LETTER

doi:10.1038/nature09410

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

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Most common human traits and diseases have a polygenic pattern of inheritance: DNA sequence variants at many genetic loci influence the phenotype. Genome-wide association (GWA) studies have identified more than 600 variants associated with human traits[1], but these typically explain small fractions of phenotypic variation, raising questions about the use 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 among variants that alter amino-acid structure of proteins and expression levels of nearby genes. Our data explain approximately 10% of the phenotypic variation in height, and we estimate that unidentified common variants of similar effect sizes would increase this figure to approximately 16% of phenotypic variation (approximately 20% of heritable variation). Although additional approaches are needed to dissect the genetic architecture of polygenic human traits fully, 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 polymorphisms (SNPs) present in the HapMap Phase 2 European–American reference panel[4]. 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 method[5,6] and then combined in a fixed effects based meta-analysis. We then applied a second genomic control 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 1 megabase (Mb) 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 Figs 1 and 2 and Supplementary Table 1). Additional tests, including genotyping of a randomly-selected subset of 33 SNPs in an independent sample of individuals from the fifth to tenth and ninetieth to ninety-fifth 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 and Supplementary Table 2).

Genome-wide association studies can be susceptible to false positive associations from population stratification[7]. 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 variation[8]. This is particularly true for height, where more than 80% of the variation within a given population is estimated to be attributable to additive genetic factors[9], but over 40 previously published variants explain less than 5% of the variance[10–17]. One possible explanation is that many common variants of small effects contribute to phenotypic variation, and current GWA studies remain underpowered to detect most 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[18] ($0.05 > P > 5 \times 10^{-8}$) increased the variance explained to 13.3% (range 9.7–16.8%) (Fig. 1a). 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 and Supplementary Tables 5 and 6).

As a separate approach, we used a recently developed method[19] 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 Fig. 1b. We estimate that there are 697 loci (95% confidence interval: 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% confidence interval: 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 genetic variants to phenotypic variation.

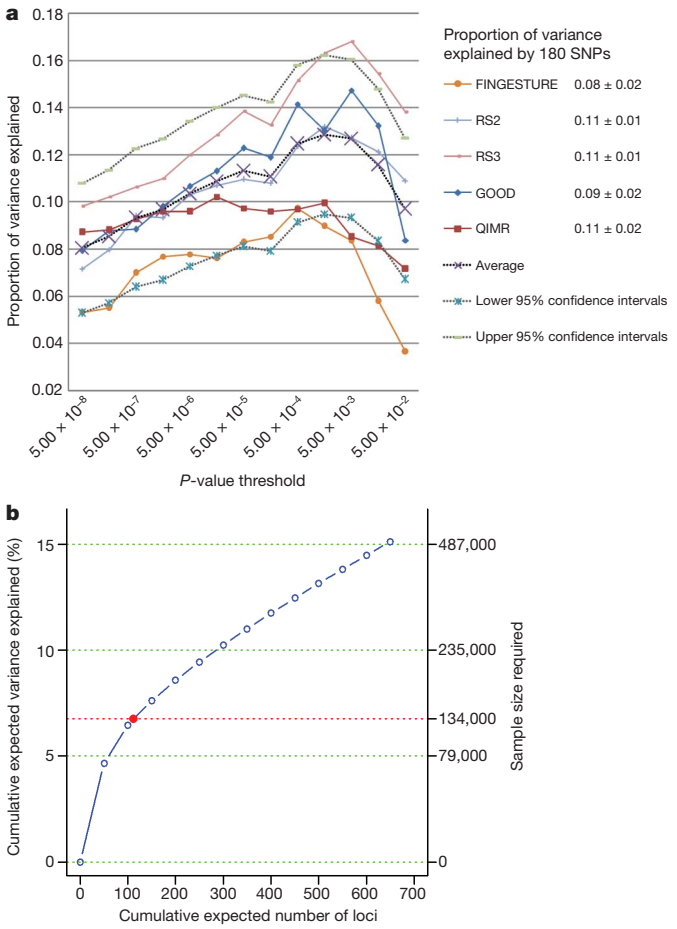

Figure 1 | Phenotypic variance explained by common variants. **a**, Variance explained is higher when SNPs not reaching genome-wide significance are included in the prediction model. The *y* axis represents the proportion of variance explained at different *P*-value thresholds from stage 1. Results are given for five studies that were not part of stage 1. The proportion of variation explained by the 180 SNPs is shown in the column to the right of the graph. **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.

