

UCLA

UCLA Previously Published Works

Title

Genetics of Childhood-onset Schizophrenia

Permalink

<https://escholarship.org/uc/item/8qb5q9gd>

Journal

Child and Adolescent Psychiatric Clinics of North America, 22(4)

ISSN

1056-4993

Authors

Asarnow, Robert F
Forsyth, Jennifer K

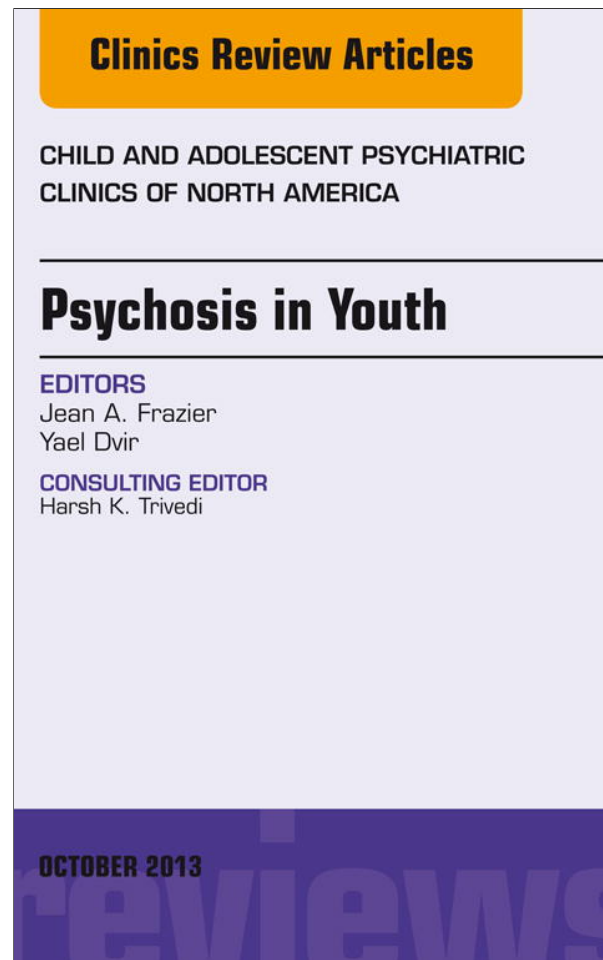
Publication Date

2013-10-01

DOI

10.1016/j.chc.2013.06.004

Peer reviewed



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/authorsrights>

Genetics of Childhood-onset Schizophrenia

Robert F. Asarnow, PhD^{a,b,*}, Jennifer K. Forsyth, MA^b

KEYWORDS

- Childhood-onset schizophrenia • Genetics • Common alleles • GWAS
- Copy number variants • Rare alleles • Autism

KEY POINTS

- Childhood-onset schizophrenia (COS) shares considerable genetic overlap with adult-onset schizophrenia (AOS).
- Causal genes for COS seem to involve both common and rare genetic variants.
- COS is associated with greater familial aggregation of schizophrenia spectrum disorders and a higher rate of rare allelic variants than AOS.
- COS shares genetic overlap with autism.
- The current usefulness of genetic screening for diagnosis and individualized treatment is limited; however, identifying common neural pathways on which multiple genetic variants act offers great promise toward developing novel pharmacologic interventions.

OVERVIEW

Childhood-onset schizophrenia (COS) is an early-onset variant of the more common adult-onset schizophrenia (AOS). Schizophrenia with onset before age 12 years is infrequent. The prevalence rate of COS is fewer than 1 in 10,000.¹ In contrast, the lifetime prevalence of AOS is 4.0 in 1000.² Before the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), there were no uniform diagnostic criteria for COS. Thus, early studies of COS included children who today would receive DSM-IV³ diagnoses of autistic disorder, pervasive developmental disorders (PDDs),

Funding Sources: Della Martin Foundation, NIMH grant MH 72697 (R.F. Asarnow); Della Martin Foundation (J.K. Forsyth).

Conflicts of Interest: None.

^a Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles, CA 90024, USA; ^b Department of Psychology, University of California at Los Angeles, Los Angeles, CA 90024, USA

* Corresponding author. Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles, CA 90024.

E-mail address: rasarnow@mednet.ucla.edu

Child Adolesc Psychiatric Clin N Am 22 (2013) 675–687

<http://dx.doi.org/10.1016/j.chc.2013.06.004>

childpsych.theclinics.com

1056-4993/13/\$ – see front matter © 2013 Elsevier Inc. All rights reserved.

schizophrenia, or disintegrative psychosis. In addition, there were significant variations among clinicians in how childhood schizophrenia was diagnosed.⁴

Epidemiologic and family studies indicate that genetic variations play a major role in the cause of AOS. Because of the low prevalence of COS, less is known about the role of genetic variations in COS. This article summarizes what is known about the role of genetic variations as risk factors for COS and compares results of genetic studies of COS with those of AOS. Genetic studies of COS parallel genetic studies of the more common AOS. Many genetic studies of COS were designed to determine whether the same genetic risk factors present in AOS occur in COS. The question underlying many of these studies was whether COS was a variant of AOS. To highlight the historical evolution of genetic studies of COS, this article reviews 3 classes of genetic studies: familial aggregation studies, common allele studies, and rare allele studies, in the order in which they historically occurred. The siblings of probands with COS typically have not entered the classic age of risk for schizophrenia. As a result, this review of familial aggregation of schizophrenia-related diagnoses and neurobiological abnormalities in relatives of AOS and COS probands focuses on studies of risk in parents of probands separately from risk in siblings.

