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Human Height: A Model Common Complex Trait

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Abstract

Human height is a reflection of a combination of environmental and genetic factors. Indeed, multiple aspects of diet and lifestyle have a significant impact on determining one's height. However, some aspects of height determination are encoded in one's DNA. Twin and family-based analyses have revealed that up to 90% of human height variation is determined by genetic factors. Given the growing body of evidence that height determination is highly polygenic, in other words, that it is influenced by many genes, characterising the full repertoire of genetic contributions to height is challenging.

Keywords

Genetics; Genomics; Height; GWAS; polygenic scores

Introduction

Ever since antiquity, scholars have studied human height and the factors that influence it (Tanner 1981). The subject has received extensive attention for several main reasons. Firstly, there have been efforts to predict and/or influence adult height. For example, many of the first growth studies were started in the 18th century in order to ensure a suitable supply of

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tall soldiers (Tanner 1981). In modern times, there is keen interest in early identification and subsequent hormone intervention for those trending towards acutely short stature (Dauber et al. 2020; Lu et al. 2021). A second motivation are the serious medical conditions associated with height, most notably cancer and cardiovascular disease. The positive relationship with cancer incidence has been well established, and is believed to be a function of the greater number of cell divisions in taller individuals (Nunney 2018; Choi et al. 2019). In contrast, the inverse relationship with cardiovascular disease is less well understood, and multiple hypotheses have been proposed in this context (Paajanen et al. 2010; Nüesch et al. 2016; Pes et al. 2018; Moon and Hwang 2019; Marouli et al. 2019; Yano 2022). As such, a better understanding of the factors influencing height, in particular genetic contributors, should elucidate the biology of these associated diseases and provide new avenues for therapeutic intervention.

A final key reason for the abundance of research into height is that the trait is relatively easy and inexpensive to observe in comparison to others. It can therefore serve as a model to test new methods and gain insights relevant to other phenotypes with lower incidence rates and higher investigational costs. Taking this approach, our review will focus on summarising what is known about the genetic contributions to height, with particular attention to the ways in which our current understanding of height may reflect and inform the biology of complex-phenotypes overall.

Establishing Height as a Model Common Complex Phenotype

The use of human height as a model common trait has a long history in genetics dating back to the 19th century. The first major work in this vein was Galton's famous demonstration that average parental height predicts that of offspring (Galton 1886). A few decades later, in another seminal work, R.A. Fisher proposed a model that used height as its illustrative phenotype to show how polygenic inheritance could explain the observed variation in a continuous trait (Fisher 1919). However, when both these papers were written neither author knew the validity of extrapolating results from height to other traits. Before we consider the same possibility of generalising results for height, we will first consider how height's characteristics compare to those of other common complex phenotypes.

Apart from the ease of measurement, height is also a very useful model common complex trait due to its above average heritability relative to other complex phenotypes (Polderman et al. 2015; Watanabe et al. 2019). Twin and family-based analyses estimate that between 30 and 90% of human height variation is determined by genetic factors, with most estimates towards the upper end of that range (Preece 1996; Silventoinen et al. 2000; Silventoinen et al. 2001; Macgregor et al. 2006; Perola et al. 2007). This proportion is lower at birth and rises during childhood reaching a peak post-puberty (Burk et al. 2012; Mook-Kanamori et al. 2012; van Soelen et al. 2013; Jelenkovic et al. 2016; Silventoinen et al. 2019). Since it has been well documented that environmental factors, such as childhood net nutrition and socioeconomic status (Tanner 1981; Silventoinen 2003; Deaton 2007; Perkins et al. 2016), have a strong effect on adult height, high heritability likely means that the effect sizes and/or the quantity of genetic variants that impact the phenotype must be higher for height than for

the vast majority of other traits. Both possibilities would make it relatively easy to identify genetic factors influencing the trait.

Evaluating the likelihood of each of these possibilities is a question of polygenicity, that is the degree to which height's genetic modulators are scattered throughout the genome in many variants of low effect or concentrated in a smaller number of high-effect loci. Several approaches have been used to quantify the polygenicity of height relative to other complex phenotypes, and the results have been somewhat mixed. For a given sample size the number of loci and variants associated with height is comparable to those of other complex traits (Chakravarti and Turner 2016). Similarly, an analysis of 588 complex phenotypes estimated that the proportion of independent and causal single nucleotide polymorphisms (SNPs) for height is near the 40th percentile (Watanabe et al. 2019). In contrast, a more targeted analysis of 5 of the 588 complex traits found that height had nearly double the next highest proportion of putative causal SNPs even though the other four traits had been scored as more polygenic in the prior analysis (Johnson et al. 2021). From the available evidence, it is difficult to precisely quantify the polygenicity of height, but it is generally presumed that it is broadly similar to most other complex traits.

