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Authors

Lango Allen, Hana
Estrada, Karol
Lettre, Guillaume
[et al.](#)

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Hundreds of variants clustered in genomic loci and biological pathways affect human height

A full list of authors and affiliations appears at the end of the article.

Abstract

Most common human traits and diseases have a polygenic pattern of inheritance: DNA sequence variants at many genetic loci influence phenotype. Genome-wide association (GWA) studies have identified >600 variants associated with human traits¹, but these typically explain small fractions of phenotypic variation, raising questions about the utility of further studies. Here, using 183,727 individuals, we show that hundreds of genetic variants, in at least 180 loci, influence adult height, a highly heritable and classic polygenic trait^{2,3}. The large number of loci reveals patterns with important implications for genetic studies of common human diseases and traits. First, the 180 loci are not random, but instead are enriched for genes that are connected in biological pathways ($P=0.016$), and that underlie skeletal growth defects ($P<0.001$). Second, the likely causal gene is often located near the most strongly associated variant: in 13 of 21 loci containing a known skeletal growth gene, that gene was closest to the associated variant. Third, at least 19 loci have multiple independently associated variants, suggesting that allelic heterogeneity is a frequent feature of polygenic traits, that comprehensive explorations of already-discovered loci should discover additional variants, and that an appreciable fraction of associated loci may have been identified. Fourth, associated variants are enriched for likely functional effects on genes, being over-represented amongst variants that alter amino acid structure of proteins and expression levels of nearby genes. Our data explain ~10% of the phenotypic variation in height, and we estimate that unidentified common variants of similar effect sizes would increase this figure to ~16% of phenotypic variation (~20% of heritable variation). Although additional approaches are needed to fully dissect the genetic architecture of polygenic human traits, our findings indicate that GWA studies can identify large numbers of loci that implicate biologically relevant genes and pathways.

In Stage 1 of our study, we performed a meta-analysis of GWA data from 46 studies, comprising 133,653 individuals of recent European ancestry, to identify common genetic variation associated with adult height. To enable meta-analysis of studies across different genotyping platforms, we performed imputation of 2,834,208 single nucleotide

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Corresponding Authors: Michael Weedon, Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, EX1 2LU, UK, michael.weedon@pms.ac.uk, Gonçalo Abecasis, Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA, goncalo@umich.edu, Kari Stefansson, deCODE Genetics, 101 Reykjavik, Iceland, kstefans@decode.is, Timothy Frayling, Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, EX1 2LU, UK, tim.frayling@pms.ac.uk, Joel Hirschhorn, Children's Hospital, Harvard Medical School, Broad Institute, Boston, Massachusetts 02115, USA, joelh@broadinstitute.org.

*These authors contributed equally

Author Contributions: Full author contributions and roles are listed in the Supplementary Information.

polymorphisms (SNPs) present in the HapMap Phase 2 European-American reference panel⁴. After applying quality control filters, each individual study tested the association of adult height with each SNP using an additive model (Supplementary Methods). The individual study statistics were corrected using the genomic control (GC) method^{5,6} and then combined in a fixed effects based meta-analysis. We then applied a second GC correction on the meta-analysis statistics, although this approach may be overly conservative when there are many real signals of association (Supplementary Methods). We detected 207 loci (defined as 1Mb on either side of the most strongly associated SNP) as potentially associated with adult height ($P < 5 \times 10^{-6}$).

To identify loci robustly associated with adult height, we took forward at least one SNP (Supplementary Methods) from each of the 207 loci reaching $P < 5 \times 10^{-6}$ into an additional 50,074 samples (Stage 2) that became available after completion of our initial meta-analysis. In the joint analysis of our Stage 1 and Stage 2 studies, SNPs representing 180 loci reached genome-wide significance ($P < 5 \times 10^{-8}$; Supplementary Figures 1 and 2, Supplementary Table 1). Additional tests, including genotyping of a randomly-selected subset of 33 SNPs in an independent sample of individuals from the 5th-10th and 90th-95th percentiles of the height distribution (N=3,190)⁷, provided further validation of our results, with all but two SNPs showing consistent direction of effect (sign test $P < 7 \times 10^{-8}$) (Supplementary Methods, Supplementary Table 2).

Genome wide association studies can be susceptible to false positive associations from population stratification⁷. We therefore performed a family-based analysis, which is immune to population stratification in 7,336 individuals from two cohorts with pedigree information. Alleles representing 150 of the 180 genome-wide significant loci were associated in the expected direction (sign test $P < 6 \times 10^{-20}$; Supplementary Table 3). The estimated effects on height were essentially identical in the overall meta-analysis and the family-based sample. Together with several other lines of evidence (Supplementary Methods), this indicates that stratification is not substantially inflating the test statistics in our meta-analysis.

Common genetic variants have typically explained only a small proportion of the heritable component of phenotypic variation⁸. This is particularly true for height, where >80% of the variation within a given population is estimated to be attributable to additive genetic factors⁹, but over 40 previously published variants explain <5% of the variance¹⁰⁻¹⁷. One possible explanation is that many common variants of small effects contribute to phenotypic variation, and current GWA studies remain underpowered to detect the majority of common variants. Using five studies not included in Stage 1, we found that the 180 associated SNPs explained on average 10.5% (range 7.9-11.2%) of the variance in adult height (Supplementary Methods). Including SNPs associated with height at lower significance levels ($0.05 > P > 5 \times 10^{-8}$) increased the variance explained to 13.3% (range 9.7-16.8%) (Figure 1a)¹⁸. In addition, we found no evidence that non-additive effects including gene-gene interaction would increase the proportion of the phenotypic variance explained (Supplementary Methods, Supplementary Tables 5 and 6).

As a separate approach, we used a recently developed method¹⁹ to estimate the total number of independent height-associated variants with effect sizes similar to the ones identified. We obtained this estimate using the distribution of effect sizes observed in Stage 2 and the power to detect an association in Stage 1, given these effect sizes (Supplementary Methods). The cumulative distribution of height loci, including those we identified and others as yet undetected, is shown in Figure 1b. We estimate that there are 697 loci (95% confidence interval (CI): 483-1040) with effects equal or greater than those identified, which together would explain approximately 15.7% of the phenotypic variation in height or 19.6% (95% CI: 16.2-25.6) of height heritability (Supplementary Table 4). We estimated that a sample size of 500,000 would detect 99.6% of these loci at $P < 5 \times 10^{-8}$. This figure does not account for variants that have effect sizes smaller than those observed in the current study and, therefore, underestimates the contribution of undiscovered common loci to phenotypic variation.

A further possible source of missing heritability is allelic heterogeneity – the presence of multiple, independent variants influencing a trait at the same locus. We performed genome-wide conditional analyses in a subset of Stage 1 studies, including a total of 106,336 individuals. Each study repeated the primary GWA analysis but additionally adjusted for SNPs representing the 180 loci associated at $P < 5 \times 10^{-6}$ (Supplementary Methods). We then meta-analysed these studies in the same way as for the primary GWA study meta-analysis. Nineteen SNPs within the 180 loci were associated with height at $P < 3.3 \times 10^{-7}$ (a Bonferroni-corrected significance threshold calculated from the ~15% of the genome covered by the conditioned 2Mb loci; Supplementary Methods, Table 1, Figure 2, Supplementary Figure 3). The distances of the second signals to the lead SNPs suggested that both are likely to be affecting the same gene, rather than being coincidentally in close proximity. At 17 of 17 loci (excluding two contiguous loci in the *HMGAI* region), the second signal occurred within 500kb, rather than between 500kb and 1 Mb, of this lead SNP (binomial test $P = 2 \times 10^{-5}$). Further analyses of allelic heterogeneity may identify additional variants that increase the proportion of variance explained. For example, within the 180 2Mb loci, a total of 45 independent SNPs reached $P < 1 \times 10^{-5}$ when we would expect < 2 by chance.

Whilst GWA studies have identified many variants robustly associated with common human diseases and traits, the biological significance of these variants, and the genes on which they act, is often unclear. We first tested the overlap between the 180 height-associated variants and two types of putatively functional variants, nonsynonymous (ns) SNPs and cis-eQTLs (variants strongly associated with expression of nearby genes). Height variants were 2.4-fold more likely to overlap with cis-eQTLs in lymphocytes than expected by chance (47 variants: $P = 4.7 \times 10^{-11}$) (Supplementary Table 7) and 1.7-fold more likely to be closely correlated ($r^2 > 0.8$ in HapMap CEU) with nsSNPs (24 variants $P = 0.004$) (Supplementary Methods, Supplementary Table 8). Although the presence of a correlated eQTL or nsSNP at an individual locus does not establish the causality of any particular variant, this enrichment shows that common functional variants contribute to the causal variants at height-associated loci. We also noted five loci where the height associated variant was strongly correlated ($r^2 > 0.8$) with variants associated with other traits and diseases ($P < 5 \times 10^{-8}$), including bone mineral density, rheumatoid arthritis, type 1 diabetes, psoriasis and obesity, suggesting that

these variants have pleiotropic effects on human phenotypes (Supplementary Methods; Supplementary Table 9).

