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REVIEW

Using height association studies to gain insights into human idiopathic short and syndromic stature phenotypes

Guillaume Lettre

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Abstract Variation in adult height is not the most clinically relevant human quantitative trait, yet its study provides the foundation of many quantitative genetics theories and important statistical concepts (e.g. regression). Even today, the analysis of adult height by genome-wide association studies (GWAS) continues to significantly impact human genetics: these studies have led to the discovery of >200 loci associated with variation in adult height and have highlighted the very polygenic nature of human continuous traits. In this brief review, I discuss and provide examples on how such genetic associations, identified in individuals of *normal* height, could help understand the complex genetics behind such phenotypes as idiopathic short stature (ISS) or extreme/syndromic height phenotypes of unknown cause.

Keywords Adult height · Stature · Idiopathic short stature · Syndromic height · Genome-wide association study · Genetics

Introduction

Childhood growth is one of the main traits monitored by pediatricians around the world to ensure that a child's development is normal. Although the study of height variation in humans has been at the center stage of quantitative genetics since the birth of this discipline [1–3], surprisingly little is known about the factors that regulate developmental growth, especially in terms of explaining the interindividual variation in height observed among children of the same age. The environment undoubtedly plays an important role (e.g. nutrition, infections), but it is also clear that genetic programs influence birth length, puberty growth spurt, growth velocity and final adult height [4–6]. However, it is only with the emergence of new genomic technologies that the first genetic polymorphisms that influence height were recently identified [7, 8]. These initial discoveries paved the way for larger follow-up studies that have so far yielded >200 single nucleotide polymorphisms (SNPs) convincingly associated with height variation in adults [9]. In this review, I focus on how such genetic discoveries, which help understand variation in height observed in the general population, could also help to elucidate the genetic basis of *abnormal* phenotypes, such as idiopathic short stature (ISS) or extreme short/tall height, caused by mutations in unknown genes.

Genetic association studies of adult height

The recent insights into adult height variation through genome-wide association studies (GWAS) have extensively been reviewed [10–12]. Therefore, I will briefly summarize here only the main findings that will help guide our discussion. In 2010, the Genetic Investigation of ANthropometric Traits (GIANT) Consortium (an international consortium that gathers >50 studies with GWAS results; http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium) published what is still to date one of the largest meta-analysis of genome-wide association results for a human continuous trait: the GIANT investigators combined results from >180,000 participants and identified 180 SNPs associated with adult height at genome-wide significance [9]. Importantly, this study confirmed the polygenic architecture of height—which is that the segregation of hundreds of genetic variants, each with a small effect on height, is sufficient to account for the variation in stature among human populations. The 180 GIANT SNPs together explain approximately 10 % of the phenotypic

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

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variation in adult height. Besides the logistical *tour de force* of the study itself, the GIANT study identified several genomic regions and biological pathways previously unsuspected to play a role in human height (Table 1). For most of these loci, two important questions remain: (1) which genes play a role in human stature and (2) how genetic variation within these loci influences the functions of these genes? The few examples of successful functional characterization of GWAS hits suggest that the translation from genetic results to biological insights requires an integrative approach that considers genetic and genomic datasets, as well as molecular and cell biology experiments and characterization in animal models [13–16].

The GIANT study analyzed exclusively Europeans or individuals of European ancestry [9], but large meta-analyses of GWAS have also analyzed adult height in other ethnic groups. For example, the KARE Consortium analyzed height in 8,842 South Koreans and found 15 loci associated with height, many of which had already been reported by the GIANT study [17, 18]. Two large association studies were recently performed in African-ancestry individuals, and both reported a limited number of associations not previously identified in populations of European ancestry. Furthermore, both studies also replicated most associations that were initially reported by the GIANT Consortium [19, 20]. Although population-specific associations were observed for this trait, these results suggest that most height-associated genetic polymorphisms have *trans*-ethnic effect.

Genetic associations during childhood growth

Much less is known about the genetic factors that modulate growth during childhood despite high heritability estimates [21]. This lack of information is attributed partly to the heterogeneity of growth timing and velocity, even in children of the same sex and age. Therefore, the study of the genetics of human growth requires longitudinal height measures obtained over several years (ideally from birth to the end of growth at 18–21 years of age). Fortunately, such large longitudinal cohorts do exist, and attempts have been made to identify genetic determinants of growth, focusing on birth length, growth rate at different periods during development and timing of puberty [22–25]. These studies have confirmed that the SNPs associated with adult height do play an important role in childhood growth. A genetic score based on genotypes at the 180 height SNPs identified by the GIANT Consortium associates strongly with birth length and growth rate [25]. The results of a study in twins suggest that the SNPs associated with adult height affect more prepubertal height than the pubertal growth spurt [24]. Common DNA polymorphisms (SNPs) at the *LIN28B* locus, however, associate with growth velocity, and the effect was proposed by the respective authors to be sex-specific [22, 24]. It is likely that combining genome-wide association results for growth through meta-analyses, as has been done for stature, would yield novel associations because of increased statistical power.