A final element to consider when evaluating the suitability of height as a model for other complex phenotypes is the number of tissues and cell types involved in its etiology. Studies have consistently shown that height-associated genetic variants are enriched in expressed genes, functional genomic elements and pathways relevant to musculoskeletal and connective tissues (Wood et al. 2014; Finucane et al. 2015; Finucane et al. 2018; Luo et al. 2021). Recent analyses have even found enrichments relevant to cardiovascular-relevant tissues and the uterus (Finucane et al. 2015; Finucane et al. 2018; Luo et al. 2021). Although the tissues relevant to a given phenotype are distinct, the studies that compared height to other complex traits and diseases found it had a comparable number of relevant cell types and tissues (Finucane et al. 2015; Finucane et al. 2018; Luo et al. 2021). In summary, height appears similar to other complex phenotypes for the key metrics outlined above, apart from its relative ease of study and high heritability – both of which give it an advantage as a model common complex trait.

Identifying Genetic Factors for Height

Before the advent of genome wide appraisals, candidate gene studies and family-based linkage analyses had been widely employed to study complex phenotypes, though with much lower success. In the case of height, most of the “discovered” regions failed to replicate (Perola et al. 2007; Weedon and Frayling 2008) and the handful of true genetic factors identified were principally driven by mutations in genes yielding rare, monogenic forms of extreme stature (Godfrey and Hollister 1988; Vissing et al. 1989; Shiang et al. 1994; Rao et al. 1997; Maheshwari et al. 1998; Hasegawa et al. 2000; Tartaglia et al. 2001; Durand and Rappold 2013). The key development of genome wide association studies (GWAS) in the mid-2000s expanded this insight into the genetics of complex traits and height drastically. Initial GWAS uncovered tens of common genetic polymorphic variants contributing to height (Weedon et al. 2007; Sanna et al. 2008; Gudbjartsson et al. 2008;

Lettre et al. 2008; Weedon et al. 2008; Soranzo et al. 2009) and subsequently led to a flood of many thousands more loci being reported.

The first GWAS for height was published in 2007 and involved approximately 5,000 subjects of European ancestry (Weedon et al. 2007). The main observation in that initial study was a signal at *HMGA2*, which encodes the mobility group-A2 oncogene. This result was confirmed in a follow-up effort in approximately 10,000 additional subjects (Yang et al. 2010). The next major GWAS of height revealed strong evidence for a second signal, namely at the *GDF5-UQCC* locus (Sanna et al. 2008). These first reports were followed by a set of meta-analyses, where datasets from various investigative groups were combined to increase statistical power to gain a collective larger sample size. Together these efforts uncovered in excess of 40 more loci for height (Gudbjartsson et al. 2008; Lettre et al. 2008; Weedon et al. 2008; Soranzo et al. 2009). But differences were observed in the outcomes of these different meta-analyses, likely partly due to differences in statistical power (Weedon and Frayling 2008), but perhaps also due to underlying co-morbidities that were not fully accounted for in the analyses of the participants in the study (Yaghootkar et al. 2017).

Over the next decade, GWAS sample sizes continued to increase in both size and diversity leading to an ever-growing number of loci associated with height. To illustrate, a 2010 study in 130,000 European ancestry individuals more than quadrupled the number of associated loci to over 180 (Lango Allen et al. 2010). Four years later, the next major GWAS of over 250,000 European-ancestry individuals identified 423 loci (Wood et al. 2014), a number that would be dramatically surpassed just another four years later by a GWAS in ~450,000 British individuals that identified over 700 loci (Yengo et al. 2018). Though not all the loci identified in each of these GWAS would replicate in later studies, each study showed an increasing proportion of phenotypic variation captured by the significantly associated variants as well as increasing numbers of secondary signals at associated loci. Apart from simply increasing European ancestry sample sizes, several GWAS over this period sought to identify associated loci in samples drawn in part or exclusively from non-European individuals (N'Diaye et al. 2011; He et al. 2015; Akiyama et al. 2019; Graff et al. 2021). In addition to replicating many of the loci identified in the European-ancestry GWAS, these analyses also identified several ancestry-specific loci and variants and leveraged differing patterns of linkage disequilibrium across ancestries to fine-map the location of putative causal variants.

In comparison to other complex phenotypes, height has not always been at the leading edge of the GWAS field as initial focus was on disease outcomes directly. Indeed, it was not the first trait to be studied in a GWAS (Ozaki et al. 2002; Klein et al. 2005; Ikegawa 2012; Loos 2020), nor was it the first to pass major milestones such as having a sample size over 1 million individuals (Loos 2020). Height also suffers from many of the same problems that affect other phenotypes, most obviously an under-representation of non-European ancestry individuals that limits statistical power and the subsequent portability of results across populations (Mills and Rahal 2020; Loos 2020). In contrast to this history of height as a typical but non-leading GWAS trait, the latest GWAS of height has presented ground-breaking results that could have important implications for all common complex phenotypes.