We next addressed the extent to which height variants cluster near biologically relevant genes; specifically, genes mutated in human syndromes characterized by abnormal skeletal growth. We limited this analysis to the 652 genes occurring within the recombination hotspot-bounded regions surrounding each of the 180 index SNPs. We showed that the 180 loci associated with variation in normal height contained 21 of 241 genes (8.7%) found to underlie such syndromes (Supplementary Table 10), compared to a median of 8 (range 1-19) genes identified in 1,000 matched control sets of regions ($P < 0.001$: 0 observations of 21 or more skeletal growth genes among 1,000 sets of matched SNPs). In 13 of these 21 loci the closest gene to the most associated height SNP in the region is the growth disorder gene, and in 9 of these cases, the most strongly associated height SNP is located within the growth disorder gene itself (Supplementary Methods, Supplementary Table 11). These results suggest that GWA studies may provide more clues about the identity of the functional genes at each locus than previously suspected.

We also investigated whether significant and relevant biological connections exist between the genes within the 180 loci, using two different computational approaches. We used the GRAIL text-mining algorithm to search for connectivity between genes near the associated SNPs, based on existing literature²⁰. Of the 180 loci, 42 contained genes that were connected by existing literature to genes in the other associated loci (the pair of connected genes appear in articles that share scientific terms more often than expected at $P < 0.01$). For comparison, when we used GRAIL to score 1,000 sets of 180 SNPs not associated with height (but matched for number of nearby genes, gene proximity, and allele frequency), we only observed 16 sets with 42 or more loci with a connectivity $P < 0.01$, thus providing strong statistical evidence that the height loci are functionally related ($P = 0.016$) (Figure 3a). For the 42 regions with GRAIL connectivity $P < 0.01$, the implicated genes and SNPs are highlighted in Figure 3b. The most strongly connected genes include those in the Hedgehog, TGF-beta, and growth hormone pathways.

As a second approach to find biological connections, we applied a novel implementation of gene set enrichment analysis (GSEA) (Meta-Analysis Gene-set Enrichment of variant Associations, MAGENTA²¹) to perform pathway analysis (Supplementary Methods). This analysis revealed 17 different biological pathways and 14 molecular functions nominally enriched ($P < 0.05$) for associated genes, many of which lie within the validated height loci. These gene-sets include previously reported^{11,13} (e.g. Hedgehog signaling) and novel (e.g. TGF-beta signaling, histones, and growth and development-related) pathways and molecular functions (Supplementary Table 12). Several SNPs near genes in these pathways narrowly missed genome-wide significance, suggesting that these pathways likely contain additional associated variants. These results provide complementary evidence for some of the genes and pathways highlighted in the GRAIL analysis. For instance, genes such as *TGFB2* and *LTBP1-3* highlight a role for the TGF-beta signaling pathway in regulating human height, consistent with the implication of this pathway in Marfan syndrome²².

Finally, to examine the evidence for the potential involvement of specific genes at individual loci, we aggregated evidence from our data (eQTLs, proximity to the associated variant, pathway-based analyses), and human and mouse genetic databases (Supplementary Table 13). Of 32 genes with highly correlated ($r^2 > 0.8$) nsSNPs, several are newly identified strong candidates for playing a role in human growth. Some are in pathways enriched in our study (such as *ECM2*, implicated in extracellular matrix), while others have similar functions to known growth-related genes, including *FGFR4* (*FGFR3* underlies several classic skeletal dysplasias²³) and *STAT2* (*STAT5B* mutations cause growth defects in humans²⁴). Interestingly, *Fgfr4*^{-/-} *Fgfr3*^{-/-} mice show severe growth retardation not seen in either single mutant²⁵, suggesting that the *FGFR4* variant might modify *FGFR3*-mediated skeletal dysplasias. Other genes at associated loci, such as *NPPC* and *NPR3* (encoding the C-type natriuretic peptide and its receptor), influence skeletal growth in mice and will likely also influence human growth¹⁷. Many of the remaining 180 loci have no genes with obvious connections to growth biology, but at some our data provide modest supporting evidence for particular genes, including *C3orf63*, *PML*, *CCDC91*, *ZNFX1*, *ID4*, *RYBP*, *SEPT2*, *ANKRD13B*, *FOLH1*, *LRR37B*, *MFAP2*, *SLBP*, *SOCS5*, and *ZBTB24* (Supplementary Table 13).

We have identified >100 novel loci that influence the classic polygenic trait of normal variation in human height, bringing the total to 180. Our results have potential general implications for genetic studies of complex traits. We show that loci identified by GWA studies highlight relevant genes: the 180 loci associated with height are non-randomly clustered within biologically relevant pathways and are enriched for genes that are involved in growth-related processes, that underlie syndromes of abnormal skeletal growth, and that are directly relevant to growth-modulating therapies (*GHI*, *IGF1R*, *CYP19A1*, *ESR1*). The large number of loci with clearly relevant genes suggests that the remaining loci could provide potential clues to important and novel biology.

We provide the strongest evidence yet that the causal gene will often be located near the most strongly associated DNA sequence variant. At the 21 loci containing a known growth disorder gene, that gene was on average 81 kb from the associated variant, and in over half of the loci it was the closest gene to the associated variant. Despite recent doubts about the benefits of GWA studies²⁶, this finding suggests that GWA studies are useful mapping tools to highlight genes that merit further study. The presence of multiple variants within associated loci could help localize the relevant genes within these loci.

By increasing our sample size to >100,000 individuals, we identified common variants that account for approximately 10% of phenotypic variation. Although larger than predicted by some models²⁶, this figure suggests that GWA studies, as currently implemented, will not explain a majority of the estimated 80% contribution of genetic factors to variation in height. This conclusion supports the idea that biological insights, rather than predictive power, will be the main outcome of this initial wave of GWA studies, and that new approaches, which could include sequencing studies or GWA studies targeting variants of lower frequency, will be needed to account for more of the “missing” heritability. Our finding that many loci exhibit allelic heterogeneity suggests that many as yet unidentified causal variants, including common variants, will map to the loci already identified in GWA studies, and that the

fraction of causal *loci* that have been identified could be substantially greater than the fraction of causal *variants* that have been identified.

In our study, many associated variants are tightly correlated with common nsSNPs, which would not be expected if these associated common variants were proxies for collections of rare causal variants, as has been proposed²⁷. Although a substantial contribution to heritability by less common and/or quite rare variants may be more plausible, our data are not inconsistent with the recent suggestion²⁸ that a large number of common variants of very small effect mostly explain the regulation of height.

In summary, our findings indicate that additional approaches, including those aimed at less common variants, will likely be needed to dissect more completely the genetic component to complex human traits. Our results also strongly demonstrate that GWA studies can identify large numbers of loci that together implicate biologically relevant pathways and mechanisms. We envision that thorough exploration of the genes at associated loci through additional genetic, functional, and computational studies will lead to novel insights into human height and other polygenic traits and diseases.

Methods summary

The primary meta-analysis (Stage 1) included 46 GWA studies of 133,653 individuals. The *in-silico* follow up (Stage 2) included 15 studies of 50,074 individuals. All individuals were of European ancestry and >99.8% were adults. Details of genotyping, quality control, and imputation methods of each study are given in Supplementary Methods Table 1-2. Each study provided summary results of a linear regression of age-adjusted, within-sex Z scores of height against the imputed SNPs, and an inverse-variance meta-analysis was performed in METAL (<http://www.sph.umich.edu/csg/abecasis/METAL/>). Validation of selected SNPs was performed through direct genotyping in an extreme height panel (N=3,190) using Sequenom iPLEX, and in 492 Stage 1 samples using the KASPar SNP System. Family-based testing was performed using QFAM, a linear regression-based approach that uses permutation to account for dependency between related individuals²⁹, and FBAT, which uses a linear combination of offspring genotypes and traits to determine the test statistic³⁰. We used a previously described method to estimate the amount of genetic variance explained by the nominally associated loci (using significance threshold increments from $P < 5 \times 10^{-8}$ to $P < 0.05$)¹⁸. To predict the number of height susceptibility loci, we took the height loci that reached a significance level of $P < 5 \times 10^{-8}$ in Stage 1 and estimated the number of height loci that are likely to exist based on the distribution of their effect sizes observed in Stage 2 and the power to detect their association in Stage 1. Gene-by-gene interaction, dominant, recessive and conditional analyses are described in Supplementary Methods. Empirical assessment of enrichment for coding SNPs used permutations of random sets of SNPs matched to the 180 height-associated SNPs on the number of nearby genes, gene proximity, and minor allele frequency. GRAIL and GSEA methods have been described previously^{20,21}. To assess possible enrichment for genes known to be mutated in severe growth defects, we identified such genes in the OMIM database (Supplementary Table 10), and evaluated the extent of their overlap with the 180 height-associated regions through comparisons with 1000 random sets of regions with similar gene content ($\pm 10\%$).

