	-1.445927147	0.367056194	0.571151528	-2.531599892	0.011354347	0.093068036
Xetro.K01642	42.66008523	-1.335913121	0.39614126	0.303825497	-4.39697502	1.10E-05	0.00098568

Xetro.K01645	271.0900874	-0.981423286	0.506479827	0.375489431	-2.613717468	0.008956307	0.080314714
Xetro.K01699	352.2419512	2.490238978	5.618710148	0.914890204	2.721899271	0.006490792	0.066835744
Xetro.K01782	1775.161445	1.078804798	2.112285432	0.232948242	4.631092247	3.64E-06	0.000482442
Xetro.K01885	526.7130858	2.643408787	6.248062076	0.975965916	2.70850523	0.006758705	0.068241735
Xetro.K01927	184.352555	1.298819966	2.460275653	0.495513955	2.621157191	0.008763185	0.079349224
Xetro.K01936	40.14755691	1.53008804	2.888034628	0.477076505	3.207217339	0.001340257	0.023687158
Xetro.K01961	37.47104453	-1.2406843	0.42317189	0.337431716	-3.676845541	0.000236136	0.007869936
Xetro.K01972	22.73848897	2.781860694	6.877387781	0.823380551	3.378584413	0.000728601	0.015744961
Xetro.K01974	24.33433471	1.68078768	3.206029454	0.630985621	2.663749576	0.007727507	0.07442809
Xetro.K02049	496.7800806	-2.092305923	0.234505567	0.647586298	-3.230929884	0.001233882	0.02240984
Xetro.K02128	9.946757746	1.756591716	3.378989145	0.632685829	2.776404392	0.00549638	0.060536285
Xetro.K02133	19.32648768	1.920279188	3.784962975	0.666316699	2.881931656	0.003952455	0.04900569
Xetro.K02188	127.2249476	1.832102311	3.560555426	0.521431284	3.513602594	0.000442074	0.01145695
Xetro.K02218	13.07266616	3.792186217	13.85357309	0.882123504	4.298928893	1.72E-05	0.001355842
Xetro.K02219	8.368145859	4.055277866	16.62494735	1.067134257	3.800157139	0.000144604	0.005806165
Xetro.K02408	85.39405429	-1.141203553	0.453381191	0.306285094	-3.725951981	0.000194579	0.00699281
Xetro.K02460	63.94655042	-3.874378212	0.068186115	0.750254546	-5.164084954	2.42E-07	6.59E-05
Xetro.K02537	348.6356386	0.995935681	1.994373587	0.370730312	2.686415571	0.00722232	0.071247675
Xetro.K02551	769.8964443	0.550227081	1.464316162	0.2113466	2.603434734	0.009229484	0.082242081
Xetro.K02554	9.511426418	2.599408839	6.060382446	0.860542768	3.020662001	0.002522227	0.03639106
Xetro.K02586	9.774623213	-2.195608584	0.218301117	0.741797399	-2.959849397	0.003077895	0.041431213
Xetro.K02614	989.5158616	-0.793792122	0.576825911	0.254930843	-3.113754748	0.00184723	0.029905262
Xetro.K02637	102.6794928	1.973958953	3.928446608	0.50554178	3.904640588	9.44E-05	0.00450245
Xetro.K02682	34.54125132	-2.031825939	0.244545371	0.452242782	-4.492776929	7.03E-06	0.000731175
Xetro.K02732	165.5853055	1.051592166	2.072816157	0.384047412	2.738183189	0.006177965	0.06496105
Xetro.K02938	10.82408555	2.378211486	5.198918307	0.948608423	2.507052887	0.012174249	0.097178863
Xetro.K02942	31.58163076	-1.251207727	0.420096384	0.405355891	-3.086689387	0.00202399	0.031667553
Xetro.K02973	35.54119234	-2.043234918	0.242619108	0.661452109	-3.089014141	0.002008219	0.031523148
Xetro.K03034	22.97253449	2.716044867	6.570689947	0.899682754	3.018891776	0.002537011	0.036458821
Xetro.K03049	44.49439025	-1.629192546	0.323269086	0.467160789	-3.487434269	0.000487679	0.012240229
Xetro.K03129	687.5955665	1.562065162	2.952762175	0.49531107	3.153705334	0.001612118	0.027100449
Xetro.K03133	334.8207748	-0.943642154	0.519918662	0.18241309	-5.173105459	2.30E-07	6.40E-05
Xetro.K03248	1093.467678	-0.875619764	0.545019682	0.186191504	-4.7027912	2.57E-06	0.000401844