The First Saturated GWAS

This latest GWAS of height (Yengo et al. 2022) is the first of what is referred to as a “saturation” GWAS. Such a GWAS is so highly powered that further increases in the sample size without increases in participant diversity or variant inclusion are unlikely to reveal any additional genetic insights. In this landmark study conducted in 5.4 million individuals, the largest sample ever assembled for a GWAS, *Yengo et al.* identified an unprecedented 12,111 independent signals associated with height clustered into 7,209 non-overlapping loci that are enriched near genes with known Mendelian effects on skeletal growth. Together these loci comprise 21% of the genome, a result consistent with previous estimates (Shi et al. 2016). The results are notable not only because of their potential use in the discovery of novel height-modifying genes but also because they showed for the first time near exhaustion of GWAS’s ability to discover further associations, particularly in European ancestry populations. Such an outcome had been previously hypothesized to be possible but never actually demonstrated (Visscher et al. 2017; Kim et al. 2017; Wray et al. 2018).

The authors primarily showed saturation of their GWAS by examining the proportion of estimated single nucleotide polymorphism (SNP) based heritability captured by the associated loci. SNP-based heritability is distinct from the total heritability estimated in twin studies and represents the portion of total heritability attributable to SNPs under an additive GWAS model (Yang et al. 2017). In their analysis, *Yengo et al.* found that in individuals of European ancestry, associated regions accounted for approximately 100% of the estimated common SNP-based heritability, and across the other four tested ancestries the proportion was over 90%, even in the more genetically diverse African ancestry group. Like most other published GWAS, this study was heavily dominated by individuals of European ancestry (75.8% of the sample), so the higher saturation of European ancestry results was expected. The results appeared robust, as the enrichment of heritability within these loci did not transfer to another tested trait, namely body mass index (BMI), and random SNPs matched on allele frequency and linkage disequilibrium score did not show similar enrichment. Based on these results, the authors concluded that height-associated loci are largely shared across ancestries and that the generated list of loci is exhaustive i.e., saturated, for European ancestry.

While estimated SNP-based heritability enrichment strongly supported the comprehensiveness of the catalogued height loci for individuals of European ancestry, it was unknown whether the entire sample had been necessary to achieve such completeness. To better understand when saturation occurs, *Yengo et al.* reanalysed prior height GWAS (Lango Allen et al. 2010; He et al. 2015; Graff et al. 2021) and down-sampled their own study to produce five samples of individuals of European ancestry ranging from ~130,000 to ~4 million people. Using these samples, and their trans-ancestry meta-analysis, the authors found different points of saturation across various metrics of interest. For example, they found that the number of prioritised genes by summary-data-based Mendelian randomisation (Zhu et al. 2016) of GTEx (Aguet et al. 2020) and expression quantitative trait loci, only plateaued when all 4 million individuals of European ancestry were analysed. Moreover, the number of loci discovered and the proportion of the genome covered by GWAS loci could not be saturated without including non-European ancestry individuals.

While the latest study by Yengo *et al.* is the first GWAS to show saturation of European ancestry in associated loci, it should be mentioned that a complementary effort at building a prediction model of height using an L1-penalized regression (LASSO) captured a comparable proportion of the total heritability as Yengo *et al.* (Lello *et al.* 2018). The proportion captured by the LASSO model was slightly lower, but it is not known whether this difference is significant. However, even putting this difference aside, Yengo *et al.*'s contributions are still novel and significant in four main ways. Firstly, Yengo *et al.* was able to demonstrate near saturation in non-European ancestries whereas the Lasso model only considered European individuals. Secondly, Yengo *et al.* analysed other metrics of saturation beyond heritability. Thirdly, Yengo *et al.* only required 21% of the genome to capture the total estimated SNP-based heritability whereas the activated variants in the LASSO model spanned the entire genome roughly uniformly. And lastly, and most importantly, the effect size estimates from a LASSO model depend upon the specific variants retained in the model whereas GWAS does not have that issue. This distinction makes the results of GWAS useful for downstream analyses such as fine mapping for which LASSO results would be unsuitable.