Supplementary Material

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Authors

Hana Lango Allen^{1,*}, Karol Estrada^{2,3,4,*}, Guillaume Lettre^{5,6,*}, Sonja I. Berndt^{7,*}, Michael N. Weedon^{1,*}, Fernando Rivadeneira^{2,3,4,*}, Cristen J. Willer⁸, Anne U. Jackson⁸, Sailaja Vedantam^{9,10}, Soumya Raychaudhuri^{11,12}, Teresa Ferreira¹³, Andrew R. Wood¹, Robert J. Weyant⁸, Ayellet V. Segrè^{11,14,15}, Elizabeth K. Speliotes^{10,16}, Eleanor Wheeler¹⁷, Nicole Soranzo^{17,18}, Ju-Hyun Park⁷, Jian Yang¹⁹, Daniel Gudbjartsson²⁰, Nancy L. Heard-Costa²¹, Joshua C. Randall¹³, Lu Qi^{22,23}, Albert Vernon Smith^{24,25}, Reedik Mägi¹³, Tomi Pastinen^{26,27,28}, Liming Liang²⁹, Iris M. Heid^{30,31}, Jian'an Luan³², Gudmar Thorleifsson²⁰, Thomas W. Winkler³⁰, Michael E. Goddard^{33,34}, Ken Sin Lo⁵, Cameron Palmer^{9,10}, Tsegaselassie Workalemahu²², Yurii S. Aulchenko^{2,4}, Åsa Johansson^{35,36}, M.Carola Zillikens³, Mary F. Feitosa³⁷, Tõnu Esko^{38,39,40}, Toby Johnson^{41,42,43,44}, Shamika Ketkar³⁷, Peter Kraft^{45,46}, Massimo Mangino¹⁸, Inga Prokopenko^{13,47}, Devin Absher⁴⁸, Eva Albrecht³¹, Florian Ernst⁴⁹, Nicole L. Glazer⁵⁰, Caroline Hayward⁵¹, Jouke-Jan Hottenga⁵², Kevin B. Jacobs⁵³, Joshua W. Knowles⁵⁴, Zoltán Kutalik^{41,42}, Keri L. Monda⁵⁵, Ozren Polasek^{56,57}, Michael Preuss⁵⁸, Nigel W. Rayner^{13,47}, Neil R. Robertson^{13,47}, Valgerdur Steinthorsdottir²⁰, Jonathan P. Tyrer⁵⁹, Benjamin F. Voight^{11,14,15}, Fredrik Wiklund⁶⁰, Jianfeng Xu⁶¹, Jing Hua Zhao³², Dale R. Nyholt⁶², Niina Pellikka^{63,64}, Markus Perola^{63,64}, John R.B. Perry¹, Ida Surakka^{63,64}, Mari-Liis Tammesoo³⁸, Elizabeth L. Altmaier^{9,10}, Najaf Amin², Thor Aspelund^{24,25}, Tushar Bhangale⁶⁵, Gabrielle Boucher⁵, Daniel I. Chasman^{66,67}, Constance Chen⁶⁸, Lachlan Coin⁶⁹, Matthew N. Cooper⁷⁰, Anna L. Dixon⁷¹, Quince Gibson⁷², Elin Grundberg^{17,26,27}, Ke Hao⁷³, M. Juhani Juntila⁷⁴, Lee M. Kaplan^{16,67,75}, Johannes Kettunen^{63,64}, Inke R. König⁵⁸, Tony Kwan^{26,27}, Robert W. Lawrence⁷⁰, Douglas F. Levinson⁷⁶, Mattias Lorentzon⁷⁷, Barbara McKnight⁷⁸, Andrew P. Morris¹³, Martina Müller^{31,79,80}, Julius Suh Ngwa⁸¹, Shaun Purcell^{14,82,83}, Suzanne Rafelt⁸⁴, Rany M. Salem^{9,10}, Erika Salvi^{85,86}, Serena Sanna⁸⁷, Jianxin Shi⁷, Ulla Sovio⁶⁹, John R. Thompson^{88,89}, Michael C. Turchin^{9,10}, Liesbeth Vandenput⁷⁷, Dominique J. Verlaan^{26,27}, Veronique Vitart⁵¹, Charles C. White⁸¹, Andreas Ziegler⁹⁰, Peter Almgren⁹¹, Anthony J. Balmforth⁹², Harry Campbell⁹³, Lorena Citterio⁹⁴, Alessandro De Grandi⁹⁵, Anna Dominiczak⁹⁶, Jubao Duan⁹⁷, Paul Elliott⁶⁹, Roberto Elosua⁹⁸, Johan G. Eriksson^{99,100,101,102,103}, Nelson B. Freimer¹⁰⁴, Eco J.C. Geus⁵², Nicola Glorioso¹⁰⁵, Shen Haiqing⁷², Anna-Liisa Hartikainen¹⁰⁶, Aki S. Havulinna¹⁰⁷, Andrew A. Hicks⁹⁵, Jennie Hui^{70,108,109}, Wilmar Igl³⁵, Thomas Illig³¹, Antti Jula¹¹⁰, Eero Kajantie¹⁰⁰, Tuomas O. Kilpeläinen³², Markku Koiranen¹¹¹, Ivana Kolcic⁵⁶, Seppo Koskinen¹⁰⁷, Peter Kovacs¹¹², Jaana Laitinen¹¹³, Jianjun Liu¹¹⁴, Marja-Liisa Lokki¹¹⁵, Ana Marusic¹¹⁶, Andrea Maschio⁸⁷, Thomas Meitinger^{117,118}, Antonella Mulas⁸⁷, Guillaume Paré¹¹⁹, Alex N. Parker¹²⁰, John F. Peden^{13,121}, Astrid Petersmann¹²², Irene Pichler⁹⁵, Kirsi H. Pietiläinen^{123,124}, Anneli Pouta^{106,125}, Martin Ridderstråle¹²⁶, Jerome I. Rotter¹²⁷, Jennifer G. Sambrook^{128,129}, Alan R. Sanders⁹⁷, Carsten Oliver

Schmidt¹³⁰, Juha Sinisalo¹³¹, Jan H. Smit¹³², Heather M. Stringham⁸, G.Bragi Walters²⁰, Elisabeth Widen⁶³, Sarah H. Wild⁹³, Gonneke Willemsen⁵², Laura Zagato⁹⁴, Lina Zgaga⁵⁶, Paavo Zitting¹³³, Helene Alavere³⁸, Martin Farrall^{13,121,134}, Wendy L. McArdle¹³⁵, Mari Nelis^{38,39,40}, Marjolein J. Peters^{3,4}, Samuli Ripatti^{63,64}, Joyce B.J. van Meurs^{2,3,4}, Katja K. Aben¹³⁶, Kristin G Ardlie¹¹, Jacques S. Beckmann^{41,137}, John P. Beilby^{108,109,138}, Richard N. Bergman¹³⁹, Sven Bergmann^{41,42}, Francis S. Collins¹⁴⁰, Daniele Cusi⁸⁵, Martin den Heijer¹⁴¹, Gudny Eiriksdottir²⁴, Pablo V. Gejman⁹⁷, Alistair S. Hall⁹², Anders Hamsten¹⁴², Heikki V. Huikuri^{74,74}, Carlos Iribarren^{143,144}, Mika Kähönen¹⁴⁵, Jaakko Kaprio^{63,123,146}, Sekar Kathiresan^{11,14,147,148,149}, Lambertus Kiemeneij^{136,150,151}, Thomas Kocher¹⁵², Lenore J. Launer¹⁵³, Terho Lehtimäki¹⁵⁴, Olle Melander¹²⁶, Tom H. Mosley Jr¹⁵⁵, Arthur W. Musk^{109,156}, Markku S. Nieminen^{131,131}, Christopher J. O'Donnell^{148,157}, Claes Ohlsson⁷⁷, Ben Oostra¹⁵⁸, Lyle J. Palmer^{70,109}, Olli Raitakari¹⁵⁹, Paul M. Ridker^{66,67}, John D. Rioux^{5,6}, Aila Rissanen¹²⁴, Carlo Rivolta⁴¹, Heribert Schunkert¹⁶⁰, Alan R. Shuldiner^{72,161}, David S. Siscovick^{162,163}, Michael Stumvoll^{164,165}, Anke Tönjes^{164,166}, Jaakko Tuomilehto^{167,168,169}, Gert-Jan van Ommen¹⁷⁰, Jorma Viikari¹⁷¹, Andrew C. Heath¹⁷², Nicholas G. Martin¹⁷³, Grant W. Montgomery¹⁷⁴, Michael A. Province^{37,175}, Manfred Kayser¹⁷⁶, Alice M. Arnold^{78,177}, Larry D. Atwood²¹, Eric Boerwinkle¹⁷⁸, Stephen J. Chanock⁷, Panos Deloukas¹⁷, Christian Gieger³¹, Henrik Grönberg⁶⁰, Per Hall⁶⁰, Andrew T. Hattersley¹, Christian Hengstenberg^{179,180}, Wolfgang Hoffman¹³⁰, G.Mark Lathrop¹⁸¹, Veikko Salomaa¹⁰⁷, Stefan Schreiber¹⁸², Manuela Uda⁸⁷, Dawn Waterworth¹⁸³, Alan F. Wright⁵¹, Themistocles L. Assimes⁵⁴, Inês Barroso^{17,184}, Albert Hofman^{2,4}, Karen L. Mohlke¹⁸⁵, Dorret I. Boomsma⁵², Mark J. Caulfield⁴⁴, L.Adrienne Cupples⁸¹, Jeanette Erdmann¹⁶⁰, Caroline S. Fox¹⁸⁶, Vilmundur Gudnason^{24,25}, Ulf Gyllensten³⁵, Tamara B. Harris¹⁵³, Richard B. Hayes¹⁸⁷, Marjo-Riitta Jarvelin^{69,111,125,188}, Vincent Mooser¹⁸³, Patricia B. Munroe⁴⁴, Willem H. Ouwehand^{17,128,129}, Brenda W. Penninx^{132,189,190}, Peter P. Pramstaller^{95,191,192}, Thomas Quertermous⁵⁴, Igor Rudan^{51,116}, Nilesh J. Samani^{84,88}, Timothy D. Spector¹⁸, Henry Völzke¹³⁰, Hugh Watkins^{13,121} **on behalf of Procardis Consortium**, James F. Wilson⁹³, Leif C. Groop⁹¹, Talin Haritunians¹²⁷, Frank B. Hu^{22,23,45}, Robert C. Kaplan¹⁹³, Andres Metspalu^{38,39,40}, Kari E. North^{55,194}, David Schlessinger¹⁹⁵, Nicholas J. Wareham³², David J. Hunter^{22,23,45}, Jeffrey R. O'Connell⁷², David P. Strachan¹⁹⁶, H.-Erich Wichmann^{31,80,197}, Ingrid B. Borecki^{37,175}, Cornelia M. van Duijn^{2,4}, Eric E. Schadt^{198,199}, Unnur Thorsteinsdottir^{20,200}, Leena Peltonen^{17,63,64,82,201}, André Uitterlinden^{2,3,4}, Peter M. Visscher¹⁹, Nilanjan Chatterjee⁷, Ruth J.F. Loos³², Michael Boehnke⁸, Mark I. McCarthy^{13,47,202}, Erik Ingelsson⁶⁰, Cecilia M. Lindgren^{13,47}, Gonçalo R. Abecasis^{8,*}, Kari Stefansson^{20,200,*}, Timothy M. Frayling^{1,*}, and Joel N Hirschhorn^{9,10,203,*} **for the GIANT Consortium**

