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REVIEW PAPER

# Recent progress in the study of the genetics of height

**Guillaume Lettre**

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**Abstract** Adult height is a classic polygenic trait of high narrow-sense heritability ($h^2 = 0.8$). In the late nineteenth to early twentieth century, variation in adult height was used as a model to set the foundation of the fields of statistics and quantitative genetics. More recently, with our increasing knowledge concerning the extent of genetic variation in the human genome, human geneticists have used genome-wide association studies to identify hundreds of loci robustly associated with adult height, providing new insights into human growth and development, and into the architecture of complex human traits. In this review, I highlight the progress made in the last 2 years in understanding how genetic variation controls height variation in humans, including non-Caucasian populations and children.

## Introduction

In his seminal 1918 paper, the great English statistician and geneticist Ronald A. Fisher proposed that the normal variation observed in height within a population could be explained by the segregation of many genetic factors, each of small effect size (Fisher 1918). Although the human genetic community generally accepted that concept, we have to wait almost 90 years for the advent of genome-wide association (GWA) studies to find evidence of association between a common DNA sequence variant—a single nucleotide polymorphism (SNP) in a gene called *HMGA2*—and adult height variation (Weedon et al. 2007). In the early years of the GWA study era (2007–2008), 47 loci were shown to carry SNPs associated with stature in Europeans or European Americans; these discoveries, along with their numerous implications on genetics and human development, have been recently summarized (Hirschhorn and Lettre 2009; Lettre 2009; Weedon and Frayling 2008). In the current review, I focus on the progress made in the last 2 years in the study of the genetics of height regulation, highlighting efforts in European- and non-European-derived populations. I also comment on the recent studies that have applied the GWA approach to understand the genetics of growth in children.

## A GIANT step

In October 2010, the Genetic Investigation of ANthropometric Traits (GIANT) Consortium published a large meta-analysis of genome-wide height association results in population of European descent (Lango Allen et al. 2010). GIANT investigators combined GWA height results from 133,653 individuals and replicated the top SNPs in 50,074 independent samples to identify 180 loci that reached the accepted level to declare genome-wide significance ($P < 5 \times 10^{-8}$) (Altshuler et al. 2005), making height the single most successful phenotype—in terms of independent loci identified—so far investigated by the GWA study approach (Hindorff et al. 2009). Secondary analyses revealed many interesting features of the 180 GIANT height-associated SNPs: (1) they are enriched for SNPs that control gene expression in *cis* (*cis*-eQTLs), (2) they significantly correlate with potentially functional non-synonymous

G. Lettre (✉)
Montreal Heart Institute, 5000 Bélanger Street,
Montreal, QC H1T 1C8, Canada
e-mail: guillaume.lettre@mhi-humangenetics.org

G. Lettre
Département de Médecine, Université de Montréal, C.P. 6128,
succursale Centre-ville, Montreal, QC H3C 3J7, Canada

genetic variants, and (3) in pathway-based analysis, they cluster together into biologically relevant pathways (e.g. the hedgehog and TGF-$\beta$ signaling pathways, both essential for chondrocyte proliferation and differentiation, signaling at the growth plates, and bone formation, and the growth hormone signaling pathway, which is the master regulator pathway of human growth) (Lango Allen et al. 2010). Moreover, GIANT investigators also considered the 180 height SNPs in relation with the several known genes that cause severe skeletal or growth syndromes in humans when mutated. They queried the Online Mendelian Inheritance in Men (OMIM) database and found 241 skeletal/growth syndrome genes. They then tested if the genes near the 180 SNPs associated with height were significantly enriched in the list of syndrome genes when compared with matched sets of SNPs. Indeed, they found 21 SNPs near an OMIM skeletal/growth gene (enrichment $P < 0.001$); for 13 of these SNPs, the SNPs themselves were located within the OMIM skeletal/growth gene (Table 1) (Lango Allen et al. 2010). These results indicate that the SNPs found by GWA studies to be associated with adult height are not randomly distributed across the human genome, and probably underlie relevant functional and biological information to the study of human growth (Goldstein 2009; Hirschhorn 2009). The results also suggest that allelic series might be important in humans, with common and rare DNA sequence variants in the same gene affecting common trait (e.g. height variation) and causing extreme phenotypes (e.g. skeletal dysplasia).