An issue always worth considering when discussing any GWAS results is the effect of assortative mating. A shortcoming of Yengo *et al.*'s work is that they did not do so. There is an extensive literature documenting human assortative mating in general (Burgess and Wallin 1943; Price and Vandenberg 1980; Mascie-Taylor 1989; McLeod 1995; Allison *et al.* 1996; Du Fort *et al.* 1998; Maes *et al.* 1998; Hippisley-Cox *et al.* 2002; Stimpson and Peek 2005; Jurj *et al.* 2006; Meyler *et al.* 2007; Di Castelnuovo *et al.* 2009; Alford *et al.* 2011; Ask *et al.* 2012; Peyrot *et al.* 2016; Luo 2017; Jeong and Cho 2018; Horwitz *et al.* 2023) and specifically, on the basis of height (Stulp *et al.* 2017; Torvik *et al.* 2022). Assortative mating can inflate SNP-based heritability estimates. For example, an analysis of ~335,000 individuals of British ancestry found that assortative mating inflated the heritability of height by 14–23% (Border *et al.* 2022). However, that same study also demonstrated that sufficient sample sizes should cause the heritability estimates derived from the restricted maximum likelihood approach employed by Yengo *et al.* (Yang *et al.* 2011; Yang *et al.* 2012) to converge to the true SNP-based heritability. It is plausible that the large sample size of this most recent GWAS is sufficient to ensure such convergence.

Though Yengo *et al.* did not set out to study phenotypes apart from height, given the demonstrated similarity of height to other complex traits, the potential implications of this study for the broader field of complex phenotypes are worth reflection. The remainder of this review considers these possible impacts especially as regards the 'omnigenic model', polygenic risk scores, and causal gene identification.

Relevance to the Omnigenic Model

Perhaps the most important implication of the Yengo *et al.* saturation results are for the validity of the widely cited omnigenic model (Boyle *et al.* 2017). This model was originally proposed to explain the challenge of "missing heritability" (Manolio *et al.* 2009), that is the proportion of total heritability not captured by significant GWAS loci and variants uncovered at a specific point in time. Under the model, this heritability was attributed to a large set

of variants dispersed widely across the genome, each with individually small effects. The model was predicated upon the hypothesis that all genes expressed in phenotype-relevant cells impact in some capacity the function of genes central to the phenotype and therefore the phenotype itself. A more extreme version of the model also emerged which hypothesised that with sufficient power, GWAS would effectively implicate every gene and genomic region (Flint and Ideker 2019).

The results presented by Yengo *et al.* seemingly contradict the more extreme version of the omnigenic model. The authors showed that only a subset, albeit a large subset, of genomic regions appear to be implicated in the trait in individuals of European ancestry. Though expanding non-European ancestry representation or incorporating new variants from databases of whole genome sequences would likely increase the proportion of the genome associated with the phenotype in future height GWAS, it seems highly improbable that the whole remaining ~79% of the genome will also be implicated.

Rare and structural variant associations could also implicate additional regions of the genome, but it seems similarly doubtful that the proportion would grow considerably. Regarding rare variants, Yengo *et al.* found suggestive evidence that variants with minor allele frequency between 0.1% and 1% concentrate in the same 21% of the genome as the common variants. This result is consistent with those obtained by recent rare variant analyses for height. ~70% of the 83 low-frequency coding variants identified in a 2017 study (Marouli *et al.* 2017) lie within loci identified by Yengo *et al.* and a later analysis of 492 traits showed strong colocalisation of rare and common variants (Backman *et al.* 2021). Comprehensive results for structural variation are more limited than for rare variants, but we similarly note that 80% of the height-related copy number variants in a recent cataloguing effort (Hujoeel *et al.* 2022) overlapped the loci identified by Yengo *et al.*

As for the original conception of the model, it could be the case that the associated 21% of the genome captures the complete set of genes expressed in height-relevant cell types, but this too seems unlikely. As described, several tissues and a large number of cell types are believed to play a role in height etiology. It seems improbable that 21% of the genome captures all the genes they express but more research would be needed to confirm this hypothesis. Should the patterns observed with height be repeated in the saturation of other complex phenotypes, a highly polygenic model seems a more valid explanation of complex trait inheritance than a truly omnigenic one.

Implications for Polygenic Scores

Aside from exploring how well their GWAS saturated the discovery of height genetics, Yengo *et al.* also investigated the ability of their results to accurately predict height across ancestries using polygenic scores. Polygenic scores and risk scores predict individuals' values and risks of complex traits and diseases respectively. Generally, these terms refer to statistical models that make genetic-based predictions using GWAS-estimated variant effect sizes (Sugrue and Desikan 2019; Wang *et al.* 2022) though under some definitions they may denote any genetics-based statistical or machine-learning model designed to predict phenotypes (Wand *et al.* 2021). Prior to the latest height GWAS, polygenic scores and

risk scores had shown relatively modest success at predicting traits and disease risk for individuals drawn from the population used to create the scoring metrics (Schrodi et al. 2014; Hu et al. 2017). Though generally used on unrelated individuals, at least in the case of height polygenic scores, they can differentiate between siblings (Lello et al. 2020). It has been similarly shown that in order for these scores to obtain their maximum accuracy, they should include both coding and non-coding associated variants (Yong et al. 2020).