Affiliations

¹ Genetics of Complex Traits, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, EX1 2LU, UK ² Department of Epidemiology, Erasmus MC, Rotterdam, 3015GE, The Netherlands ³ Department of Internal Medicine,

Erasmus MC, Rotterdam, 3015GE, The Netherlands ⁴ Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA) ⁵ Montreal Heart Institute, Montreal, Quebec, H1T 1C8, Canada ⁶ Department of Medicine, Université de Montréal, Montreal, Quebec, H3T 1J4, Canada ⁷ Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, USA ⁸ Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA ⁹ Divisions of Genetics and Endocrinology and Program in Genomics, Children's Hospital, Boston, Massachusetts 02115, USA ¹⁰ Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts 02142, USA ¹¹ Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA ¹² Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115 USA ¹³ Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK ¹⁴ Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ¹⁵ Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ¹⁶ Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ¹⁷ Wellcome Trust Sanger Institute, Hinxton, Cambridge, CB10 1SA, UK ¹⁸ Department of Twin Research and Genetic Epidemiology, King's College London, Lambeth Palace Rd, London, SE1 7EH, UK ¹⁹ Queensland Statistical Genetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia ²⁰ deCODE Genetics, 101 Reykjavik, Iceland ²¹ Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, USA ²² Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA ²³ Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA ²⁴ Icelandic Heart Association, Kopavogur, Iceland ²⁵ University of Iceland, Reykjavik, Iceland ²⁶ McGill University and Genome Québec Innovation Centre, Montréal, Québec H3A 1A4, Canada ²⁷ Department of Human Genetics, McGill University Health Centre, McGill University, Montréal, Québec H3G 1A4, Canada ²⁸ Department of Medical Genetics, McGill University Health Centre, McGill University, Montréal, Québec H3G 1A4, Canada ²⁹ Departments of Epidemiology and Biostatistics, Harvard School of Public Health, Cambridge, Massachusetts 02138, USA ³⁰ Regensburg University Medical Center, Department of Epidemiology and Preventive Medicine, 93053 Regensburg, Germany ³¹ Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany ³² MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, CB2 0QQ, UK ³³ University of Melbourne, Parkville 3010, Australia ³⁴ Department of Primary Industries, Melbourne, Victoria 3001, Australia ³⁵ Department of Genetics and Pathology, Rudbeck Laboratory, University of Uppsala, SE-75185 Uppsala, Sweden ³⁶ Department of Cancer Research and Molecular

Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, N-7489, Norway ³⁷ Department of Genetics, Washington University School of Medicine, St Louis, Missouri 63110, USA ³⁸ Estonian Genome Center, University of Tartu, Tartu 50410, Estonia ³⁹ Estonian Biocenter, Tartu 51010, Estonia ⁴⁰ Institute of Molecular and Cell Biology, University of Tartu, Tartu 51010, Estonia ⁴¹ Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland ⁴² Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland ⁴³ Clinical Pharmacology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, UK ⁴⁴ Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK ⁴⁵ Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA ⁴⁶ Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, USA ⁴⁷ Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, OX3 7LJ, UK ⁴⁸ Hudson Alpha Institute for Biotechnology, Huntsville, Alabama 35806, USA ⁴⁹ Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany ⁵⁰ Cardiovascular Health Resarch Unit and Department of Medicine, University of Washington, Seattle, Washington 98101, USA ⁵¹ MRC Human Genetics Unit, Institute for Genetics and Molecular Medicine, Western General Hospital, Edinburgh, EH4 2XU, Scotland, UK ⁵² Department of Biological Psychology, VU University Amsterdam, 1081 BT Amsterdam, The Netherlands ⁵³ Core Genotyping Facility, SAIC-Frederick, Inc., NCI-Frederick, Frederick, Maryland 21702, USA ⁵⁴ Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA ⁵⁵ Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514 USA ⁵⁶ Andrija Stampar School of Public Health, Medical School, University of Zagreb, 10000 Zagreb, Croatia ⁵⁷ Gen-Info Ltd, 10000 Zagreb, Croatia ⁵⁸ Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik, 23562 Lübeck, Germany ⁵⁹ Department of Oncology, University of Cambridge, Cambridge, CB1 8RN, UK ⁶⁰ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77 Stockholm, Sweden ⁶¹ Center for Human Genomics, Wake Forest University, Winston-Salem, North Carolina 27157, USA ⁶² Neurogenetics Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia ⁶³ Institute for Molecular Medicine Finland (FIMM), University of Helsinki, 00014, Helsinki, Finland ⁶⁴ National Institute for Health and Welfare, Department of Chronic Disease Prevention, Unit of Public Health Genomics, 00014, Helsinki, Finland ⁶⁵ Department of Genome Sciences, University of Washington, Seattle, 98195 Washington, USA ⁶⁶ Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts 02215, USA ⁶⁷ Harvard Medical School, Boston, Massachusetts 02115, USA ⁶⁸ Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA ⁶⁹ Department of Epidemiology and Biostatistics,

School of Public Health, Faculty of Medicine, Imperial College London, London, W2 1PG, UK ⁷⁰ Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia 6009, Australia ⁷¹ Royal National Hospital for Rheumatic Diseases and University of Bath, Bath, BA1 1RL, UK ⁷² Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA ⁷³ Genetics Department, Rosetta Inpharmatics, a Wholly Owned Subsidiary of Merck & Co. Inc., Seattle, Washington 98109, USA ⁷⁴ Department of Internal Medicine, University of Oulu, 90014 Oulu, Finland ⁷⁵ MGH Weight Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ⁷⁶ Stanford University School of Medicine, Stanford, California 93405, USA ⁷⁷ Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden ⁷⁸ Departments of Biostatistics, University of Washington, Seattle, Washington 98195, USA ⁷⁹ Ludwig-Maximilians-University, Department of Medicine I, University Hospital Grosshadern, 81377 Munich, Germany ⁸⁰ Ludwig-Maximilians-Universität, Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, 81377 Munich, Germany ⁸¹ Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA ⁸² The Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02142, USA ⁸³ Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA ⁸⁴ Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK ⁸⁵ University of Milan, Department of Medicine, Surgery and Dentistry, 20139 Milano, Italy ⁸⁶ KOS Genetic Srl, 20123 Milan, Italy ⁸⁷ Istituto di Neurogenetica e Neurofarmacologia del CNR, Monserrato, 09042, Cagliari, Italy ⁸⁸ Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK ⁸⁹ Department of Health Sciences, University of Leicester, University Road, Leicester, LE1 7RH, UK ⁹⁰ Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik, 23562 Lübeck, Germany ⁹¹ Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden ⁹² Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LIGHT), University of Leeds, Leeds LS2 9JT, UK ⁹³ Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland ⁹⁴ University Vita-Salute San Raffaele, Division of Nephrology and Dialysis, 20132 Milan, Italy ⁹⁵ Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano/Bozen, 39100, Italy. Affiliated Institute of the University of Lübeck, Lübeck, Germany ⁹⁶ British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, G12 8TA, UK ⁹⁷ Northshore University Healthsystem, Evanston, Illinois 60201, USA ⁹⁸ Cardiovascular Epidemiology and Genetics, Institut Municipal D'investigacio Medica and CIBER Epidemiología y Salud Pública, Barcelona, Spain ⁹⁹ Department of General Practice and Primary health Care, University of Helsinki, Helsinki, Finland ¹⁰⁰ National Institute for Health and Welfare, 00271 Helsinki, Finland ¹⁰¹ Helsinki University Central Hospital, Unit of General Practice, 00280 Helsinki, Finland ¹⁰² Folkhalsan Research Centre, 00250 Helsinki, Finland ¹⁰³ Vasa