FAMILIAL AGGREGATION STUDIES

The first genetic studies of AOS and COS examined family members of patients with AOS or COS to test the hypothesis that schizophrenia, schizophrenia spectrum disorders, and neurobiological abnormalities related to schizophrenia showed familial transmission.

Familial Aggregation of Schizophrenia

Every modern study that has used narrow, operationalized criteria for schizophrenia and collected data through both personal interview and interviews of family members has found that schizophrenia strongly aggregates in families of patients with AOS relative to families of community controls. Adoption and twin studies suggest that genetic factors greatly increase the risk of schizophrenia.⁵ Modern family studies showed a 3-fold increase in the relative risk (RR; ie, risk in relatives of AOS probands vs risk in relatives of community controls) for schizophrenia in parents of schizophrenia probands.⁵ The morbid risk for parents of AOS probands is 6% compared with 9% for siblings.⁶ Thus, there are significant differences in the risk for schizophrenia in the parents and siblings of probands with AOS.

Two early studies^{7,8} that used different diagnostic criteria for COS than were used by modern studies found that rates of schizophrenia in families of COS probands were comparable with rates in AOS probands. One study⁷ did not use operationalized criteria for schizophrenia but simply stated that the children had psychotic symptoms. Although the other study⁸ predated DSM-III it required that, to be diagnosed with COS, children had hallucinations, delusions, or formal thought disorder, but the criteria for these symptoms were not operationalized. An early twin study⁷ found a concordance for COS diagnosis for monozygotic twins of 88.2% compared with a concordance of 22.3% in dizygotic twins, resulting in an estimate of heritability of 84.5%. Two modern studies used DSM-III Revised (DSM-III-R) and collected data through both personal interview and interviews of family members. The UCLA study⁹ found an RR of 17 for schizophrenia in parents of COS probands. The National Institutes of Mental Health (NIMH) Child Psychiatry Branch¹⁰ study of 95 patients with COS found only 1 case of schizophrenia in parents of COS probands and none in parents of community control probands.

Familial Aggregation of Schizophrenia Spectrum Disorders

Modern family studies find that, in addition to schizophrenia, several other psychiatric disorders tend to aggregate in families of AOS probands. These disorders are termed schizophrenia spectrum disorders. The narrow schizophrenia spectrum includes schizoaffective disorder (depressed type), schizotypal personality disorder, schizophreniform and atypical psychosis, and paranoid personality disorder. The only two studies that determined the RR of schizophrenia spectrum disorders separately for parents (ie, not combined with siblings) of AOS probands found RRs of schizotypal personality and/or paranoid personality disorders of 6.6¹¹ and 3.0¹² in parents of AOS probands.

In the two modern family studies of COS probands, the RR for schizotypal personality and/or paranoid personality disorders in parents was 10.5⁹ and 15.2.¹⁰ In addition, there was an RR of 5.6 for avoidant personality disorder.⁹ When schizophrenia was included as a schizophrenia spectrum disorder, the RR for schizophrenia spectrum disorders was 16.9⁹ and 15.9¹⁰ in parents of COS probands. The RR for just schizophrenia, schizotypal, or paranoid personality disorders was 15.1 in parents of COS probands.⁹ Compared with the RR of 5.8 for schizophrenia, schizotypal, or paranoid personality disorder in a large family study of AOS probands that used similar diagnostic approaches to the UCLA study,¹¹ the RR risk of schizophrenia and schizophrenia spectrum disorders seems to be greater in parents of COS probands than in parents of AOS probands. The increased rate of schizophrenia spectrum disorders of COS probands is consistent with familial transmission. The greater concordance for schizophrenia in monozygotic than dizygotic twins in the Kallman and Roth⁷ twin study suggests that schizophrenia is highly heritable in COS.