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 approximately 15% of the genome covered by the conditioned 2 Mb loci; Table 1, Fig. 2, Supplementary Methods and Supplementary Figs 1 and 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 *HMGA1* region), the second signal occurred within 500 kilobases (kb), rather than between 500 kb 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 2-Mb loci, a total of 45 independent SNPs reached $P < 1 \times 10^{-5}$ when we would expect less than 2 by chance.

Although 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, non-synonymous (ns) SNPs and cis-expression quantitative trait loci (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 ($r^2 \geq 0.8$ in the HapMap CEU sample) with nsSNPs (24 variants, $P = 0.004$) (Supplementary Methods and Supplementary Table 8). Although the presence of a correlated cis-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 and Supplementary Table 9).

Table 1 | Secondary signals at associated loci after conditional analysis

Second signal SNP	Conditioned SNP	Chromosome	Second signal SNP position	Distance of conditioned SNP from index SNP (base pairs)	HapMap* r^2	Second signal *P* value after conditioning	Second signal *P* value pre-conditioning	Gene†
rs2280470	rs16942341	15	87,196,630	6,721	0.009	1×10^{-14}	1×10^{-15}	*ACAN*
rs10859563	rs11107116	12	92,644,470	141,835	0.003	3×10^{-12}	8×10^{-10}	*SOCS2*
rs750460	rs5742915	15	72,028,559	95,127	0.004	4×10^{-12}	7×10^{-8}	*PML*
rs6938239	rs2780226‡	6	34,791,613	484,583	0.019	6×10^{-12}	9×10^{-14}	*HMGA1*
rs7652177	rs572169	3	173,451,771	196,650	0.006	7×10^{-11}	1×10^{-11}	*GHSR*
rs7916441	rs2145998	10	80,595,583	196,119	0.112	6×10^{-10}	3×10^{-7}	*PPIF*
rs3792752	rs1173727	5	32,804,391	61,887	0.020	7×10^{-10}	4×10^{-8}	*NPR3*
rs10958476	rs7460090	8	57,258,362	98,355	0.020	1×10^{-9}	5×10^{-13}	*SDR16C5*
rs2353398	rs7689420	4	145,742,208	45,594	0.022	2×10^{-9}	1×10^{-10}	*HHIP*
rs2724475	rs6449353	4	17,555,530	87,056	0.098	2×10^{-9}	8×10^{-16}	*LCORL*
rs2070776	rs2665838	17	59,361,230	41,033	0.150	9×10^{-9}	1×10^{-14}	*GH region*
rs1401796	rs227724	17	52,194,758	60,942	0.005	2×10^{-8}	7×10^{-7}	*NOG*
rs4711336	rs2780226‡	6	33,767,024	540,046	0.111	3×10^{-8}	5×10^{-8}	*HMGA1*
rs6892884	rs12153391	5	170,948,228	187,815	0.000	4×10^{-8}	2×10^{-5}	*FBXW11*
rs1367226	rs3791675	2	55,943,044	21,769	0.204	4×10^{-8}	0.1245	*EFEMP1*
rs2421992	rs17346452	1	170,507,874	187,964	0.019	5×10^{-8}	1×10^{-5}	*DNM3*
rs225694	rs7763064	6	142,568,835	270,147	0.001	1×10^{-7}	2×10^{-6}	*GPR126*
rs10187066	rs12470505	2	219,223,003	393,610	0.022	2×10^{-7}	5×10^{-8}	*IHH*
rs879882	rs2256183	6	31,247,431	241,077	0.016	2×10^{-7}	8×10^{-8}	*MICA*

*HapMap CEU phase II release 23. †Nearest gene unless there is a known skeletal growth disorder gene in the locus. Positions are based on National Center for Biotechnology Information build 36. ‡Nearest conditioned SNP where second signal occurs within 1 Mb of two conditioned SNPs.