Central Hospital, 65130 Vasa, Finland ¹⁰⁴ Center for Neurobehavioral Genetics, University of California, Los Angeles, California 90095, USA ¹⁰⁵ Hypertension and Cardiovascular Prevention Center, University of Sassari, 07100 Sassari, Italy ¹⁰⁶ Department of Clinical Sciences/Obstetrics and Gynecology, University of Oulu, 90014 Oulu, Finland ¹⁰⁷ National Institute for Health and Welfare, Department of Chronic Disease Prevention, Chronic Disease Epidemiology and Prevention Unit, 00014, Helsinki, Finland ¹⁰⁸ PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands, Western Australia 6009, Australia ¹⁰⁹ Busselton Population Medical Research Foundation Inc., Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia ¹¹⁰ National Institute for Health and Welfare, Department of Chronic Disease Prevention, Population Studies Unit, 20720 Turku, Finland ¹¹¹ Institute of Health Sciences, University of Oulu, 90014 Oulu, Finland ¹¹² Interdisciplinary Centre for Clinical Research, University of Leipzig, 04103 Leipzig, Germany ¹¹³ Finnish Institute of Occupational Health, 90220 Oulu, Finland ¹¹⁴ Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore ¹¹⁵ Transplantation Laboratory, Haartman Institute, University of Helsinki, 00014, Helsinki, Finland ¹¹⁶ Croatian Centre for Global Health, School of Medicine, University of Split, Split 21000, Croatia ¹¹⁷ Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universität München, 81675 Munich, Germany ¹¹⁸ Institute of Human Genetics, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany ¹¹⁹ Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario L8N3Z5, Canada ¹²⁰ Amgen, Cambridge, Massachusetts 02139, USA ¹²¹ Department of Cardiovascular Medicine, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU ¹²² Institut für Klinische Chemie und Laboratoriumsmedizin, Universität Greifswald, 17475 Greifswald, Germany ¹²³ Finnish Twin Cohort Study, Department of Public Health, University of Helsinki, 00014, Helsinki, Finland ¹²⁴ Obesity Research unit, Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland ¹²⁵ National Institute for Health and Welfare, 90101 Oulu, Finland ¹²⁶ Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden ¹²⁷ Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA ¹²⁸ Department of Haematology, University of Cambridge, Cambridge CB2 0PT, UK ¹²⁹ NHS Blood and Transplant, Cambridge Centre, Cambridge, CB2 0PT, UK ¹³⁰ Institut für Community Medicine, 17489 Greifswald, Germany ¹³¹ Division of Cardiology, Cardiovascular Laboratory, Helsinki University Central Hospital, 00029 Helsinki, Finland ¹³² Department of Psychiatry/EMGO Institute, VU University Medical Center, 1081 BT Amsterdam, The Netherlands ¹³³ Department of Psychiatries, Lapland Central Hospital, 96101 Rovaniemi, Finland ¹³⁴ Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Oxford, OX3 7BN, UK ¹³⁵ Avon Longitudinal Study of Parents and Children (ALSPAC) Laboratory, Department of Social Medicine, University of Bristol, Bristol, BS8 2BN, UK ¹³⁶ Comprehensive Cancer Center East, 6501 BG Nijmegen, The Netherlands ¹³⁷ Service of Medical Genetics, Centre Hospitalier

Universitaire Vaudois (CHUV) University Hospital, 1011 Lausanne, Switzerland ¹³⁸
 School of Pathology and Laboratory Medicine, University of Western Australia,
 Nedlands, Western Australia 6009, Australia ¹³⁹ Department of Physiology and
 Biophysics, Keck School of Medicine, University of Southern California, Los
 Angeles, California 90033, USA ¹⁴⁰ National Human Genome Research Institute,
 National Institutes of Health, Bethesda, Maryland 20892, USA ¹⁴¹ Department of
 Endocrinology, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen,
 The Netherlands ¹⁴² Atherosclerosis Research Unit, Department of Medicine, Solna,
 Karolinska Institutet, Karolinska University Hospital, 171 76 Stockholm, Sweden ¹⁴³
 Division of Research, Kaiser Permanente Northern California, Oakland, California
 94612, USA ¹⁴⁴ Department of Epidemiology and Biostatistics, University of
 California, San Francisco, San Francisco, California 94107, USA ¹⁴⁵ Department of
 Clinical Physiology, University of Tampere and Tampere University Hospital, 33520
 Tampere, Finland ¹⁴⁶ National Institute for Health and Welfare, Department of
 Mental Health and Substance Abuse Services, Unit for Child and Adolescent Mental
 Health, 00271 Helsinki, Finland ¹⁴⁷ Cardiovascular Research Center and Cardiology
 Division, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ¹⁴⁸
 Framingham Heart Study of the National, Heart, Lung, and Blood Institute and
 Boston University, Framingham, Massachusetts 01702, USA ¹⁴⁹ Department of
 Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA ¹⁵⁰
 Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen
 Medical Centre, 6500 HB Nijmegen, The Netherlands ¹⁵¹ Department of Urology,
 Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands
¹⁵² Zentrum für Zahn-, Mund- und Kieferheilkunde, 17489 Greifswald, Germany ¹⁵³
 Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging,
 National Institutes of Health, Bethesda, Maryland 20892, USA ¹⁵⁴ Department of
 Clinical Chemistry, University of Tampere and Tampere University Hospital, 33520
 Tampere, Finland ¹⁵⁵ Department of Medicine, Division of Geriatrics, University of
 Mississippi Medical Center, Jackson, Mississippi 39216, USA ¹⁵⁶ School of
 Medicine and Pharmacology, University of Western Australia, Perth, Western
 Australia 6009, Australia ¹⁵⁷ National, Lung, and Blood Institute, National Institutes
 of Health, Framingham, Massachusetts 01702, USA ¹⁵⁸ Department of Clinical
 Genetics, Erasmus MC, Rotterdam, 3015GE, The Netherlands ¹⁵⁹ Research Centre
 of Applied and Preventive Cardiovascular Medicine, University of Turku and the
 Department of Clinical Physiology, Turku University Hospital, 20520 Turku, Finland
¹⁶⁰ Universität zu Lübeck, Medizinische Klinik II, 23562 Lübeck, Germany ¹⁶¹
 Geriatrics Research and Education Clinical Center, Baltimore Veterans
 Administration Medical Center, Baltimore, Maryland 21201, USA ¹⁶² Cardiovascular
 Health Research Unit, University of Washington, Seattle, Washington 98101, USA
¹⁶³ Departments of Medicine and Epidemiology, University of Washington, Seattle,
 Washington 98195, USA ¹⁶⁴ Department of Medicine, University of Leipzig, 04103
 Leipzig, Germany ¹⁶⁵ LIFE Study Centre, University of Leipzig, Leipzig, Germany ¹⁶⁶
 Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16-18, 04103
 Leipzig, Germany ¹⁶⁷ National Institute for Health and Welfare, Diabetes Prevention

Unit, 00271 Helsinki, Finland ¹⁶⁸ Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland ¹⁶⁹ South Ostrobothnia Central Hospital, 60220 Seinajoki, Finland ¹⁷⁰ Department of Human Genetics and Center of Medical Systems Biology, Leiden University Medical Center, 2333 ZC Leiden, the Netherlands ¹⁷¹ Department of Medicine, University of Turku and Turku University Hospital, 20520 Turku, Finland ¹⁷² Department of Psychiatry and Midwest Alcoholism Research Center, Washington University School of Medicine, St Louis, Missouri 63108, USA ¹⁷³ Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia ¹⁷⁴ Molecular Epidemiology Laboratory, Queensland Institute of Medical Research, Queensland 4006, Australia ¹⁷⁵ Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri 63110, USA ¹⁷⁶ Department of Forensic Molecular Biology, Erasmus MC, Rotterdam, 3015GE, The Netherlands ¹⁷⁷ Collaborative Health Studies Coordinating Center, Seattle, Washington 98115, USA ¹⁷⁸ Human Genetics Center and Institute of Molecular Medicine and Division of Epidemiology, University of Texas Health Science Center, Houston, Texas 77030, USA ¹⁷⁹ Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, 93053 Regensburg, Germany ¹⁸⁰ Regensburg University Medical Center, Innere Medizin II, 93053 Regensburg, Germany ¹⁸¹ Centre National de Genotypage, Evry, Paris 91057, France ¹⁸² Christian-Albrechts-University, University Hospital Schleswig-Holstein, Institute for Clinical Molecular Biology and Department of Internal Medicine I, Schittenhelmstrasse 12, 24105 Kiel ¹⁸³ Genetics Division, GlaxoSmithKline, King of Prussia, Pennsylvania 19406, USA ¹⁸⁴ University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, CB2 0QQ, Cambridge, UK ¹⁸⁵ Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA ¹⁸⁶ Division of Intramural Research, National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, Massachusetts 01702, USA ¹⁸⁷ New York University Medical Center, New York, New York 10016, USA ¹⁸⁸ Biocenter Oulu, University of Oulu, 90014 Oulu, Finland ¹⁸⁹ Department of Psychiatry, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands ¹⁹⁰ Department of Psychiatry, University Medical Centre Groningen, 9713 GZ Groningen, The Netherlands ¹⁹¹ Department of Neurology, General Central Hospital, Bolzano, Italy ¹⁹² Department of Neurology, University of Lübeck, Lübeck, Germany ¹⁹³ Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York 10461, USA ¹⁹⁴ Carolina Center for Genome Sciences, School of Public Health, University of North Carolina Chapel Hill, Chapel Hill, North Carolina 27514, USA ¹⁹⁵ Laboratory of Genetics, National Institute on Aging, Baltimore, Maryland 21224, USA ¹⁹⁶ Division of Community Health Sciences, St George's, University of London, London, SW17 0RE, UK ¹⁹⁷ Klinikum Grosshadern, 81377 Munich, Germany ¹⁹⁸ Pacific Biosciences, Menlo Park, California 94025, USA ¹⁹⁹ Sage Bionetworks, Seattle, Washington 98109, USA ²⁰⁰ Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland ²⁰¹ Department of Medical Genetics, University of Helsinki, 00014 Helsinki, Finland ²⁰² NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LJ, UK ²⁰³

Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA

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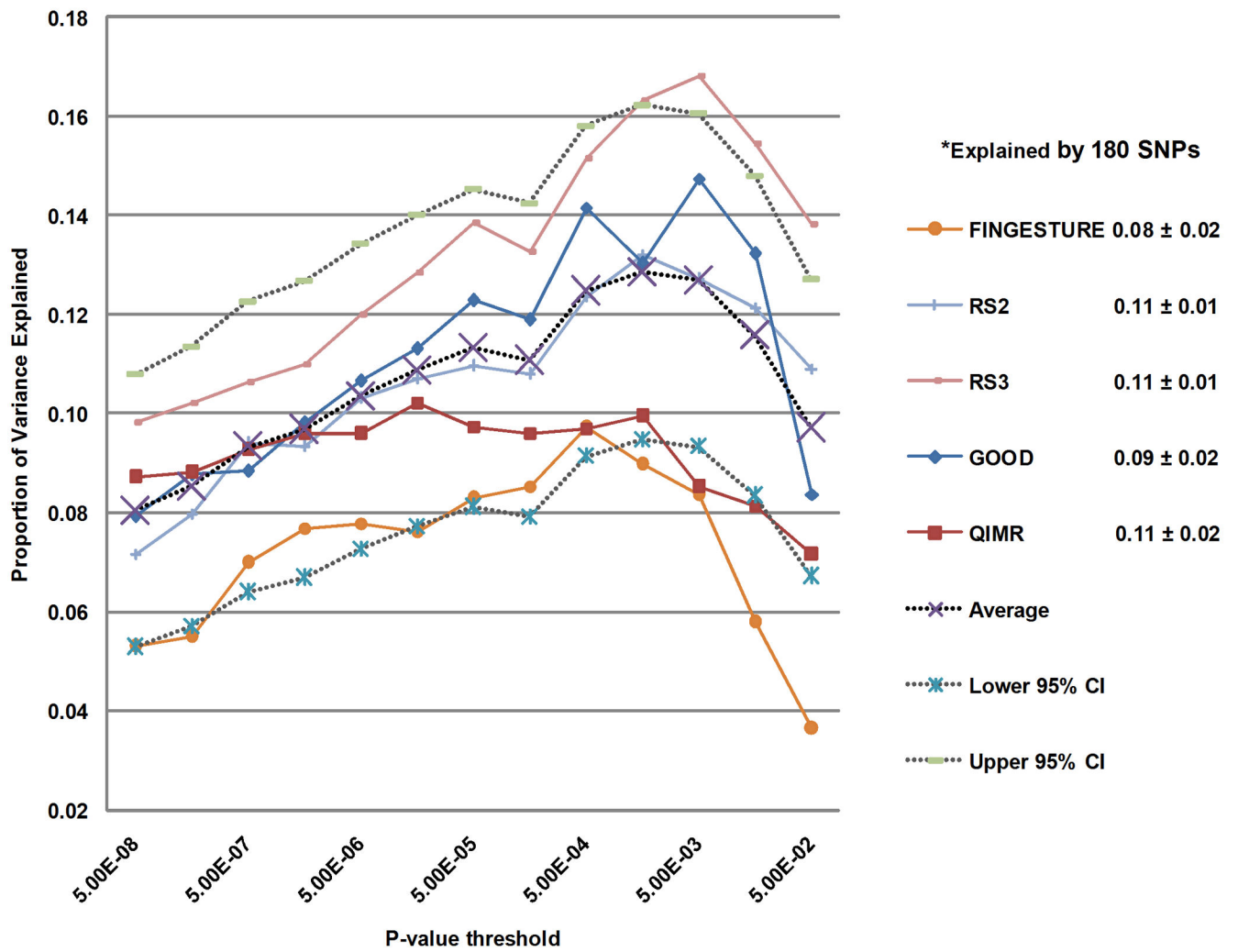
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Reynolds Foundation; Emil and Vera Cornell Foundation; Erasmus MC; Estonian Government (SF0180142s08); European Commission (201413, ECOGENE:205419, BBMRI:212111, OPENGENE:245536, ENGAGE:HEALTH-F4-2007-201413, EURODIA:LSHG-CT-2004-518153, EU/WLRT-2001-01254, HEALTH-F2-2008-ENGAGE, HEALTH-F4-2007-201550, LSH-2006-037593, LSHG-CT-2006-018947, LSHG-CT-2006-01947, Procardis:LSHM-CT-2007-037273, POLYGENE:LSHC-CT-2005, QLG1-CT-2000-01643, QLG2-CT-2002-01254, DG XII, Marie Curie Intra-European Fellowship); Eve Appeal; Finnish Ministry of Education; Finnish Diabetes Research Foundation; Finnish Diabetes Research Society; Finnish Foundation for Cardiovascular Research; Finnish Medical Society; Finska Läkaresällskapet; Folkhälsan Research Foundation; Fondation LeDucq; Foundation for Life and Health in Finland; Foundation for Strategic Research (SSF); GEN-AU-Programme "GOLD"; Genetic Association InformationNetwork (GAIN); German Bundesministerium fuer Forschung und Technology (01 AK 803 A-H, 01 IG 07015 G); German Federal Ministry of Education and Research (BMBF) (01GS0831); German Ministry for Health, Welfare and Sports; German Ministry of Cultural Affairs; German Ministry of Education, Culture and Science; German National Genome Research Net (NGFN2 and NGFNplus) (01GS0823, 01ZZ0103, 01ZZ0403, 01ZZ9603, 03ZIK012); German Research Council (KFO-152); GlaxoSmithKline; Göteborg Medical Society; Gyllenberg Foundation; Helmholtz Center Munich; Juvenile Diabetes Research Foundation International (JDRF) (U01 DK062418); Karolinska Institute; Knut and Alice Wallenberg Foundation; Lundberg Foundation; March of Dimes (6-FY-09-507); MC Health; Medical Research Council UK (G0000649, G0000934, G0500539, G0600331, G0601261, G9521010D, PrevMetSyn); Microarray Core Facility of the Interdisciplinary Centre for Clinical Research (IZKF) (B27); Mid-Atlantic Nutrition and Obesity Research Center of Maryland (P30 DK072488); Ministry of Health and Department of Educational Assistance (South Tyrol, Italy); Ministry of Science, Education and Sport of the Republic of Croatia (216-1080315-0302); Montreal Heart Institute Foundation; Närpes Health Care Foundation; National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre; NIHR Oxford Biomedical Research Centre; NIHR comprehensive Biomedical Research Centre; National Institutes of Health (263-MA-410953, AA014041, AA07535, AA10248, AA13320, AA13321, AA13326, CA047988, CA49449, CA50385, CA65725, CA67262, CA87969, DA12854, DK062370, DK063491, DK072193, DK079466, DK080145, DK58845, HG002651, HG005214, HG005581, HL043851, HL084729, HL69757, HL71981, K08-AR055688, K23-DK080145, K99-HL094535, M01-RR00425, MH084698, N01-AG12100, N01-AG12109, N01-HC15103, N01-HC25195, N01-HC35129, N01-HC45133, N01-HC55015, N01-HC55016, N01-HC55018 through N01-HC55022, N01-HC55222, N01-HC75150, N01-HC85079 through N01-HC85086, N01-HG65403, R01-AG031890, R01 CA104021, R01-DK068336, R01-DK073490, R01-DK075681, R01-DK075787, R01-HL086694, R01-HL087641, R01-HL087647, R01-HL087652, R01-HL087676, R01-HL087679, R01-HL087700, R01-HL088119, R01-HL59367, R01-MH059160, R01-MH59565, R01-MH59566, R01-MH59571, R01-MH59586, R01-MH59587, R01-MH59588, R01-MH60870, R01-MH60879, R01-MH61675, R01-MH63706, R01-MH67257, R01-MH79469, R01-MH81800, RL1-MH083268, T32-HG00040, U01-CA098233, U01-GM074518, U01-HG004399, U01-HG004402, U01-HL080295, U01-HL084756, U01-HL72515, U01-MH79469, U01-MH79470, U54-RR020278, UL1-RR025005, Z01-AG00675, Z01-AG007380, Z01-HG000024; contract HHSN268200625226C; ADA Mentor-Based Postdoctoral Fellowship; Pew Scholarship for the Biomedical Sciences); Netherlands Genomics Initiative (NGI)/Netherlands Consortium for Healthy Aging (NCHA) (050-060-810); Netherlands Organisation for Scientific Research (NWO) (Investments nr. 175.010.2005.011, 911-03-012); Netherlands Organization for the Health Research and Development (ZonMw) (10-000-1002); Netherlands Scientific Organization (904-61-090, 904-61-193, 480-04-004, 400-05-717, Center for Medical Systems Biology (NOW Genomics), SPI 56-464-1419); NIA Intramural Research Program; Nordic Center of Excellence in Disease Genetics; Novo Nordisk Foundation; Ollqvist Foundation; Oxford NIHR Biomedical Research Centre; Paavo Nurmi Foundation; Perklén Foundation; Petrus and Augusta Hedlunds Foundation; Queensland Institute of Medical Research; Radboud University Nijmegen Medical Centre; Research Institute for Diseases in the Elderly (014-93-015); Royal Swedish Academy of Science; Sahlgrenska Center for Cardiovascular and Metabolic Research (A305:188); Siemens Healthcare, Erlangen, Germany; Signe and Ane Gyllenberg Foundation; Sigrid Juselius Foundation; Social Insurance

Institution of Finland; Social Ministry of the Federal State of Mecklenburg-West Pomerania; South Tyrolean Sparkasse Foundation; Stockholm County Council (560183); Support for Science Funding programme; Susan G. Komen Breast Cancer Foundation; Swedish Cancer Society; Swedish Cultural Foundation in Finland; Swedish Foundation for Strategic Research; Swedish Heart-Lung Foundation; Swedish Medical Research Council (K2007-66X-20270-01-3, 8691); Swedish National Cancer Institute; Swedish Research Council; Swedish Society of Medicine; Swiss National Science Foundation (33CSCO-122661); Torsten and Ragnar Söderberg's Foundation; Vandervell Foundation; Västra Götaland Foundation; Wellcome Trust (072960, 075491, 079557, 079895, 083270, 068545/Z/02, 076113/B/04/Z, 076113/C/04/Z, 076113/C/04/Z, 077016/Z/05/Z, 081682/Z/06/Z, 084183/Z/07/Z, 085301/Z/08/Z, 086596/Z/08/Z, 091746/Z/10/Z; WT Research Career Development Fellowship); Western Australian Genetic Epidemiology Resource and the Western Australian DNA Bank (both National Health and Medical Research Council of Australia Enabling Facilities). Detailed list of acknowledgments by study is given in the Supplementary Information.