Familial Aggregation of Neurobiological Abnormalities

Several neurobiological abnormalities present in patients with AOS are also present in a substantial number of their nonpsychotic first-degree relatives. These abnormalities are sometimes referred to as endophenotypes. Endophenotypes are features that lie intermediate to the phenotype and genotype of schizophrenia¹³ and are therefore hypothesized to be closer to the effects of schizophrenia genes than are DSM-IV³ symptoms of schizophrenia. Given the complexity of the genetic architecture and the heterogeneity of schizophrenia, some have argued that identifying endophenotypes may help in elucidating the causal pathways between putative risk genes and their expression as a clinically identifiable phenotype.¹⁴

Abnormalities found in the nonpsychotic first-degree relatives of patients with AOS include impairments in neurocognitive functioning, abnormalities in smooth-pursuit eye movements, brain structure, brain electrical activity, and autonomic activity. Many of the abnormalities found in nonpsychotic relative of AOS probands are also found in the nonpsychotic relatives of COS probands. For example, a combination of scores on 3 tests that detect neurocognitive deficits in nonpsychotic relatives of AOS probands identified 20% of mothers and fathers of COS probands compared with 0% of the mothers or fathers of community control probands. There was some diagnostic specificity of the neurocognitive impairments: 12% of mothers of COS probands were identified compared with 0% of attention-deficit/hyperactivity disorder (ADHD) mothers. A cutoff that identified 2% of the fathers of ADHD probands similarly classified 17% of the fathers of COS probands.¹⁵ Nonpsychotic first-degree relatives of patients with COS showed impairments on a measure of attention/executive function¹⁶ and in smooth-pursuit eye tracking,¹⁷ and nonpsychotic siblings of COS probands showed deficits on a procedural skill learning task supported by a cortical-striatal

network.¹⁸ A longitudinal study¹⁹ found that before adolescence the nonpsychotic siblings of patients with COS show reduced cortical gray matter in the superior temporal prefrontal areas, but that this reduction normalizes during adolescence. In general, the first-degree relatives of patients with COS show subtle impairments on some of the tasks identified as potential endophenotypes in studies of relatives of patients with AOS.

The presence of these neurobiological abnormalities in nonpsychotic relatives of patients with COS indicates that they do not merely reflect the effects of psychosis. Moreover, a family study of first-degree and second-degree relatives of community control probands with and without family histories of schizophrenia¹⁵ found that impairments in neurocognitive functioning and schizophrenia spectrum disorders were independent expressions of familial liability to schizophrenia. Given that schizophrenia is a complex, polygenic disorder, the genes associated with neurobiological endophenotypes may not be the same set of genes that are associated with psychotic symptoms.

Paralleling the heterogeneity of findings in studies of patients with COS and AOS, many first-degree relatives of patients with schizophrenia do not have neurobiological abnormalities. In addition, there is considerable heterogeneity among relatives who do show neurobiological abnormalities in what abnormalities they have. Not all relatives show the same abnormalities. The neurobiological abnormalities identified in nonpsychotic relatives of patients with COS seem to tap diverse neural networks. It remains to be seen whether there is a common pathway for the neural networks underlying these neurobiological abnormalities. An alternative is that the heterogeneity of neurobiological abnormalities may indicate that impairments in specific neural networks are associated with different sets of susceptibility genes. If this is the case, endophenotypes might identify biologically meaningful subtypes of schizophrenia linked to specific genotypes, thereby providing a clearer link between genetic and phenotypic variation.²⁰

STUDIES OF COMMON ALLELES

Studies of complex diseases, including AOS, have been guided until recently by the common disease/common variant hypothesis. This hypothesis proposes that common polymorphisms, classically defined as genetic variants present in more than 1% of the population, might contribute to susceptibility to common diseases.²¹ The common disease/common variant hypothesis was stimulated by findings from population genetics that humans have limited genetic variation: most genetic variation in an individual is shared with other members of the species. Studies of some common genetic variants for diseases such as age-related macular degeneration, type 2 diabetes, and Crohn disease have identified numerous common variants associated with increased risk for these complex, polygenic diseases.²¹ However, in most complex polygenic disorders, each variation has a small effect on the disease phenotype. It is thought that one of the reasons these polygenic diseases are not rapidly removed through selection is that so many genes influence the phenotype.

Because of the low incidence of COS there are few molecular genetic studies of COS. Of the existing studies, most used a candidate gene approach to examine whether common genetic polymorphisms are associated with COS. The candidate gene approach used a limited number of single-nucleotide polymorphisms (SNPs) to tag common variations in genes selected on an a priori basis. Candidate genes selected for investigation in these studies were chosen largely based on positive associations in AOS samples. A summary of the positive gene associations with COS is shown in **Table 1**.