The OMIM skeletal/growth gene result also suggests that the 180 height loci might contain causal genes for skeletal or growth syndromes of unknown etiology. The genetic characterization of *TRIP11*—encoding Golgin GMAP-210, a protein important for glycosylation and intracellular protein transport—in humans and mice clearly illustrates this point: GWA studies found SNPs near *TRIP11* to be strongly associated with adult height (Gudbjartsson et al. 2008; Lettre et al. 2008), while the positional cloning of a mutagenesis screen-induced mutation that causes severe autosomal recessive skeletal dysplasia in the mouse led to the discovery of a mutation in the *Trip11* homolog (Smits et al. 2010). Interestingly, because the mouse phenotype was reminiscent of defects observed in human patients with achondrogenesis type 1A, a neonatal

**Table 1** Adult height-associated SNPs located near OMIM skeletal/growth syndrome genes

| SNP | Chromosome (position) | GIANT height *P* value | Growth/skeleton syndrome gene (OMIM #) | Distance between SNP and OMIM gene (kb) |
|---|---|---|---|---|
| rs10874746 | 1 (93096559) | $6.7 \times 10^{-11}$ | *RPL5* (603634) | 16.5 |
| rs11684404 | 2 (88705737) | $9.9 \times 10^{-14}$ | *EIF2AK3* (604032) | 0 |
| rs12470505 | 2 (219616613) | $8.9 \times 10^{-12}$ | *IHH* (600726) | 10.8 |
| rs572169 | 3 (173648421) | $2.8 \times 10^{-18}$ | *GHSR* (601898) | 0 |
| rs422421 | 5 (176449932) | $1.1 \times 10^{-12}$ | *NSD1* (117550) | 43.5 |
| rs6457821 | 6 (35510783) | $2.1 \times 10^{-12}$ | *FANCE* (600901) | 17.3 |
| rs9472414 | 6 (45054484) | $1.8 \times 10^{-9}$ | *RUNX2* (119600) | 349.5 |
| rs473902 | 9 (97296056) | $2.3 \times 10^{-17}$ | *PTCH1* (601309) | 0 |
| rs10838801 | 11 (48054856) | $3.5 \times 10^{-12}$ | *SLC39A13* (612350) | 660.2 |
| rs1351394 | 12 (64638093) | $1.7 \times 10^{-65}$ | *HMGA2* (600698) | 0 |
| rs7971536 | 12 (100897919) | $8.2 \times 10^{-14}$ | *GNPTAB* (607840) | 149.2 |
| rs7155279 | 14 (91555634) | $1.9 \times 10^{-13}$ | *TRIP11* (604505) | 0 |
| rs16964211 | 15 (49317787) | $1.7 \times 10^{-9}$ | *CYP19A1* (107910) | 0 |
| rs16942341 | 15 (87189909) | $3.8 \times 10^{-27}$ | *ACAN* (155760) | 0 |
| rs2871865 | 15 (97012419) | $2.9 \times 10^{-21}$ | *IGF1R* (147370) | 0 |
| rs3764419 | 17 (26188149) | $1.8 \times 10^{-21}$ | *RNF135* (611358) | 133.9 |
| rs227724 | 17 (52133816) | $7.4 \times 10^{-15}$ | *NOG* (602991) | 105.9 |
| rs2665838 | 17 (59320197) | $5.1 \times 10^{-25}$ | *GH1* (139250) | 28.1 |
| rs9967417 | 18 (45213498) | $9.3 \times 10^{-25}$ | *DYM* (607461) | 0 |
| rs17782313 | 18 (56002077) | $3.8 \times 10^{-11}$ | *MC4R* (155541) | 187.5 |
| rs4072910 | 19 (8550031) | $3.6 \times 10^{-13}$ | *ADAMTS10* (608990) | 1.1 |
| rs143384 | 20 (33489170) | $1 \times 10^{-58}$ | *GDF5* (601146) | 0 |

Positions are on build NCBI36.3/hg18. Height *P* values are from (Lango Allen et al. 2010). Gene proximity with height SNPs is defined here using linkage disequilibrium (LD) and recombination hotspots. Several additional growth/skeleton syndrome genes (*e.g. ESR1*, *IGFBP3*, *COL11A1*) are located near height SNPs highlighted by the GIANT Consortium, but fall outside the genomic intervals delimited by LD and recombination

lethal form of skeletal dysplasia, the authors re-sequenced the *TRIP11* gene in 10 unrelated achondrogenesis type 1A patients and found for each of them loss-of-function causal mutations (Smits et al. 2010).