Measuring the accuracy between height and their polygenic score based on the 12,111 genome-wide significant signals, Yengo *et al.* obtained an accuracy of around 40% in individuals of European ancestry. As could also be expected based on its equal heritability saturation, the previously mentioned LASSO model also obtained an accuracy around 40% (Lello et al. 2018). These accuracies were not significantly different from that obtained by taking the average of parental heights and were comparable to that obtained by using all the SNPs input into the GWAS (42% accuracy). That the gap was so close between the accuracies of the polygenic score based on all input SNPs and the polygenic score based on only the 12,111 significant SNPs was expected given the saturation of common-SNP heritability observed in individuals of European-ancestry. Building on these results, Yengo *et al.* also demonstrated that a weighted combination of parental average height and the 12,111 SNP polygenic score achieved an accuracy above 54%. This result showed how polygenic scores can be used jointly with family history to appreciably improve predictions and gives an insight into what gains could be expected when polygenic score and risk score accuracy for other phenotypes achieve eventual saturation.

Lamentably, Yengo *et al.*'s polygenic score showed reduced performance in the non-European ancestries studied. Given the large skew of Yengo *et al.*'s sample towards European ancestry and the well-known poor portability of polygenic scores across ancestries (Duncan et al. 2019; Lewis and Vassos 2020; Adeyemo et al. 2021) this result was not surprising. In fact, the sensitivity to ancestry differences is so great for polygenic scores that the level of deterioration can be seen to correlate with any admixture (Bitarello and Mathieson 2020) and can be observed even in subtly stratified groups within a single continental ancestry (Berg et al. 2019; Isshiki et al. 2021).

Adding individuals of non-European ancestry to capture the missing 5–10% of common SNP-based heritability in these populations should improve the accuracy of polygenic scores in non-European populations by allowing for discovery of disease associated variants that are rare in Europeans but common in other groups (Wojcik et al. 2019; Bentley et al. 2020). Increasing diversity is a necessary step for ensuring that polygenic prediction techniques work well for all people and should be a goal for future research in height as in other complex traits. In addition to benefiting polygenic scores and variant discovery, building cohorts of greater diversity should also enable future studies to more precisely fine-map putative causal variants by leveraging differing patterns of linkage disequilibrium across ancestries; cohorts of African ancestry with their smaller haplotype blocks are especially useful in this regard (Hutchinson et al. 2020; Lu et al. 2022; Yuan et al. 2023). There are several large-scale ongoing efforts including All of Us (The “All of Us” Research Program 2019), the Million Veterans Program (Gaziano et al. 2016), and H3Africa (Owolabi et al.

2019) that aim to recruit participants from these underrepresented ancestry-groups. These efforts clearly should continue and even expand.

The Ongoing Challenge of Gene Discovery

Despite the fact that many of the loci identified by Yengo *et al.* reside near known genes relevant to cartilage and bone biology, such as *HHIP*, *BMPs*, *GDF5* and *ACAN*, it is now clear that a systematic approach is required to more accurately characterize the causal effector genes at each of the 12,111 height loci. Indeed, the genetics community is now grappling broadly with the issue of whether the nearest gene to a GWAS-implicated signal is actually always the main culprit 'effector' gene at a particular locus (Broekema *et al.* 2020; Li and Ritchie 2021). Some key lessons can be learned from the *FTO* obesity locus.

Obesity is principally defined by the relationship between height and weight, as defined by BMI. GWAS for BMI and obesity has consistently show the signal at the *FTO* locus to be the strongest association with the trait (Frayling *et al.* 2007; Rosen and Ingelfinger 2015; Yengo *et al.* 2018; Huang *et al.* 2022). This signal lies within an intron of the *FTO* gene (Frayling *et al.* 2007) and has been widely replicated across multiple populations (Hassanein *et al.* 2010; Okada *et al.* 2012; Wen *et al.* 2012). Despite the *FTO* gene product receiving wide attention by the research community, two key papers presented compelling evidence that *IRX3* and *IRX5* were actually the main effector genes at this particular genomic location (Smemo *et al.* 2014; Claussnitzer *et al.* 2015). As such, the findings suggested that the strongly associated obesity variant was embedded in one gene but was driving the expression of other, neighboring genes. These seminal findings have now moved the interpretation of GWAS findings forward, where it is no longer presumed that the nearest gene(s) to a given GWAS signal is the causal effector gene(s), and indeed, this should not come as a surprise given that gene expression can be driven by long range proximal regulatory elements, such as enhancers and silencers, and can exert their effect as far as hundreds of kilobases in distance.

Combined with the results from this latest GWAS of height, these findings indicate the magnitude of the challenge that now faces the genetics community. If the associated proportion of the genome is approximately consistent across complex traits, then each complex phenotype has on average thousands of genes that modulate pathogenesis. Identifying the causal gene(s) at each locus and validating the observations is, and will continue to be, a challenging task requiring multiple approaches, particularly algorithmic and high-throughput experimental techniques.