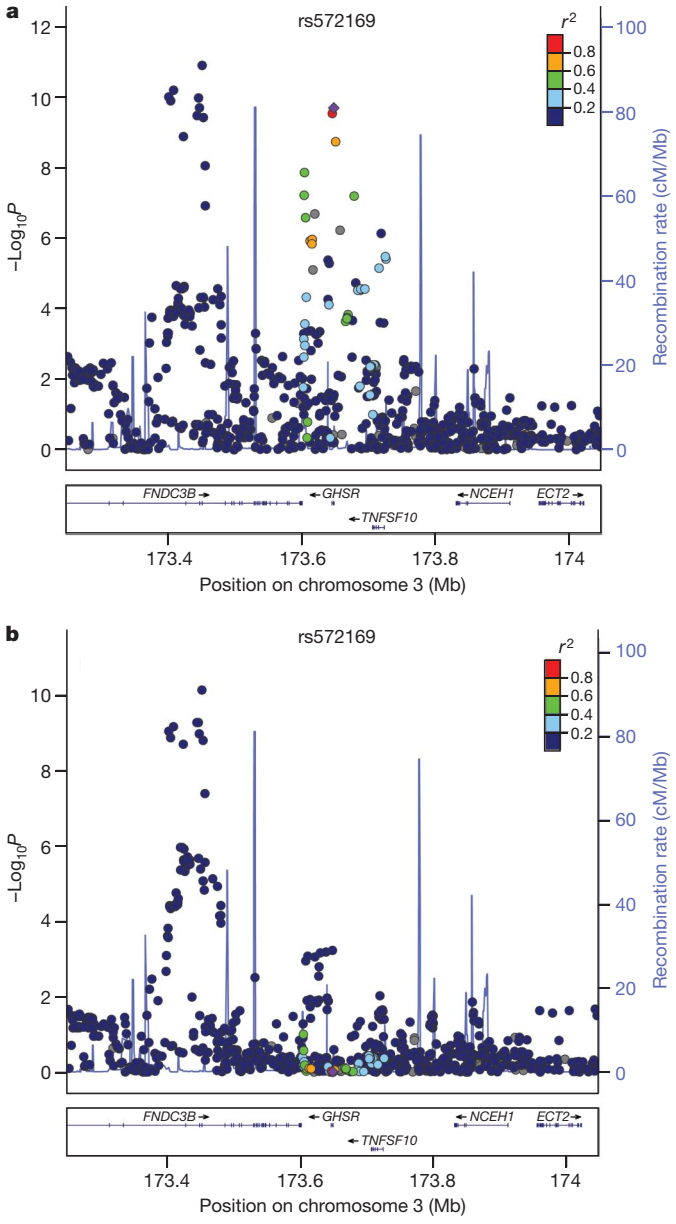

Figure 2 | Example of a locus with a secondary signal before (a) and after (b) conditioning. The plot is centred on the conditioned SNP (purple diamond) at the locus. The values of r^2 are based on the CEU HapMap II samples. The blue line and right-hand *y* axis represent CEU HapMap II recombination rates. The figure was created using LocusZoom (http://csg.sph.umich.edu/locuszoom/).

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 Fig. 1 and Supplementary Table 10), compared with 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 nine of these cases the most strongly associated height SNP is located within the growth disorder gene itself (Supplementary Methods and 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 literature[20]. 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 ($P = 0.016$) (Fig. 3a). For the 42 regions with GRAIL connectivity $P < 0.01$, the implicated genes and SNPs are highlighted in Fig. 3b. The most strongly connected genes include those in the Hedgehog, TGF-β and growth hormone pathways.

As a second approach to find biological connections, we applied a novel implementation of gene set enrichment analysis (meta-analysis gene-set enrichment of variant associations, MAGENTA[21]) 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] (for example, Hedgehog signalling) and novel (for example, TGF-β signalling, 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-β signalling pathway in regulating human height, consistent with the implication of this pathway in Marfan syndrome[22].

Finally, to examine the evidence for the potential involvement of specific genes at individual loci, we aggregated evidence from our data (expression quantitative trait loci, 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), whereas others have similar functions to known growth-related genes, including *FGFR4* (*FGFR3* underlies several classic skeletal dysplasias[23]) and *STAT2* (*STAT5B* mutations cause growth defects in humans[24]). Interestingly, $Fgfr4^{-/-}$ $Fgfr3^{-/-}$ mice show severe growth retardation not seen in either single mutant[25], 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 growth[17]. 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*, *LRRC37B*, *MFAP2*, *SLBP*, *SOCS5* and *ZBTB24* (Supplementary Table 13).

We have identified more than 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 (*GH1*, *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.