| Table 1 Genes associated with childhood-onset and early-onset schizophrenia in candidate gene studies | | | | |
|--|--|---|--|-------------------|
| Investigators and Year | Study Design | Sample | Significant Associations | Smallest P |
| Addington et al, ²² 2004 | Family-based transmission disequilibrium for 8 G72/G30 locus and 2-marker haplotypes and DAO SNPs | 53 COS proband trios, 11 COS proband dyads, 16 psychosis NOS proband trios, 8 psychosis NOS dyads (mixed ethnicity) | 3 G72/G30 locus SNPs associated with COS; two 2-marker G72/G30 SNP haplotypes associated with COS; no DAO SNPs associated with COS | .015 |
| Addington et al, ²³ 2005 | Family-based transmission disequilibrium for 14 GAD1, all haplotypes with 2, 3, and 4 SNPs, and 3 GAD2 SNPs | 55 COS + psychosis NOS trios, 11 COS + psychosis NOS dyads (mixed ethnicity) | 3 GAD1 SNPs associated with COS; one 4 SNP haplotype associated with COS | .005 |
| Gornick et al, ²⁴ 2005 | Family-based transmission disequilibrium for 14 dysbindin SNPs | 73 COS + psychosis NOS proband trios, 19 COS + psychosis NOS proband dyads (mixed ethnicity) | 1 dysbindin SNP associated with COS; two 2-marker haplotypes containing P3521 associated with COS | .008 |
| Addington et al, ²⁵ 2007 | Family-based transmission disequilibrium for 56 NRG1 SNPs and 2 microsatellites | 59 COS + psychosis NOS proband trios, 11 COS + psychosis NOS proband dyads (mixed ethnicity) | Several NRG1 SNPs associated with COS; several 2, 3, and 4 SNP haplotypes associated with COS | .0004 |
| Sekizawa et al, ²⁶ 2004 | Childhood-onset case vs control design for tryptophan hydroxylase gene polymorphism | 51 COS (onset before 16 y) vs 148 healthy controls (Japanese) | AA genotype associated with COS (OR = 1.97) | .0058 |
| Pakhomova et al, ²⁷ 2011 | Early-onset case vs control design for BDNF Val/Met polymorphism, 5-HTTLPR, type 2A serotonin receptor, T 102c, D2 dopamine receptor (Taq1A) | 65 EOS (onset before 15 y) vs 111 healthy controls (Russian) | ValVal BDNF polymorphism associated with EOS | .03 |

Abbreviation: OR, odds ratio.

The NIMH Child Psychiatry Branch COS study is the largest and most thoroughly characterized sample of individuals with COS to date. Initiated in 1990, the investigators genotyped COS probands and their parents to determine whether specific genetic polymorphisms were associated with proband status using family-based transmission tests. Results indicated that COS was significantly associated with common polymorphisms in G72/G30,²² GAD1,²³ dysbindin,²⁴ and NRG1.²⁵ Polymorphisms in these genes were also associated with neurobiological and clinical features in COS probands. Individuals with COS with the NRG1 risk alleles showed larger gray and white matter volume in childhood and a steeper rate of volume decline into adolescence relative to individuals with COS without these risk alleles.²⁵ GAD1 polymorphisms were similarly associated with increased rate of frontal gray matter volume loss.²³ G72/G30 risk alleles were associated with later age of onset and better premorbid functioning in these individuals.²² In addition, the dysbindin allele was also associated with later age of onset.²⁴ Other candidate gene studies of individuals with COS and early-onset schizophrenia (EOS) using independent samples have compared the frequencies of gene polymorphisms in COS/EOS cases versus healthy controls. Results from these studies indicated that COS was associated with a polymorphism in the tryptophan hydroxylase gene in a Japanese sample²⁶ and with the ValVal polymorphism of the BDNF gene in a Russian sample.²⁷

Genome-wide Association Studies of AOS

In contrast with candidate gene studies, which examine a limited number of SNPs, genome-wide association studies (GWASs) use a broader array of SNPs to systematically examine the genome independently of any prior hypotheses about susceptibility genes. GWAS approaches are particularly important in studies of schizophrenia because the limited knowledge about the pathobiology of this disorder severely constrains the ability to choose high-quality candidate genes. However, because of the large number of statistical comparisons that are made, strict thresholds of statistical significance are required that place a premium on large sample sizes.²⁸ Taken collectively, the NIMH COS and UCLA studies have collected data from fewer than 200 patients with COS. Given that an AOS study with a sample size of 16,161 participants did not yield a genome-wide significant result,²⁸ the COS samples cannot yet support a GWAS study.

Given the similarity of results of familial aggregation and candidate gene studies of COS and AOS probands, it is reasonable to expect that the results of GWAS studies of patients with AOS might extend to patients with COS. Recent reviews and meta-analysis of GWAS studies of AOS probands^{28,29} have concluded that:

1. There is a genome-wide significant association between AOS and the major histocompatibility locus on chromosome 6p with an odds ratio of 1.14 to 1.16, as well as with TCF4, a neuronal transcription factor implicated in neurogenesis.
2. The data support a polygenic model of AOS, involving hundreds of genes with small individual effects; polygenic variants collectively account for approximately 30% of the total variation in genetic liability to schizophrenia, and much of the genetic variation in schizophrenia is not accounted for by variations in common alleles.
3. GWAS results have frequently not supported prior reports of associations with classic candidate genes.
4. There is genetic overlap of schizophrenia with autism and bipolar disorder.