## New leaps in complex trait genetics

Adult height is one of the most heritable human phenotypes, yet SNPs within the original 47 height loci identified by earlier GWA studies in Caucasians explained less than 5% of the phenotypic variation observed (Estrada et al. 2009; Gudbjartsson et al. 2008; Lettre et al. 2008; Sanna et al. 2008; Soranzo et al. 2009; Tonjes et al. 2009; Weedon et al. 2007; 2008). By adding the new loci identified by the GIANT Consortium, the 180 SNPs explain approximately 10% of the variation in adult height, far from the 80% expected from heritability studies (Perola et al. 2007; Visscher et al. 2006). In comparison, the classic method proposed by Sir Francis Galton in 1886 to use mid-parental height to predict the height of children explains 40% of the height variance (Aulchenko et al. 2009; Galton 1886; Visscher et al. in press). To explore the difference in prediction of height using traditional or genetic profiles, the GIANT study applied two methods on the height dataset. In the first method, they considered SNPs with less significant P-values ($P < 0.05$) to build a genetic predictor, in order to include SNPs of weak effect on height that did not reach genome-wide significance in the GIANT meta-analysis (Purcell et al. 2009). In the second method, they modeled the distribution of effect sizes for all height variants, including those not yet identified, based on the observed effect sizes of the known height SNPs (Park et al. 2010). Using these approaches, they calculated that the GIANT height data explain up to 15% of the phenotypic variation in height (or ~20% of the heritable variation) (Lango Allen et al. 2010).

One outstanding question left open is where are the remaining genetic factors that additively contribute to height variation in the general population? The identification of several independent association signals for a given phenotype at the same locus, also known as allelic heterogeneity, can explain additional phenotypic variation, as has been shown for many complex human diseases and traits (Galarneau et al. 2010; Graham et al. 2007; Lango Allen et al. 2010; Loos et al. 2008). Visscher and colleagues studied the hidden heritability question of height a step further and showed that by fitting a linear model with simultaneously ~300,000 SNPs genotyped in 3,925 individuals, these common genetic markers could explain in aggregate 45% of the variance in height (Yang et al. 2010). In fact, more variance could actually be explained when accounting for incomplete linkage disequilibrium (LD) between, and allele frequency differences of, causal and genotyped SNPs (Yang et al. 2010). This result is not inconsistent with the GIANT findings because it suggests that the variation in height is controlled in large part by common DNA sequence variants with weak effects, which require extremely large sample size to be identified. But common DNA polymorphisms are likely to be only part of the story, with rare sequence variants also influencing height variation. Consistent with this possibility, a recent large study using a gene-centric genotyping array identified a rare variant in the *IL11* gene associated with adult height (rs4252548; minor allele frequency 3%; $P = 3\times10^{-12}$); this SNP is not covered by commercial genome-wide genotyping arrays and was not identified by the GIANT Consortium (Lanktree et al. 2011). In the GIANT report, only three height SNPs (rs6457821, rs16942341, rs12902421) had a minor allele frequency less than or equal to 3%, emphasizing one limitation of the GWA approach (Fig. 1) (Lango Allen et al. 2010).

## GWA studies of height in non-Caucasian populations

The first GWA studies for complex human diseases and traits focused almost exclusively on Europeans and populations of European descent. However, the GWA study approach has gain momentum in non-Caucasian populations. The KARE Project genotyped 8,842 South Koreans and identified 15 loci associated with height, including eight loci that had not been previously implicated in height variation (Cho et al. 2009; Kim et al. 2010). Five of these height loci were also shown to associate with idiopathic short stature in South Koreans, a condition with a prevalence of 1–2% and defined by an adult height of two

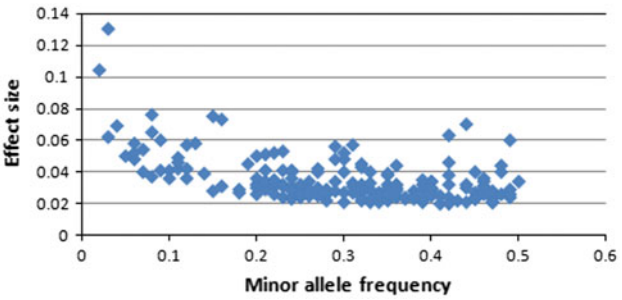


**Fig. 1** Distribution of effect size for the 180 height SNPs identified by the GIANT Consortium in relation to their respective minor allele frequency (Lango Allen et al. 2010). The absolute value of the effect size is given in standard deviation (SD) units. The two stronger SNPs are also the rarer ones (*PPARD/FANCE* (rs6457821), minor allele frequency 2%, effect size 0.104 SD, $P = 2\times10^{-12}$; *ACAN* (rs16942341), minor allele frequency 3%, effect size 0.130 SD, $P = 4\times10^{-27}$). A similar distribution of effect size for height SNPs was also observed by (Lanktree et al. 2011)