Xetro.K03275	11.18304586	3.848523289	14.40525495	1.053098753	3.654475211	0.000257709	0.008330353
Xetro.K03284	88.45556018	1.88666644	3.697798059	0.498179755	3.787119851	0.000152404	0.005949731
Xetro.K03298	7.398655767	-3.712335897	0.076291392	0.98398093	-3.7727722	0.000161444	0.006176044
Xetro.K03333	47.67210477	-1.655627814	0.317399594	0.470094225	-3.521906305	0.000428456	0.011221344
Xetro.K03334	324.3321647	-0.632055732	0.645256318	0.215313272	-2.935516825	0.003329926	0.044044587
Xetro.K03364	9.575267895	2.144644765	4.421833691	0.786111126	2.728169969	0.006368678	0.066081671
Xetro.K03388	36.78916684	-1.431339005	0.370786596	0.40072196	-3.571900587	0.0003544	0.010153288
Xetro.K03413	75.73907565	-1.273348187	0.413698552	0.477303877	-2.667793514	0.007635117	0.073882785

Xetro.K03444	42.70013011	-2.642813462	0.160115684	0.547255949	-4.829209197	1.37E-06	0.000264228
Xetro.K03490	113.5339113	-0.680653073	0.623882794	0.230042223	-2.958818015	0.003088214	0.041467182
Xetro.K03539	160.3102269	1.642564554	3.12220346	0.539420798	3.045052322	0.002326398	0.034566023
Xetro.K03543	1615.191896	-0.698872963	0.616053281	0.26018395	-2.686072536	0.007229739	0.071247675
Xetro.K03598	15.74821915	2.502448892	5.666464589	0.6323945	3.957100977	7.59E-05	0.003945246
Xetro.K03629	173.4211316	-1.279378205	0.411973029	0.385241363	-3.320978295	0.000897025	0.017918443
Xetro.K03773	165.7849206	-0.927507398	0.525765945	0.339815212	-2.729446375	0.006344077	0.066030465
Xetro.K03774	250.2757466	-1.343873539	0.393961475	0.288810249	-4.653136597	3.27E-06	0.000450987
Xetro.K03783	202.0569603	-1.236265352	0.424470044	0.330158804	-3.744456714	0.000180785	0.006633508
Xetro.K03847	353.1349523	-1.070740554	0.476074561	0.345000401	-3.103592202	0.001911867	0.030599477
Xetro.K03848	73.62116063	-0.966137937	0.511874507	0.329257562	-2.934292327	0.003343092	0.044141032
Xetro.K03865	26.76930037	3.22648815	9.359867783	0.87895302	3.67083118	0.000241763	0.007979835
Xetro.K03890	14.23521666	3.248944231	9.506697343	1.146147551	2.834664899	0.004587378	0.05391847
Xetro.K03899	37.63315943	-1.548042738	0.341973695	0.575389234	-2.690427012	0.007136064	0.070807194
Xetro.K03909	42.82248004	-1.426292778	0.372085796	0.482407395	-2.956614665	0.003110366	0.041635699
Xetro.K03921	57.69266976	-0.841759161	0.557962798	0.321800256	-2.615781516	0.00890235	0.080038107
Xetro.K03958	15.46834105	-3.279476879	0.102986213	0.871856964	-3.761484983	0.000168908	0.0063924
Xetro.K03997	291.1525979	2.966880068	7.818436154	0.653545467	4.539668959	5.63E-06	0.000635771
Xetro.K04018	78.70419112	-0.829923121	0.56255922	0.28995851	-2.862213358	0.004206936	0.05110897
Xetro.K04050	31.35203164	4.738911234	26.70265399	1.472401009	3.218492249	0.001288665	0.023041051
Xetro.K04054	26.12583004	2.796604083	6.94803048	0.826863123	3.382185036	0.000719117	0.015586616
Xetro.K04104	36.01212233	6.264035297	76.85329963	1.202787821	5.207930434	1.91E-07	5.46E-05
Xetro.K04168	96.73713308	0.8124108	1.756143576	0.30544275	2.659780921	0.007819149	0.074961168
Xetro.K04178	30.82857785	-1.311109721	0.403010765	0.501018866	-2.616886929	0.008873573	0.079829026
Xetro.K04181	26.28780872	-1.526581454	0.347098863	0.523989275	-2.913383015	0.003575358	0.045986607
Xetro.K04206	268.7892039	-0.998688853	0.500454616	0.253159049	-3.944906787	7.98E-05	0.004092614
Xetro.K04268	83.78654368	-0.935047724	0.523025168	0.368543282	-2.537144943	0.011176067	0.09195925