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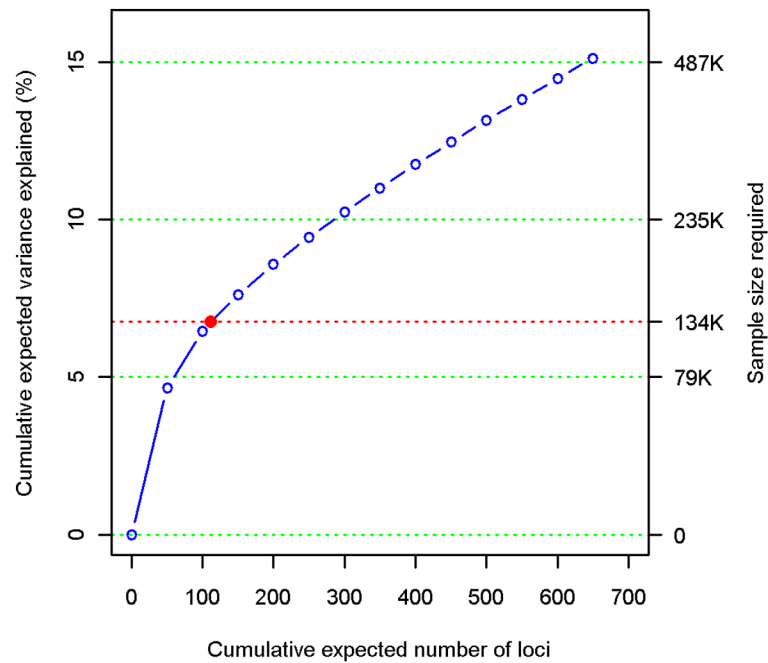
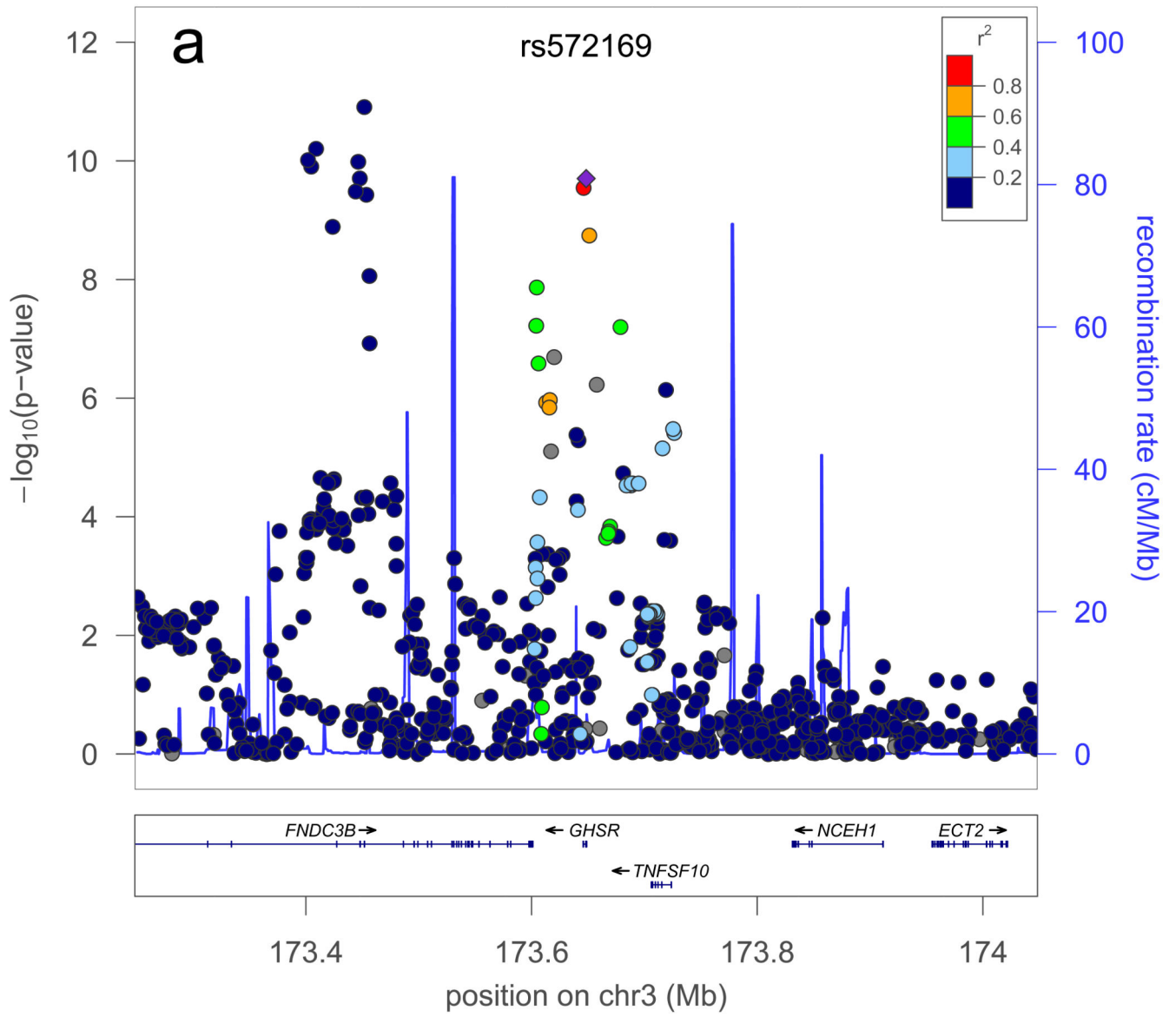


Figure 1. Phenotypic variance explained by common variants

(a) Variance explained is higher when SNPs not reaching genome-wide significance are included in the prediction model. The y-axis represents the proportion of variance explained at different P -value thresholds from Stage 1. Results are given for five studies that were not part of Stage 1. *Proportion of variation explained by the 180 SNPs. (b) Cumulative number of susceptibility loci expected to be discovered, including already identified loci and as yet undetected loci. The projections are based on loci that achieved a significance level of $P < 5 \times 10^{-8}$ in the initial scan and the distribution of their effect sizes in Stage 2. The dotted red line corresponds to expected phenotypic variance explained by the 110 loci that reached genome-wide significance in Stage 1, were replicated in Stage 2 and had at least 1% power.