Conclusion

In summary, height is broadly similar to other complex phenotypes apart from its ease of measurement and high heritability. These factors have made it a widely employed model trait for studying the topic of complex phenotype inheritance. However, throughout the GWAS era, height has not always been at the leading edge of variant and gene discovery, that is until its most recent GWAS by Yengo *et al.* In having at last closed the gap of missing common SNP-based heritability for a common trait, Yengo *et al.* may have

signaled the beginning of the end of the GWAS era. Their work demonstrates the limits to endlessly increasing GWAS sample sizes and highlights the need for greater diversity in study populations. Moreover, their results directly contradict the most extreme form of the omnigenic model and imply that highly polygenic inheritance is likely a more appropriate model for complex traits. The analyzed polygenic score results also suggest that when sample sizes across complex phenotype GWAS efforts increase to the point of heritability saturation across all ancestries, polygenic risk scores will become powerful tools for the prediction of disease risk. However, the implications of this study for the identification of individual effector disease genes are less optimistic. Should the GWAS era be drawing to a close, the era of gene identification that follows will surely be one of both great challenges and opportunities.

Data availability statement

No associated data was generated for this article.

References

- Adeyemo A, Balaconis MK, Darnes DR, Fatumo S, Granados Moreno P, Hodonsky CJ, Inouye M, Kanai M, Kato K, Knoppers BM, et al. 2021. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat Med.* 27(11):1876–1884. 10.1038/s41591-021-01549-6 [PubMed: 34782789]
- Aguet F, Anand S, Ardlie KG, Gabriel S, Getz GA, Graubert A, Hadley K, Handsaker RE, Huang KH, Kashin S, et al. 2020. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science.* 369(6509):1318–1330. 10.1126/science.aaz1776 [PubMed: 32913098]
- Akiyama M, Ishigaki K, Sakaue S, Momozawa Y, Horikoshi M, Hirata M, Matsuda K, Ikegawa S, Takahashi A, Kanai M, et al. 2019. Characterizing rare and low-frequency height-associated variants in the Japanese population. *Nat Commun.* 10(1):4393. 10.1038/s41467-019-12276-5 [PubMed: 31562340]
- Alford JR, Hatemi PK, Hibbing JR, Martin NG, Eaves LJ. 2011. The politics of mate choice. *J Polit.* 73(2):362–379.
- Allison DB, Neale MC, Kezis MI, Alfonso VC, Heshka S, Heymsfield SB. 1996. Assortative mating for relative weight: genetic implications. *Behav Genet.* 26:103–111. [PubMed: 8639146]
- Ask H, Rognmo K, Torvik FA, Røysamb E, Tambs K. 2012. Non-random mating and convergence over time for alcohol consumption, smoking, and exercise: the Nord-Trøndelag Health Study. *Behav Genet.* 42:354–365. [PubMed: 22005768]
- Backman JD, Li AH, Marcketta A, Sun D, Mbatchou J, Kessler MD, Benner C, Liu D, Locke AE, Balasubramanian S, et al. 2021. Exome sequencing and analysis of 454,787 UK Biobank participants. *Nature.* 599(7886):628–634. 10.1038/s41586-021-04103-z [PubMed: 34662886]
- Bentley AR, Callier SL, Rotimi CN. 2020. Evaluating the promise of inclusion of African ancestry populations in genomics. *Npj Genomic Med.* 5(1):5. 10.1038/s41525-019-0111-x
- Berg JJ, Harpak A, Sinnott-Armstrong N, Joergensen AM, Mostafavi H, Field Y, Boyle EA, Zhang X, Racimo F, Pritchard JK, Coop G. 2019. Reduced signal for polygenic adaptation of height in UK Biobank. Nordborg M, McCarthy MI, Nordborg M, Barton NH, Hermisson J, editors. *eLife.* 8:e39725. 10.7554/eLife.39725 [PubMed: 30895923]
- Bitarello BD, Mathieson I. 2020. Polygenic Scores for Height in Admixed Populations. *G3 GenesGenomesGenetics.* 10(11):4027–4036. 10.1534/g3.120.401658
- Border R, O'Rourke S, de Candia T, Goddard ME, Visscher PM, Yengo L, Jones M, Keller MC. 2022. Assortative mating biases marker-based heritability estimators. *Nat Commun.* 13(1):660. 10.1038/s41467-022-28294-9 [PubMed: 35115518]