standard deviations below the population mean (Kim et al. 2010). More recently, genotyping of 19,633 Japaneses yielded two new height loci and replicated several loci previously identified in Caucasians (Okada et al. 2010). Other smaller GWA studies in Japanese and Chinese populations have also been reported (Lei et al. 2009; Takeuchi et al. 2009). Comparisons of the height association results in East Asians and Caucasians are difficult given the marked difference in sample size. However, it seems that there are not multiple loci with strong effects on height in East Asians, and that the same loci—and in many cases the same SNP or SNPs in LD—control height variation in both East Asian and Caucasian populations. This result might be expected given that common genetic variants are usually old and common to several populations, although the final answer will only emerge once causal alleles are identified and validated at each locus and in each population.

Similar conclusions are also starting to take shape from the small GWA studies that have been carried out in populations of African ancestry, although once again differences in sample size can bias our interpretation (Kang et al. 2010; Shriner et al. 2009). Many height loci found in Caucasians replicated nominally in these small GWA scans, although often proxy SNPs, rather than the published Caucasian height SNPs, were more strongly associated with height variation. These trans-ethnic comparisons are potentially of great value in fine-mapping genetic intervals and guiding re-sequencing efforts to find causal DNA sequence variants. Larger meta-analyses in African Americans are currently underway and promise to deliver additional information on the genetic regulation of height in African-derived populations, and may identify population-specific height regulators.

## Genetics of human growth

Human growth is a dynamic process that can be divided into three major phases: infant growth, childhood growth, and the growth spurt following puberty. Growth is influenced by age, gender, health, and many environmental factors. However, twin studies also suggest that there is a strong genetic component to growth variation in humans (Silventoinen et al. 2008). Investigators have tested the association between adult height-associated SNPs and height in children at specific ages: although some SNPs replicated, many did not associate with children height (Weedon et al. 2007; Zhao et al. 2010). The non-validation of many adult height SNPs with pediatric stature might simply reflect the fact that human growth is highly heterogeneous among children, even in the same age group. To study the genetics of human growth, height velocity is likely to be a better phenotype, although this requires longitudinal height measurements collected over several years.

Fortunately, such longitudinal height data is available in some cohorts, most notably from large Finnish birth cohorts, such as the prospective Northern Finland Birth Cohort 1966 (NFBC66), where participants were followed from 0 to 20 years and each has on average 20 height measurements. Investigators use this rich dataset to derive height velocities at different time during growth and, using genome-wide genotyping of 3,538 NFBC66 participants, perform a GWA scan for human growth. Although this analysis did not show new associations with height velocity that reached genome-wide significance, presumably because of their limited statistical power, they did identify SNPs at loci previously associated with adult height that nominally associated with height velocity during infancy (*SF3B4/SV2A*, *LCORL*, *GDF5/UQCC*, *DLEU7*, *HHIP*, and *HIST1H1D*) and puberty (*SF3B4/SV2A*, *SOCS2*, *C17orf67*, *CABLES1*, and *DOT1L*) (Sovio et al. 2009). Few studies on the genetics of growth and height in children have been published, but these early reports suggest that some genes might modulate human growth throughout development, whereas others may act at specific developmental stages.

## *LIN28B*: a jack-of-all-trades

In a subsequent study, NFBC66 investigators focused on the increase in height between age 14 and adulthood to find genetic associations with the pubertal growth spurt (Widen et al. 2010). They found an association between SNP rs7759938 near the *LIN28B* gene and height increase ($P = 3\times10^{-8}$); this result was independently replicated in the Cardiovascular Risk in Young Finns Study ($N = 1{,}241$; combined $P = 5\times10^{-11}$). More specifically, the effect of rs7759938 was stronger in females than males on the growth spurt ($P = 7\times10^{-7}$ vs. $P = 0.005$, respectively), and the SNP seemed to modulate growth differently in each gender (strong effect on pre-pubertal growth in females and final height in males). The same *LIN28B* SNP (rs7759938) has been associated with adult height (Lango Allen et al. 2010) and age at menarche (Elks et al. 2010), suggesting that rs7759938 modulates pubertal timing (Fig. 2). A second, partially correlated SNP at the *LIN28B* locus, rs314277, was also shown in the same study to interact with gender in controlling height (Fig. 2). Thus, *LIN28B*, a gene originally identified in *C. elegans* to control developmental progression (Moss et al. 1997), is located near DNA sequence variants that regulate growth and developmental timing in humans. Although proximity between an associated DNA polymorphism and a gene does not imply causality, *LIN28B* appears as an excellent causal