Xetro.K04272	521.1003188	-0.777074001	0.583549118	0.285134652	-2.725287847	0.006424545	0.066532698
Xetro.K04332	2207.101557	-0.752266051	0.593670343	0.260409616	-2.888779845	0.003867397	0.048263535
Xetro.K04352	554.0152285	-0.638469199	0.642394213	0.227325601	-2.80861107	0.004975572	0.056798904
Xetro.K04447	219.9287563	1.110490972	2.159191156	0.357820897	3.103482723	0.001912574	0.030599477
Xetro.K04512	19.97243393	-2.144672463	0.226146181	0.527256473	-4.067607649	4.75E-05	0.002873148
Xetro.K04594	47.86968142	1.379687424	2.602119872	0.501829111	2.749317237	0.005971956	0.063709739
Xetro.K04619	65.55095385	-1.47372648	0.360051085	0.420902015	-3.501352875	0.000462902	0.011761303
Xetro.K04685	135.5000075	-0.733086153	0.601615585	0.210275701	-3.486309407	0.000489734	0.012249286
Xetro.K04712	154.8109733	-1.278961905	0.412091924	0.370043026	-3.456251881	0.000547743	0.013132212
Xetro.K04728	8.402916892	-2.407929178	0.188426113	0.726373765	-3.315000202	0.000916431	0.018099427
Xetro.K04747	16.3644248	-1.747673826	0.297781529	0.538221938	-3.247124842	0.001165772	0.021607143
Xetro.K04761	23.56059123	-1.351633115	0.39184823	0.52631359	-2.568113648	0.010225363	0.088007629
Xetro.K04815	630.3837939	-0.823603407	0.565028911	0.228341749	-3.606889291	0.00030989	0.009431741
Xetro.K04986	9.749395098	-5.869886714	0.017099682	1.127262878	-5.207203067	1.92E-07	5.46E-05

Xetro.K04988	26.14704387	1.968889456	3.914666636	0.677449058	2.906328428	0.003656974	0.046539499
Xetro.K05017	214.6690365	-0.759102345	0.590863856	0.289290645	-2.62401276	0.008690053	0.07911341
Xetro.K05058	401.5293653	2.227945546	4.684663899	0.442601671	5.033748603	4.81E-07	0.000115892
Xetro.K05111	15.63290105	3.064870756	8.367929846	1.02080125	3.002416736	0.002678452	0.037925941
Xetro.K05213	187.6869243	-0.68392892	0.622467785	0.158019427	-4.328131874	1.50E-05	0.001221368
xpo7	1436.310406	-0.345360343	0.787111355	0.137084207	-2.519329907	0.011757843	0.095175331
xpot	1887.698517	-0.438647589	0.737825937	0.166573508	-2.633357456	0.008454532	0.077950997
xrcc5	223.5405296	-1.082387531	0.47224665	0.231788151	-4.669727628	3.02E-06	0.000443859
ybx1	27096.28178	0.552804646	1.466934695	0.190148812	2.90722114	0.003646553	0.046527733
yif1b	1398.103506	-0.648423297	0.63797717	0.240206838	-2.699437301	0.006945684	0.069490489
ythdf2	2933.017956	0.320872635	1.249085848	0.128839444	2.490484477	0.012756907	0.099690142
zar1l	676.5112648	2.122572715	4.354698133	0.452781679	4.687850266	2.76E-06	0.00042462
zbed6	227.7183985	1.392939032	2.626131269	0.522274062	2.66706531	0.00765168	0.073993538
zbtb10	8542.108539	0.674444471	1.5959821	0.199314942	3.383812886	0.000714867	0.015541102
zbtb34	737.4951269	1.286840657	2.439931519	0.431446149	2.982621727	0.00285791	0.039443495
zc3h15	896.7891251	0.503158054	1.417312662	0.183831455	2.737061804	0.006199065	0.065005291
zc3h4	2939.877896	1.333549957	2.520220489	0.367167803	3.631990455	0.000281244	0.008838995
zc3h6	755.1269724	0.833798463	1.782371986	0.29784833	2.799406199	0.005119669	0.057910445
zc3h7b	645.9487452	-0.644327901	0.639790776	0.235204233	-2.739440069	0.006154393	0.064858129
zc4h2	519.5750106	0.778791522	1.715693115	0.244498982	3.185254656	0.001446267	0.025040334
zdhhc12	110.839353	-0.620873238	0.650277207	0.241286885	-2.573174407	0.010077041	0.0869235