- Boyle EA, Li YI, Pritchard JK. 2017. An Expanded View of Complex Traits: From Polygenic to Omnigenic. *Cell*. 169(7):1177–1186. 10.1016/j.cell.2017.05.038 [PubMed: 28622505]
- Broekema RV, Bakker OB, Jonkers IH. 2020. A practical view of fine-mapping and gene prioritization in the post-genome-wide association era. *Open Biol*. 10(1):190221. 10.1098/rsob.190221 [PubMed: 31937202]
- Burgess EW, Wallin P. 1943. Homogamy in social characteristics. *Am J Sociol*. 49(2):109–124.
- Burk GFE, Bartels M, Beijsterveldt TCEM van, Waal HAD de, Boomsma DI. 2012. Body Size in Five-Year-Old Twins: Heritability and Comparison to Singleton Standards. *Twin Res Hum Genet*. 9(5):646–655. 10.1375/twin.9.5.646
- Chakravarti A, Turner TN. 2016. Revealing rate-limiting steps in complex disease biology: The crucial importance of studying rare, extreme-phenotype families. *BioEssays*. 38(6):578–586. 10.1002/bies.201500203 [PubMed: 27062178]
- Choi YJ, Lee DH, Han K-D, Yoon H, Shin CM, Park YS, Kim N. 2019. Adult height in relation to risk of cancer in a cohort of 22,809,722 Korean adults. *Br J Cancer*. 120(6):668–674. 10.1038/s41416-018-0371-8 [PubMed: 30778143]
- Claussnitzer M, Dankel SN, Kim K-H, Quon G, Meuleman W, Haugen C, Glunk V, Sousa IS, Beaudry JL, Puvion-Vandier V. 2015. FTO obesity variant circuitry and adipocyte browning in humans. *N Engl J Med*. 373(10):895–907. [PubMed: 26287746]
- Dauber A, Meng Y, Audi L, Vedantam S, Weaver B, Carrascosa A, Albertsson-Wikland K, Ranke MB, Jorge AAL, Cara J, et al. 2020. A Genome-Wide Pharmacogenetic Study of Growth Hormone Responsiveness. *J Clin Endocrinol Metab*. 105(10):3203–3214. 10.1210/clinem/dgaa443 [PubMed: 32652002]
- Deaton A. 2007. Height, health, and development. *Proc Natl Acad Sci*. 104(33):13232–13237. 10.1073/pnas.0611500104 [PubMed: 17686991]
- Di Castelnuovo A, Quacquarello G, Donati MB, De Gaetano G, Iacoviello L. 2009. Spousal concordance for major coronary risk factors: a systematic review and meta-analysis. *Am J Epidemiol*. 169(1):1–8. [PubMed: 18845552]
- Du Fort GG, Bland R, Newman S, Boothroyd L. 1998. Spouse similarity for lifetime psychiatric history in the general population. *Psychol Med*. 28(4):789–802. [PubMed: 9723136]
- Duncan L, Shen H, Gelaye B, Meijssen J, Ressler K, Feldman M, Peterson R, Domingue B. 2019. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat Commun*. 10(1):3328. 10.1038/s41467-019-11112-0 [PubMed: 31346163]
- Durand C, Rappold GA. 2013. Height matters—from monogenic disorders to normal variation. *Nat Rev Endocrinol*. 9(3):171–177. 10.1038/nrendo.2012.251 [PubMed: 23337954]
- Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh P-R, Anttila V, Xu H, Zang C, Farh K, et al. 2015. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat Genet*. 47(11):1228–1235. 10.1038/ng.3404 [PubMed: 26414678]
- Finucane HK, Reshef YA, Anttila V, Slowikowski K, Gusev A, Byrnes A, Gazal S, Loh P-R, Lareau C, Shoshitaishvili N, et al. 2018. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat Genet*. 50(4):621–629. 10.1038/s41588-018-0081-4 [PubMed: 29632380]
- Fisher RA. 1919. XV.—The Correlation between Relatives on the Supposition of Mendelian Inheritance. *Earth Environ Sci Trans R Soc Edinb*. 52(2):399–433. 10.1017/S0080456800012163
- Flint J, Ideker T. 2019. The great hairball gambit. *PLOS Genet*. 15(11):e1008519. 10.1371/journal.pgen.1008519 [PubMed: 31770365]
- Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JRB, Elliott KS, Lango H, Rayner NW, et al. 2007. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. *Science*. 316(5826):889–894. 10.1126/science.1141634 [PubMed: 17434869]
- Galton F. 1886. Regression Towards Mediocrity in Hereditary Stature. *J Anthropol Inst G B Irel*. 15:246–263. 10.2307/2841583
- Gaziano JM, Concato J, Brophy M, Fiore L, Pyarajan S, Breeling J, Whitbourne S, Deen J, Shannon C, Humphries D, et al. 2016. Million Veteran Program: A mega-biobank to study genetic influences

on health and disease. *J Clin Epidemiol.* 70:214–223. 10.1016/j.jclinepi.2015.09.016 [PubMed: 26441289]