STUDIES OF RARE ALLELES

An alternative to the common disease/common allele model is the common disease/rare variant model.³⁰ Rare alleles are classically defined as genetic variants with a

minor allele that occurs in less than 1% of the population.³⁰ As applied to schizophrenia this model, as discussed by Walsh and colleagues,³¹ hypothesizes “that some mutations predisposing to schizophrenia are highly penetrant, individually rare, and of recent origin, even specific to single cases and families.” A major focus of studies of rare variants in schizophrenia has been copy number variations (CNVs). The development of microarray-based methods for conducting genome-wide scans for structural variants allowed higher resolution exploration of the structure of chromosomes that led to the discovery that variation in the number of copies of large stretches of DNA (ie, fewer or more than the expected 2 copies) is present in the normal population and also contributes to genetic risk for complex illnesses. CNVs are stretches of genomic deletions and duplications ranging from 1 kb to several Mb, and thus are likely to have larger phenotypic effects than SNPs. Studies of CNVs have begun to change the understanding of the genetic architecture underlying psychiatric illnesses. In addition to the role of common genetic variants in the genetic architecture of AOS and COS, increasing research now points to a key role for variation in chromosomal structure as well.³²

The first major study³¹ of rare structural variants (ie, microduplications and microdeletions) in schizophrenia compared the overall frequency of CNVs in patients with AOS, COS, and ancestry-matched controls. Fifteen percent of patients with schizophrenia with onset after 18 years of age had novel structural variants compared with 5% of controls. Patients with earlier ages of onset had increased frequencies of novel structural variants. Twenty percent of patients with schizophrenia with onset before 18 years of age and 28% of patients with COS carried one or more rare structural variants. Almost every rare structural variant identified in patients was unique. Some deletions and duplications were multiple megabases in size; other variants altered only 1 or a few genes. The mutations found in patients with schizophrenia disproportionately affected genes involved in signaling networks that control brain development, especially those involving neuregulin and glutamate pathways.³¹

The NIMH COS study found that, of 96 patients with COS, 10% showed large chromosomal abnormalities, including 4 individuals with the 3-Mb 22q11.21 deletion, 3 individuals with sex chromosome abnormalities, and 2 individuals with 500-kb duplications at 16p11.2; all at rates significantly higher than those seen in the general population or in AOS.³³ Two novel duplications disrupting the *MYT1L* gene on chromosome 2p25.3, one 2.5-Mb deletion on chromosome 2q31.2-31.3, 1 novel 115-kb deletion on *NRXN1*, and one 120-kb duplication overlapping exons in the *SRGAP3* gene on chromosome 3p25.3 were also found in additional patients with COS.³³ Individual case reports have identified additional rare and de novo mutations in other individuals with COS, including a novel frameshift mutation in *UPF3B*,³⁴ a de novo missense mutation in the gene encoding *SHANK3*³⁵ and a 1.58-Mb de novo 3q29 deletion encompassing numerous genes.³⁶

As noted earlier, the concordance rates for schizophrenia are greater than expected in monozygotic than dizygotic twins.⁷ Deleterious de novo mutations, which enter the gene pool for only a brief time because they reduce fecundity, are therefore rarely transmitted and may be the simplest way to account for large discrepancies between monozygotic and dizygotic concordance rates.³⁷ A similar monozygotic/dizygotic pattern is observed in twin studies of autism and AOS, disorders for which de novo variation has already been shown to be a significant contributor.³⁸ In line with this, most COS cases in the NIMH and UCLA cohorts are apparently sporadic even after detailed diagnostic evaluations of family members were conducted.

Furthermore, there is a strong monotonic increase in the risk for AOS with increasing paternal age. One explanation of this finding is that older fathers have a higher rate of

de novo mutations. Malaspina and colleagues³⁹ state that sporadic cases of AOS had significantly older fathers than cases with a family history of schizophrenia “supports the hypothesis that de novo mutations contribute to the risk of sporadic schizophrenia.” The effect of paternal age on risk for COS has not been rigorously examined.

GENE-ENVIRONMENT INTERACTION

A widely accepted working model of schizophrenia hypothesizes that abnormalities during embryonic brain development are caused by genetic variations. Tsuang⁶ states that “Environmental insults such as fetal hypoxia during delivery and infection in the second trimester of pregnancy interact with the genotype to produce the neuropathology and cognitive deficits.” In AOS, a history of obstetric complications is associated with having an earlier age of onset of schizophrenia than in patients without a history of obstetric complications.⁴⁰

The NIMH COS study did not find an increased rate of obstetric complications in COS probands.⁴¹ In contrast, a Japanese study⁴² found increased rates of obstetric complications, particularly for boys, in patients with COS compared with children with other psychiatric disorders. Histories of obstetric complications are found in children with several neuropsychiatric conditions besides COS. Neither study examined whether obstetric complications interacted with family history of schizophrenia.