ISS, one of the main reasons for referral to pediatric endocrinology clinics, is defined as a sex-, age- and population-adjusted height that is more than two standard deviations (SD) below the mean with no evidence of endocrine, nutritional or chromosomal anomalies [26]. Understanding the causes of ISS is critical in the context of our fragile healthcare system, given the costs associated with growth hormone therapy (>$15,000/child/year) [27]. It would be extremely useful for pediatric endocrinologists to be able to determine whether a child with ISS is in the *normal* range of his/her height potential given his/her genetic code and the segregation of common height-associated alleles, or whether something else (e.g. environmental factors, de novo detrimental mutations) is causing the abnormal height phenotype.

Table 1 Biological pathways (KEGG database) that are enriched ($P<0.05$) for genes located near (≤300 kb) height-associated single nucleotide polymorphisms[a]

Biological pathway (KEGG)	Genes
Hedgehog signaling pathway	*BMP6, IHH, PTCH1, WNT6, WNT9A, FBXW11, HHIP, WNT10A, WNT3A*
Gamma-hexachlorocyclohexane degradation	*DHRS1, LOC283871*
MAPK signaling pathway	*ARRB1, CACNB1, CHUK, FGFR3, FGFR4, GNA12, MKNK2, MEF2C, MAP3K3, MOS, GADD45B, NF1, NFATC4, PPM1A, MAPK9, MAP2K3, RASA2, RPS6KA1, TGFB1, TGFB2, TNF, MAP3K14, RASGRP3*
Antigen processing and presentation	*HLA-B, HLA-C, HLA-DMA, HLA-DMB, HLADOB, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DRA, HLA-DRB1, HLA-DRB5, LTA, PSME1, PSME2, TAP1, TAP2*
TGF-β signaling pathway	*AMH, BMP6, ID4, LTBP1, TGFB1, TGFB2, TNF, GDF5, CUL1, NOG*
Type II diabetes mellitus	*INSR, KCNJ11, PKM2, PRKCD, PRKCZ, MAPK9, ABCC8, TNF, SOCS2*
FC epsilon RI signaling pathway	*CSF2, IL5, IL13, LYN, PRKCD, MAPK9, MAP2K3, TNF*
Folate biosynthesis	*ATP13A2*
Citrate cycle TCA cycle	*CS, PC, PCK2, SDHB, SUCLG2*

MAPK, Mitogen-activated protein kinase; TGF-β, transforming growth factor beta; TCA, tricarboxylic acid cycle

[a]See [9] for details

In a first step to address this question, Chan and colleagues analyzed the effect of the 180 common height SNPs on stature in adult individuals with an extreme height phenotype (very short or tall; >2 SD below or above the population mean) [28]. They found that at the extreme tall end of the height distribution, phenotypes were consistent with the segregation of common DNA polymorphisms, each with a weak effect on height. However, at the extreme short end of the distribution, phenotypes were more extreme than what was expected based on the polygenic model; this was even more obvious in individuals with extremely short stature (<2.8 SD below the mean or in other words in the 0.25th percentile for height) [28]. The authors suggest that non-additive genetic or environmental factors are likely to contribute to final height mostly in extremely short individuals (Fig. 1). Validating these findings in large cohorts of ISS children would be extremely valuable in pediatric endocrinology.

Common height variation and Mendelian genetics

Another interesting finding from the GIANT study is that SNPs associated with adult height are found more often near skeletal- or growth defect-related genes than can be expected by chance [9]. This is a strong argument supporting the fact that height loci are not randomly distributed across the genome but rather clustered near meaningful candidate genes. Furthermore, it indicates that hypomorphic alleles which alter the expression level or the biological activity of genes that are otherwise known to cause severe skeletal dysplasia or extreme height phenotypes when inactivated influence *normal* height variation. Height is not alone in this category of phenotypes, and we now have several combinations of genes–phenotypes for which an allelic spectrum has been linked to variable mild-to-severe phenotypic manifestations (e.g. *PCSK9* and low-density lipoprotein cholesterol/coronary artery disease, *MC4R* and body mass index/obesity). Next-generation DNA re-sequencing of large cohorts, for height and other traits should disentangle loci/gene and determine whether allelic series are a general feature of the genetic architecture of human complex diseases and traits.