zdhhc2	126.1474551	1.341536928	2.53421149	0.441255165	3.040274731	0.002363624	0.03497535
zdhhc20	1563.8132	-0.690154353	0.619787536	0.177713549	-3.883521302	0.000102955	0.004729516
zdhhc21	452.4787918	0.93267234	1.908808456	0.31082585	3.000626679	0.002694247	0.037983182
zdhhc4	217.4977014	2.323346596	5.004918567	0.576148374	4.032549081	5.52E-05	0.003128103
zdhhc9	210.6289079	-0.818823027	0.566904243	0.284385487	-2.879271495	0.00398595	0.049327295
zic3	2090.775436	0.701567543	1.626270839	0.262393202	2.673726066	0.00750137	0.073225728
zmym4	2852.196686	-0.556523622	0.6799386	0.159373504	-3.491945693	0.000479516	0.012084851
znf142	532.4829166	0.563945511	1.478306597	0.197061668	2.861771737	0.004212802	0.051137261
znf16	86.52249161	-1.499037947	0.353789234	0.533650337	-2.809026515	0.004969155	0.056789786
znf182	43.13783346	1.508068528	2.844289921	0.478659123	3.150610645	0.001629295	0.02726241
znf236	479.5980505	0.758021352	1.691169604	0.215773181	3.51304712	0.000442999	0.01145695
znf287	302.3680689	1.27884883	2.426452856	0.333723958	3.832055799	0.000127077	0.005419324
znf295	390.3215441	0.875869987	1.83511438	0.2847753	3.075652931	0.002100422	0.03223355
znf3	193.0061335	3.147276491	8.859814488	0.725710182	4.336822841	1.45E-05	0.001194206
znf326	11654.28064	0.459494161	1.375059609	0.156411641	2.937723537	0.003306317	0.043812491
znf329	343.4118585	0.871297134	1.8293069	0.340627056	2.5579211	0.010529998	0.089130618
znf335	759.4877088	-0.36701825	0.775383398	0.139307398	-2.634592675	0.00842383	0.077870523
znf33a	361.9995546	2.299178188	4.921773232	0.729450034	3.15193376	0.001621931	0.027202147
znf367	156.523379	0.631871968	1.549574338	0.205190493	3.079440759	0.002073896	0.032032389
znf414	1015.014606	1.604379862	3.04065021	0.364655811	4.399710117	1.08E-05	0.000979422

znf511	847.9042402	1.495477991	2.819575532	0.275297247	5.432230093	5.57E-08	2.30E-05
znf593	473.8989087	0.584486823	1.49950551	0.233283057	2.50548339	0.012228414	0.097388367
znf608	1016.108334	0.910013847	1.879063533	0.249044667	3.654018611	0.000258168	0.008330353
znf639	736.9612615	0.478816183	1.393599666	0.132079966	3.625199176	0.000288739	0.00899633
znf653	152.9622446	-0.732295651	0.601945322	0.222722829	-3.287923626	0.001009292	0.01948109
znf740	1977.166673	0.591020092	1.506311445	0.147702342	4.001426696	6.30E-05	0.00344629
znf782	549.9572488	1.293217327	2.450739815	0.339834558	3.805432071	0.000141557	0.005729734
znf853	622.4347769	0.652401725	1.571782643	0.201555819	3.23682902	0.001208658	0.022118442
znhit6	819.1633583	0.654513951	1.574085549	0.246939386	2.650504484	0.008037166	0.0761674
zp2	776.8522598	2.127201324	4.36869178	0.395306808	5.381140118	7.40E-08	2.78E-05
zp3	777.4055676	2.566576151	5.924018522	0.527638285	4.864272027	1.15E-06	0.000237258
zp3.2	412.0228771	1.060992918	2.086366946	0.371175839	2.85846439	0.004256969	0.051586755
zp4.2	534.1035767	1.106962616	2.153916938	0.295465499	3.746503807	0.000179316	0.006605271
zpd	762.8470028	0.810325422	1.753606951	0.247844841	3.269486745	0.001077428	0.020438745
zswim7	7.584564319	2.351637801	5.10403351	0.888086494	2.647982844	0.008097363	0.076462171
zyg11b	533.9351849	0.782708339	1.720357431	0.213268039	3.670068617	0.000242485	0.007985446
zzef1	431.5755023	-0.754686775	0.592675048	0.252863002	-2.984567801	0.002839793	0.039399114
zzz3	2656.193241	0.394771578	1.314734581	0.152872033	2.582366252	0.009812539	0.085341503