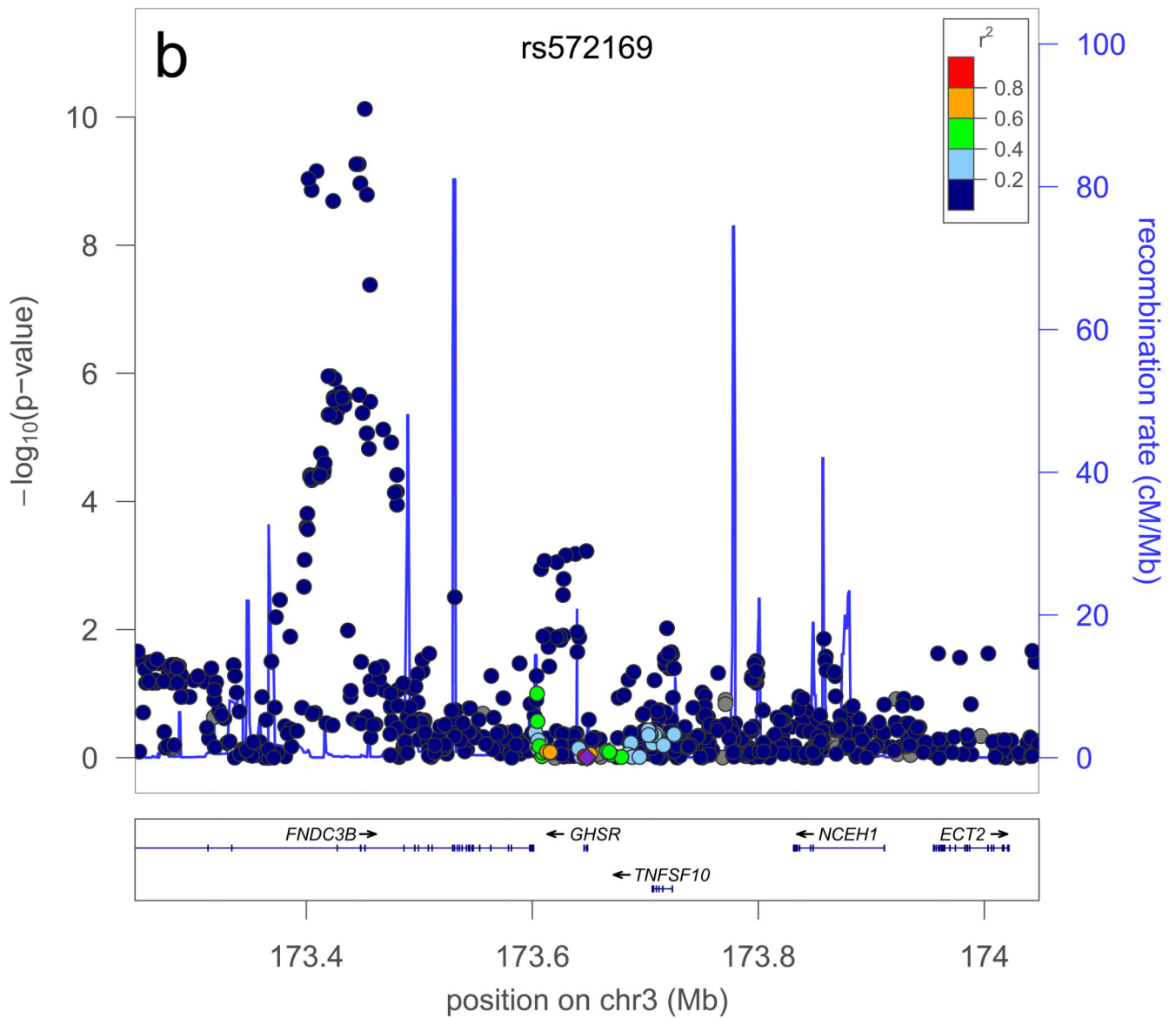


Figure 2. Example of a locus with a secondary signal before (a) and after (b) conditioning
 The plot is centered on the conditioned SNP (purple diamond) at the locus. r^2 is based on the CEU HapMap II samples. The blue line and right hand Y axis represent CEU HapMap II recombination rates. Created using LocusZoom (<http://csg.sph.umich.edu/locuszoom/>).

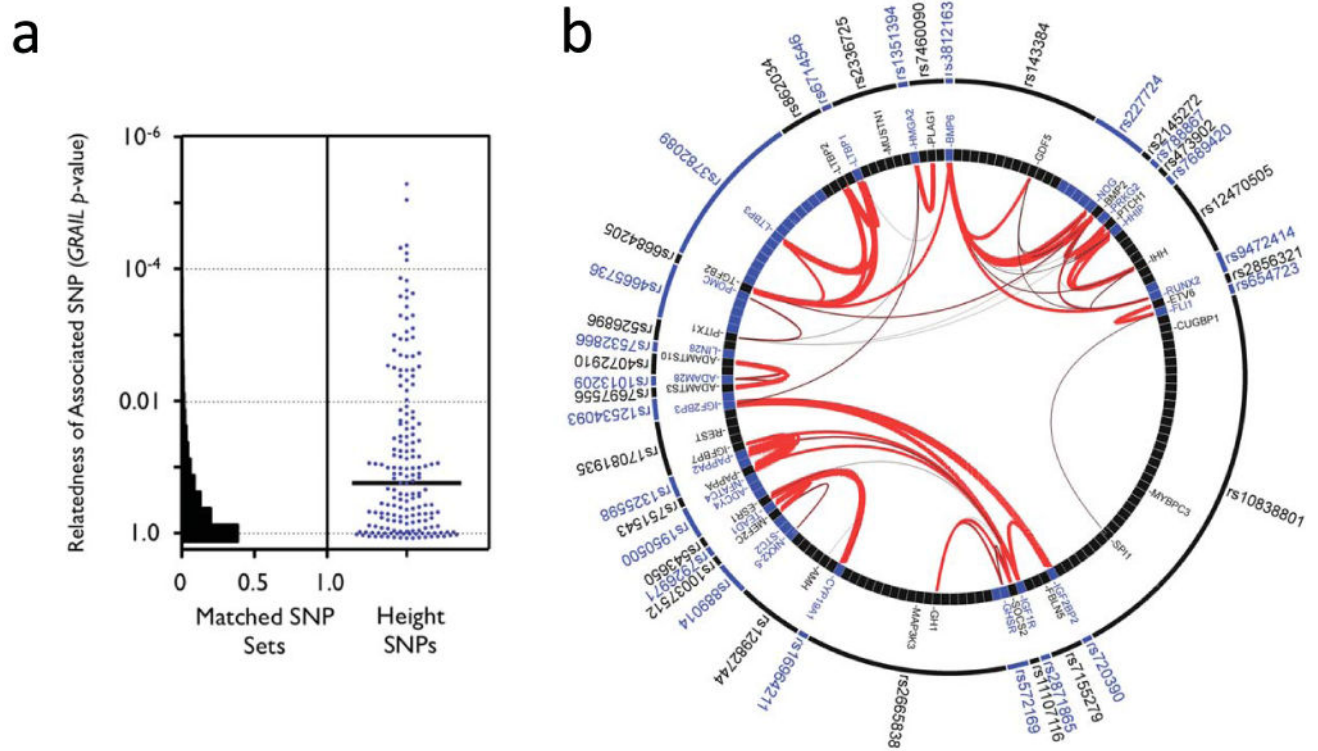


Figure 3. Loci associated with height contain genes related to each other

(a) 180 height-associated SNPs. The y-axis plots GRAIL P -values on a log scale. The histogram corresponds to the distribution of GRAIL P -values for 1,000 sets of 180 matched SNPs. The scatter plot represents GRAIL results for the 180 height SNPs (blue dots). The black horizontal line marks the median of the GRAIL P -values ($P=0.14$). The top 10 keywords linking the genes were: ‘growth’, ‘kinase’, ‘factor’, ‘transcription’, ‘signaling’, ‘binding’, ‘differentiation’, ‘development’, ‘insulin’, ‘bone’. (b) Graphical representation of the connections between SNPs and corresponding genes for the 42 SNPs with GRAIL $P<0.01$. Thicker and redder lines imply stronger literature-based connectivity.

Table 1

Secondary signals at associated loci after conditional analysis

Second signal SNP	Conditioned SNP	Chr	Second signal SNP position	Distance of conditioned SNP from index SNP (bp)	HapMap ^a r ²	Second signal P-value after conditioning	Second signal P-value pre-conditioning	Gene ^b
rs2280470	rs16942341	15	87196630	6721	0.009	1×10 ⁻¹⁴	1×10 ⁻¹⁵	<i>ACAN</i>
rs10859563	rs11107116	12	92644470	141835	0.003	3×10 ⁻¹²	8×10 ⁻¹⁰	<i>SOCS2</i>
rs750460	rs5742915	15	72028559	95127	0.004	4×10 ⁻¹²	7×10 ⁻⁰⁸	<i>PML</i>
rs6938239	rs2780226*	6	34791613	484583	0.019	6×10 ⁻¹²	9×10 ⁻¹⁴	<i>HMGAI</i>
rs7652177	rs572169	3	173451771	196650	0.006	7×10 ⁻¹¹	1×10 ⁻¹¹	<i>GHSR</i>
rs7916441	rs2145998	10	80595583	196119	0.112	6×10 ⁻¹⁰	3×10 ⁻⁰⁷	<i>PIIF</i>
rs3792752	rs1173727	5	32804391	61887	0.02	7×10 ⁻¹⁰	4×10 ⁻⁰⁸	<i>NPR3</i>
rs10958476	rs7460090	8	57258362	98355	0.02	1×10 ⁻⁰⁹	5×10 ⁻¹³	<i>SDRI6C5</i>
rs2353398	rs7689420	4	145742208	45594	0.022	2×10 ⁻⁰⁹	1×10 ⁻¹⁰	<i>HHIP</i>
rs2724475	rs6449353	4	17555530	87056	0.098	2×10 ⁻⁰⁹	8×10 ⁻¹⁶	<i>LCORL</i>
rs2070776	rs2665838	17	59361230	41033	0.15	9×10 ⁻⁰⁹	1×10 ⁻¹⁴	<i>GH region</i>
rs1401796	rs227724	17	52194758	60942	0.005	2×10 ⁻⁰⁸	7×10 ⁻⁰⁷	<i>NOG</i>
rs4711336	rs2780226*	6	33767024	540046	0.111	3×10 ⁻⁰⁸	5×10 ⁻⁰⁸	<i>HMGAI</i>
rs6892884	rs12153391	5	170948228	187815	0	4×10 ⁻⁰⁸	2×10 ⁻⁰⁵	<i>FBXW11</i>
rs1367226	rs3791675	2	55943044	21769	0.204	4×10 ⁻⁰⁸	0.1245	<i>EFEMP1</i>
rs2421992	rs17346452	1	170507874	187964	0.019	5×10 ⁻⁰⁸	1×10 ⁻⁰⁵	<i>DNM3</i>
rs225694	rs7763064	6	142568835	270147	0.001	1×10 ⁻⁰⁷	2×10 ⁻⁰⁶	<i>GPR126</i>
rs10187066	rs12470505	2	219223003	393610	0.022	2×10 ⁻⁰⁷	5×10 ⁻⁰⁸	<i>IHH</i>
rs879882	rs2256183	6	31247431	241077	0.016	2×10 ⁻⁰⁷	8×10 ⁻⁰⁸	<i>MICA</i>

^a HapMap CEU phase II release 23^b Nearest gene unless there is a known skeletal growth disorder gene in the locus (highlighted blue). Positions are based on NCBI build 36.

* Nearest conditioned SNP where second signal occurs within 1Mb of two conditioned SNPs.