The proximity between height-associated SNPs and skeletal growth genes can also be the basis of the following hypothesis: genes located near height SNPs are excellent candidates to underlie more extreme Mendelian skeletal growth phenotypes. A survey of the Online Mendelian Inheritance in Man (OMIM) database with the keywords "overgrowth," "height," "stature" or "dysplasia" revealed 316 Mendelian phenotypes or loci with an unknown molecular basis (http://ncbi.nlm.nih.gov/omim; accessed 29 Mar 2012). For those phenotypes for which disease loci have been mapped between chromosome bands, one strategy that could possibly be adopted to find the causal genes and

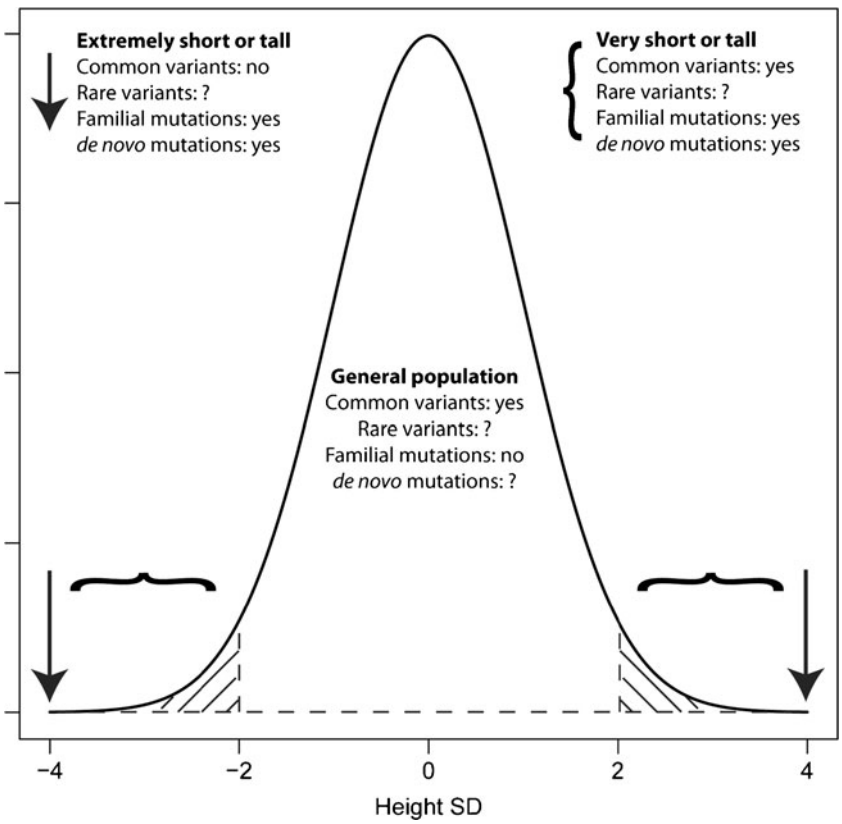

Fig. 1 Possible model of the genetic architecture of height across the phenotypic distribution. Familial and de novo mutations are too rare to account for the variation in height observed in the general population. Common DNA sequence variants [e.g. single nucleotide polymorphisms (SNPs)] are associated with height in the general population as well as in very short or tall individuals [±2 standard deviations (*SD*)], although some results suggest that they may not cause extreme height phenotypes [28]. The role of rare sequence variants in height variation is currently unknown

mutations would be to sequence the genes within the interval that falls near SNPs associated with height.

This approach has not yet been applied systematically, but there are at least two indirect examples that show its great promises, i.e. the *TRIP11* gene and the *mir-17~92* microRNA locus. In 2008, we and others found SNPs associated with adult height near the *TRIP11* gene [29, 30]. Mutations in *TRIP11* were later found to cause skeletal dysplasia in the mouse and achondrongenesis type 1A in humans [31]. More recently, using comparative genomic hybridization arrays, de Pontual and colleagues found that deletions of the microRNA cluster locus *mir-17~92* can cause Feingold syndrome, which is characterized by microcephaly, short stature and digital anomalies [32]. The GIANT Consortium had presented evidence of an association with adult height for a SNP (rs90822575) located only 17.4 kb downstream of *mir-17~92* [9]. The link between microRNAs and human height is intriguing, given the strong association of the *LIN28B* locus with adult height and human growth (see above) and the fact that we found an enrichment of *let-7* target genes among height associated loci [29].

Conclusions

After more than 100 years of research, the study of the genetics of human height continues to be at the forefront of the field of quantitative genetics. Given the progress in DNA sequencing technology and the availability of height measures in very large re-sequenced cohorts, this will continue for years to come. Discoveries from GWAS have highlighted novel biological pathways that influence adult height and also, to some extent, human growth. Although more genetic work is needed, functional studies based on these genetic findings are already changing our understanding of growth in animal models and humans [16]. Finally, SNPs associated with height and their nearby genes could have clinical applications, for example by helping us to understand the etiology of ISS or orphan syndromes with skeletal defects or other growth phenotypes.

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