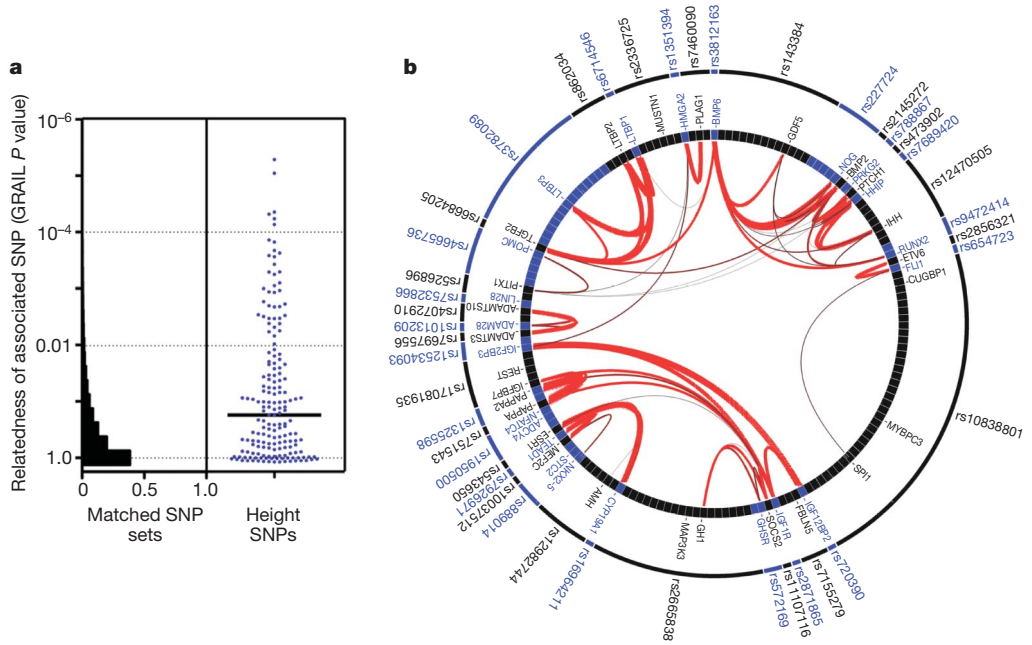

Figure 3 | Loci associated with height contain genes related to each other. **a**, One hundred and eighty height-associated SNPs. The *y*-axis plots GRAIL *P* values on a log scale. The histogram corresponds to the distribution of GRAIL *P* values for 1,000 sets of 180 matched SNPs. The scatter plot 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 ten keywords linking the genes were: 'growth', 'kinase', 'factor', 'transcription', 'signalling', 'binding', 'differentiation', 'development', 'insulin', 'bone'. **b**, 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.

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 studies[26], 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 more than 100,000 individuals, we identified common variants that account for approximately 10% of phenotypic variation. Although larger than predicted by some models[26], this figure suggests that GWA studies, as currently implemented, will not explain most 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 proposed[27]. 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 suggestion[28] that many 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 of complex human traits. Our results also strongly demonstrate that GWA studies can identify many loci that together implicate biologically relevant pathways and mechanisms. We envisage 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

A summary of the methods, together with a full description of genome-wide association analyses and follow-up analyses of loci and variants, can be found in Supplementary Information.

Received 23 April; accepted 28 July 2010.
Published online 29 September 2010.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Acknowledgements Several participating studies are members of the CHARGE and ENGAGE consortia. We acknowledge funding from the following organizations: the Academy of Finland (104781, 117797, 120315, 121584, 126925, 129269, 129494, 129680, 213506); Affymetrix for genotyping services (N02-HL-6-4278); Agency for Science, Technology and Research of Singapore; ALF/LUA Gothenburg; Althingi (the Icelandic Parliament); Amgen; AstraZeneca AB; Australian National Health and Medical Research Council (241944, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 496688, 552485, 613672); Australian Research Council (DP0770096); Biocentrum Helsinki; Boston Obesity Nutrition Research Center (DK46200); British Diabetes Association; British Heart Foundation (PG/02/128); British Heart Foundation Centre for Research Excellence, Oxford; CamStrad; Cancer Research UK; Centre for Neurogenomics and Cognitive Research; Chief Scientist Office of the Scottish Government (CZB/4/279); Council of Health of the Academy of Finland; DIAB Core project of the German Network of Diabetes; Diabetes UK; Donald W. 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; GEN-AU-Programme 'GOLD'; Genetic Association Information Network; German Bundesministerium fuer Forschung und Technology (01 AK 803 A-H, 01 IG 07015 G); German Federal Ministry of Education and Research (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 (01GS0823, 01ZZ0103, 01ZZ0403, 01ZZ9603, 03ZIK012); German Research Council (KFO-152); GlaxoSmithKline; Göteborg Medical Society; Gyllenberg Foundation; Helmholtz Center Munich; Juvenile Diabetes Research Foundation International (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 (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 Cancer Institute; National Institute for Health Research Cambridge Biomedical Research Centre; National Institute for Health Research Oxford Biomedical Research Centre; National Institute for Health Research 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–N01-HC55022, N01-HC55222, N01-HC75150, N01-HC85079–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/Netherlands Consortium for Healthy Aging (050-060-810); Netherlands Organisation for Scientific Research (investment number 175.010.2005.011, 911-03-012); Netherlands Organization for the Health Research and Development (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; 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; Wellcome Trust 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). A detailed list of acknowledgements by study is given in the Supplementary Information.

Author Contributions This work was done under the auspices of the Genetic Investigation of ANthropocentric Traits (GIANT) Consortium. Author contributions and roles are listed in the Supplementary Information.

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