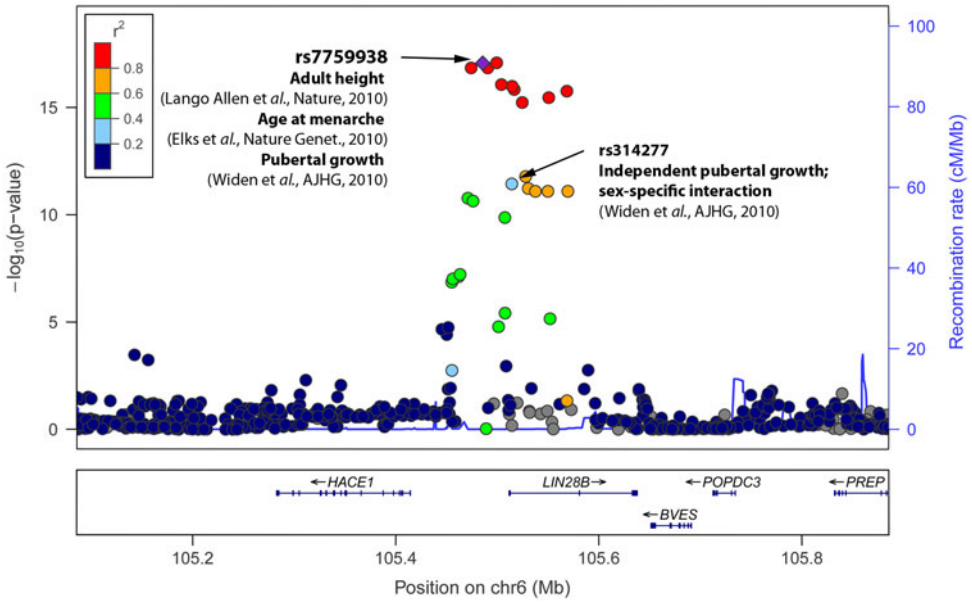


**Fig. 2** SNPs at the *LIN28B* locus associate with adult height, pubertal growth spurt, and age at menarche. The plot, drawn using LocusZoom (Pruim et al. 2010), shows association results to adult height from the GIANT Consortium (Lango Allen et al. 2010). The *x*-axis and *y*-axis correspond to the physical position on chromosome 6 and the strength of association to adult height in the $-\log_{10}$ scale of the *P* values, respectively. Each *dot* represents one SNP (genotyped or imputed). The color of the *dots* summarizes linkage disequilibrium (LD) values between these SNPs and the index SNP rs7759938, using HapMap CEU to calculate LD. The *light blue line* in the background corresponds to the recombination rate

regulator of growth in humans as mice with a *Lin28a* transgene show increased body size and delayed onset of puberty (Zhu et al. 2010). This is a particularly exciting hypothesis given that *LIN28B* encodes a RNA-binding protein that interacts with and inactivates the family of *let-7* microRNAs (Viswanathan et al. 2008), and that several targets of the *let-7* microRNAs are genes located in loci identified by GWAS for adult height (Lettre et al. 2008).

## Conclusion

GWA studies have proven extremely useful to identify genetic variation that influences adult height, providing insights not only on the biology of growth and development in humans, but also on the genetic regulation of complex human diseases and traits. Application on large cohorts of new generation of genome-wide genotyping arrays that incorporate data from the 1,000 Genomes (Durbin et al. 2010) and target lower frequency DNA polymorphisms should allow us to test for the presence of less frequent alleles and their effects on height variation. As the excitement of the community now shifts towards next-generation DNA sequencers, these technologies open interesting new possibilities in terms of the characterization of height loci found by GWA studies, the identification of height causal variants, and the assessment of the role and effect size of rare DNA sequence variants on stature variation. Clearly the search for height genetic modulators is not over, and undoubtedly many surprises lay ahead.

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