PLEIOTROPY: OVERLAP WITH AUTISM

Variation in a gene can result in multiple phenotypes. This variation is referred to as pleiotropy. For example, in humans, colon/lung cancer and familial Parkinson disease are both associated with variations in the PARK2 gene.⁴³ Based on phenomenological and follow-up data in DSM-IV, autism and schizophrenia are separate and distinct disorders. However, molecular genetic studies suggest considerable overlap between these disorders. Forty-five genes have been evaluated for positive associations with both autism and AOS or COS. Although failures to replicate have been common, at least 20 of these genes were positively associated with both autism and schizophrenia, 2 genes were positive for autism and not schizophrenia, 11 genes were positive for schizophrenia and not autism, and 12 genes were negatively associated with both disorders.⁴⁴ Moreover, there are increased rates of rare CNVs that sometimes overlap in children with autism and children with schizophrenia.^{36,45} Thus, increasing evidence suggests some overlap in genetic risk for COS and autism.

SUMMARY

Schizophrenia (AOS and COS) is a highly heritable disorder with a heterogeneous genomic architecture. Like autism, there are at least 2 distinct genetic mechanisms for acquiring schizophrenia, one through de novo mutations resulting in rare alleles in simplex families, and one through inheritance of common alleles of small effect in multiplex families. Most of the mutations associated with schizophrenia are currently thought to be rare alleles.⁴⁶

The adult-onset and childhood-onset forms of schizophrenia seem to overlap genetically. The differences between AOS and COS seem to be quantitative. There is a greater aggregation of schizophrenia and schizophrenia spectrum disorders in first-degree relatives of patients with COS compared with first-degree relatives of patients with AOS. In addition, the occurrence of rare alleles, mostly de novo, seems to be higher in patients with COS compared with patients with AOS. Other than these quantitative differences, genetic studies have offered little insight thus far into why,

in rare cases, the first onset of schizophrenia occurs before adolescence, which is perhaps the most interesting question to be addressed in future genetic studies of COS.

The recent findings on common and rare alleles shed light on a question that has long puzzled geneticists. How has schizophrenia persisted in the gene pool given the adverse effect of this disorder on fertility? Negative selection predicts the removal of most risk alleles with major deleterious effects. In schizophrenia (and other neuropsychiatric disorders such as autism), common risk alleles have small effects and alleles with large penetrance (eg, CNVs) are rare. Multiple common alleles are required to develop schizophrenia. The increase in risk conferred by any one common allele is small. Duan and colleagues²⁹ state that, "Rare risk alleles are either of recent origin if highly penetrant, or older mutations with smaller effect which have not yet been eliminated by selection."

Both the common disease/common variant and rare allele models face challenges in explicating the genetic mechanisms for the transmission of schizophrenia. The common disease/common variant model accounts for a small percentage of cases, and any 1 allelic variation, with rare exceptions, confers only a small amount of risk for schizophrenia. In contrast, alleles with large penetrance (eg, CNVs) are rare, and negative selection predicts the removal of most risk alleles with major deleterious effects from the population gene pool, which suggests that the genomes of individuals with these conditions are unusually fragile.³⁰ However, Schork and colleagues³⁰ state that, "the unique phenotypes of autism, schizophrenia and bipolar disorder seem too specific for a gross molecular lesion such as global genomic instability."

The common disease/common variant and rare allele models of schizophrenia also have the challenge of explaining how either many different common alleles of small effect, or many different rare (in many cases unique) mutations can eventuate in the same clinical phenotype: schizophrenic symptoms. The corresponding challenge for both models is to account for how many of the common allelic variants and the propensity for rare variants found in schizophrenia are also frequently present in autism and bipolar disorder.

What both sets of challenges indicate is that, in schizophrenia, the pathways from genotype to phenotype are complex. Mapping the pathways from allelic variation to the symptoms of schizophrenia requires a deeper understanding of both the schizophrenia phenotype and the genetic mechanisms that increase risk for this disorder than is implied in earlier, simpler models of the genetic transmission of schizophrenia. This process has been further complicated by research suggesting that gene expression can be regulated by genes in noncoding regions of the genome and has led to interest in sequencing the noncoding regions to identify epistatic interactions with putative susceptibility genes. Thus, it is increasingly evident that a systems biology approach that, as Duan and colleagues²⁹ put it, "integrates genomic, transcriptomic, and proteomic data, metabolomics, gene networks, epigenetics and environmental factors" must be integrated with data on neural networks in order to elucidate the pathways from allelic variations to specific schizophrenia phenotypes. The findings briefly summarized earlier on genetic mechanisms and phenotypes in schizophrenia put in focus the necessity of this approach for both COS and AOS.

RELEVANCE OF GENETICS TO CLINICIANS/IMPLICATIONS FOR CLINICAL PRACTICE

In several areas of medicine, genetic information is beginning to be used to refine diagnoses and individualize treatment. For example, BRCA mutation in either of the BRCA1 or BRCA2 genes can result in a hereditary breast-ovarian cancer syndrome

that accounts for 5% to 10% of breast cancer cases in women. Approximately 50% to 65% of women born with a deleterious mutation in BRCA1 and 40% to 57% of women with a deleterious mutation in BRCA2 develop breast cancer by age 70 years. In addition, there are implications for prognosis and treatment of having a BRAC1 versus BRAC2 mutation. For example, Imyanitov and colleagues⁴⁷ state that “multiple lines of evidence indicate that women with BRCA1-related BC may derive less benefit from taxane-based treatment than other categories of BC patients.” In contrast with BRAC1 and BRAC2 mutations in breast and ovarian cancer, the allelic mutations associated with increased risk for schizophrenia detected so far offer little immediate prospect for helping to refine diagnosis or guide treatment. Each mutation in common alleles has a very small effect on risk for schizophrenia and it seems that some combination of multiple common alleles is required to substantially increase schizophrenia risk. In contrast, rare alleles may have larger effects on risk but they are idiosyncratic and therefore not useful in screening populations for schizophrenia risk. In line with this complexity and heterogeneity of genetic risk for schizophrenia, individualized treatment based on knowledge of individual genotypes seems an unrealistic goal for the foreseeable future.

In contrast, elucidating the neurobiological pathways from genes to specific schizophrenia phenotypes offers an important opportunity to identify new therapeutic targets for drug development, which is of vital interest because of the current limited understanding of the pathobiology of schizophrenia. The limited understanding of the pathobiology of schizophrenia stems from the absence of good animal or molecular models of schizophrenia. Identifying the common pathways through which multiple genes adversely affect complex neural systems offers great promise in beginning to identify new therapeutic targets for this debilitating condition.

Summary

Implications for clinical practice

- COS is a rare variant of AOS
- COS shares genetic overlap with autism
- Causal genes for COS include both common variants of small effect and rare variants with larger effect
- The current usefulness of genetic screening for COS diagnosis and individualized treatment is limited
- Identifying common neural pathways on which multiple genetic variants act offers promise toward developing novel pharmacologic interventions

REFERENCES

1. Burd L, Kerbeshian J. A North Dakota prevalence study of schizophrenia presenting in childhood. *J Am Acad Child Adolesc Psychiatry* 1987;26:347–50.
2. McGrath J, Saha S, Chant D, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 2008;30:67–76.
3. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th edition. Washington, DC: Author; 1994.
4. Asarnow RF. Childhood schizophrenia. In: Beauchaine TP, Hinshaw SP, editors. *Child and adolescent psychopathology*; . p. 685–713.
5. Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophr Bull* 1993;19:261–85.

6. Tsuang M. Schizophrenia: genes and environment. *Biol Psychiatry* 2000;47: 210–20.
7. Kallmann FJ, Roth B. Genetic aspects of pre-adolescent schizophrenia. *Am J Psychiatry* 1956;112:599–606.
8. Kolvin I, Ounsted C, Richardson L, et al. Studies in the childhood psychoses, III: the family and social background in childhood psychoses. *Br J Psychiatry* 1971; 118:396–402.
9. Asarnow RF, Nuechterlein KH, Fogelson D, et al. Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. *Arch Gen Psychiatry* 2001;58: 581–8.
10. Nicholson R, Brookner FB, Lenane M, et al. Parental schizophrenia spectrum disorders in childhood-onset and adult-onset schizophrenia. *Am J Psychiatry* 2003;160:490–5.
11. Kendler KS, McGuire M, Gruenberg AM, et al. The Roscommon family study: I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch Gen Psychiatry* 1993;50:527–40.
12. Baron M, Gruen R, Asnis L, et al. Familial transmission of schizotypal and borderline personality disorders. *Am J Psychiatry* 1985;142:927–34.
13. Gottesman II, Shields J. Genetic theorizing and schizophrenia. *Br J Psychiatry* 1973;122:15–30.
14. Nenadic I, Gaser C, Sauer H. Heterogeneity of brain structural variation and the structural imaging endophenotypes in schizophrenia. *Neuropsychobiology* 2012; 66:44–9.
15. Asarnow RF, Nuechterlein KH, Subotnik KL, et al. Neurocognitive impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder: the University of California, Los Angeles family study. *Arch Gen Psychiatry* 2002;59:1053–60.
16. Gochman PA, Greenstein D, Sporn A, et al. Childhood onset schizophrenia: familial neurocognitive measures. *Schizophr Res* 2004;71:43–7.
17. Sporn A, Greenstein D, Gogtay N, et al. Childhood-onset schizophrenia: smooth pursuit eye-tracking dysfunction in family members. *Schizophr Res* 2005;73: 243–52.
18. Wagshal D, Knowlton BJ, Cohen JR, et al. Deficits in probabilistic classification learning and liability for schizophrenia. *Psychiatry Res* 2012;200: 167–72.
19. Mattai AA, Weisinger B, Greenstein D, et al. Normalization of cortical gray matter deficits in nonpsychotic siblings of patients with childhood-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* 2011;50:697–704.
20. Greenwood TA, Lazzeroni LC, Murray SS, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am J Psychiatry* 2011;168:930–46.
21. Altshuler D, Daly MJ, Lander ES. Genetic mapping in human disease. *Science* 2008;322:881–8.
22. Addington AM, Gornick M, Sporn AL, et al. Polymorphisms in the 13q33.2 gene G72/G30 are associated with childhood-onset schizophrenia and psychosis not otherwise specified. *Biol Psychiatry* 2004;55:976–80.
23. Addington AM, Gornick M, Duckworth J, et al. GAD1 (2q31.1), which encodes glutamic acid decarboxylase (GAD-sub-6-sub-7), is associated with childhood-onset schizophrenia and cortical gray matter volume loss. *Mol Psychiatry* 2005; 10:581–8.

24. Gornick MC, Addington AM, Sporn A, et al. Dysbindin (DTNBP1, 6p22.3) is associated with childhood-onset psychosis and endophenotypes measured by the Premorbid Adjustment Scale (PAS). *J Autism Dev Disord* 2005;35:831–8.
25. Addington AM, Gornick MC, Shaw P, et al. Neuregulin 1 (8p12) and childhood-onset schizophrenia: susceptibility haplotypes for diagnosis and brain developmental trajectories. *Mol Psychiatry* 2007;2:195–205.
26. Sekizawa T, Iwata Y, Nakamura K, et al. Childhood-onset schizophrenia and tryptophan hydroxylase gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet* 2004;128B:24–6.
27. Pakhomova SA, Korovaitseva GI, Monchakovskaya MY, et al. Molecular genetic studies of early-onset schizophrenia. *Neurosci Behav Physiol* 2011;41:532–5.
28. Gejman PV, Sanders AR, Kendler KS. Genetics of schizophrenia: new findings and challenges. *Annu Rev Genomics Hum Genet* 2011;12:121–44.
29. Duan J, Sanders AR, Gejman PV. Genome-wide approaches to schizophrenia. *Brain Res Bull* 2010;83:93–102.
30. Schork NJ, Murray SS, Frazer KA, et al. Common vs. rare allele hypotheses for complex diseases. *Curr Opin Genet Dev* 2009;19:212–9.
31. Walsh T, McClellan JM, McCarthy SE, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 2008;320:539–43.
32. Hoffman EJ, State MW. Progress in cytogenetics: implications for child psychopathology. *J Am Acad Child Adolesc Psychiatry* 2010;49:736–51.
33. Addington AM, Rapoport JL. The genetics of childhood-onset schizophrenia: when madness strikes the prepubescent. *Curr Psychiatry Rep* 2009;11:156–61.
34. Addington AM, Gauthier J, Piton A, et al. A novel frameshift mutation in UPF3B identified in brothers affected with childhood onset schizophrenia and autism spectrum disorders. *Mol Psychiatry* 2011;16:238–9.
35. Gauthier J, Champagne N, Lafreniere RG, et al. De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. *Proc Natl Acad Sci U S A* 2010;107:7863–8.
36. Sagar A, Bishop JR, Tessman C, et al. Co-occurrence of autism, childhood psychosis, and intellectual disability associated with a de novo 3q29 microdeletion. *Am J Med Genet A* 2013;161:845–9.
37. Zhao X, Leotta A, Kustanovich V, et al. A unified genetic theory for sporadic and inherited autism. *Proc Natl Acad Sci U S A* 2007;104:12831–6.
38. El-Fishawy P, State M. The genetics of autism: key issues, recent findings and clinical implications. *Psychiatr Clin North Am* 2010;33:83–105.
39. Malaspina D, Corcoran C, Fahim C, et al. Paternal age and sporadic schizophrenia: evidence for de novo mutations. *Am J Med Genet* 2002;114:299–303.
40. Geddes JR, Lawrie S. Obstetric complications and schizophrenia: a meta-analysis. *Br J Psychiatry* 1995;167:786–93.
41. Rapoport JL, Addington AM, Frangou S. The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry* 2005;10:439–49.
42. Matsumoto H, Takei N, Saito H, et al. Childhood-onset schizophrenia and obstetric complications: a case-control study. *Schizophr Res* 1999;38:93–9.
43. Veeriah S, Taylor BS, Meng S, et al. Somatic mutations of the Parkinson's disease-associated gene PARK2 in glioblastoma and other human malignancies. *Nat Genet* 2010;42:77–82.
44. Crespi B, Stead P, Elliott M. Comparative genomics of autism and schizophrenia. *Proc Natl Acad Sci U S A* 2010;107:1736–41.

45. Rapoport J, Chavez A, Greenstein D, et al. Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. *J Am Acad Child Adolesc Psychiatry* 2009;48:10–8.
46. Akil H, Brenner S, Kandel E, et al. The future of psychiatric research: genomes and neural circuits. *Science* 2010;327:1580–1.
47. Imyanitov EN, Moiseyenko VM. Drug therapy for hereditary cancers. *Hered Cancer Clin Pract* 2011;9:5.