- Godfrey M, Hollister DW. 1988. Type II achondrogenesis-hypochondrogenesis: identification of abnormal type II collagen. *Am J Hum Genet.* 43(6):904–913. [PubMed: 3195588]
- Graff M, Justice AE, Young KL, Marouli E, Zhang X, Fine RS, Lim E, Buchanan V, Rand K, Feitosa MF. 2021. Discovery and fine-mapping of height loci via high-density imputation of GWASs in individuals of African ancestry. *Am J Hum Genet.* 108(4):564–582. [PubMed: 33713608]
- Gudbjartsson DF, Walters GB, Thorleifsson G, Stefansson H, Halldorsson BV, Zusmanovich P, Sulem P, Thorlacius S, Gylfason A, Steinberg S, et al. 2008. Many sequence variants affecting diversity of adult human height. *Nat Genet.* 40(5):609–615. 10.1038/ng.122 [PubMed: 18391951]
- Hasegawa Y, Fujii K, Yamada M, Igarashi Y, Tachibana K, Tanaka T, Onigata K, Nishi Y, Kato S, Hasegawa T. 2000. Identification of Novel Human GH-1 Gene Polymorphisms that Are Associated with Growth Hormone Secretion and Height*. *J Clin Endocrinol Metab.* 85(3):1290–1295. 10.1210/jcem.85.3.6468 [PubMed: 10720078]
- Hassanein MT, Lyon HN, Nguyen TT, Akyzbekova EL, Waters K, Lettre G, Tayo B, Forrester T, Sarpong DF, Stram DO, et al. 2010. Fine mapping of the association with obesity at the FTO locus in African-derived populations. *Hum Mol Genet.* 19(14):2907–2916. 10.1093/hmg/ddq178 [PubMed: 20430937]
- He M, Xu M, Zhang B, Liang J, Chen P, Lee J-Y, Johnson TA, Li H, Yang X, Dai J. 2015. Meta-analysis of genome-wide association studies of adult height in East Asians identifies 17 novel loci. *Hum Mol Genet.* 24(6):1791–1800. [PubMed: 25429064]
- Hippisley-Cox J, Coupland C, Pringle M, Crown N, Hammersley V. 2002. Married couples' risk of same disease: cross sectional study. *Bmj.* 325(7365):636. [PubMed: 12242177]
- Horwitz TB, Balbona JV, Paulich KN, Keller MC. 2023. Correlations between human mating partners: a comprehensive meta-analysis of 22 traits and raw data analysis of 133 traits in the UK Biobank. *bioRxiv.*:2022.03.19.484997. 10.1101/2022.03.19.484997
- Hu Y, Lu Q, Powles R, Yao X, Yang C, Fang F, Xu X, Zhao H. 2017. Leveraging functional annotations in genetic risk prediction for human complex diseases. *PLOS Comput Biol.* 13(6):e1005589. 10.1371/journal.pcbi.1005589 [PubMed: 28594818]
- Huang C, Chen W, Wang X. 2022. Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. *Genes Dis [Internet].* 10.1016/j.gendis.2022.04.014
- Hujoel MLA, Sherman MA, Barton AR, Mukamel RE, Sankaran VG, Terao C, Loh P-R. 2022. Influences of rare copy-number variation on human complex traits. *Cell.* 185(22):4233–4248.e27. 10.1016/j.cell.2022.09.028 [PubMed: 36306736]
- Hutchinson A, Asimit J, Wallace C. 2020. Fine-mapping genetic associations. *Hum Mol Genet.* 29(R1):R81–R88. 10.1093/hmg/ddaa148 [PubMed: 32744321]
- Ikegawa S. 2012. A Short History of the Genome-Wide Association Study: Where We Were and Where We Are Going. *Genomics Inform.* 10(4):220–225. 10.5808/GI.2012.10.4.220 [PubMed: 23346033]
- Isshiki M, Watanabe Y, Ohashi J. 2021. Geographic variation in the polygenic score of height in Japan. *Hum Genet.* 140(7):1097–1108. 10.1007/s00439-021-02281-4 [PubMed: 33900438]
- Jelenkovic A, Sund R, Hur Y-M, Yokoyama Y, Hjelmberg J v B, Möller S, Honda C, Magnusson PKE, Pedersen NL, Ooki S, et al. 2016. Genetic and environmental influences on height from infancy to early adulthood: An individual-based pooled analysis of 45 twin cohorts. *Sci Rep.* 6(1):28496. 10.1038/srep28496 [PubMed: 27333805]
- Jeong S, Cho S-I. 2018. Concordance in the health behaviors of couples by age: a cross-sectional study. *J Prev Med Pub Health.* 51(1):6. [PubMed: 29397647]
- Johnson R, Burch KS, Hou K, Paciuc M, Pasaniuc B, Sankararaman S. 2021. Estimation of regional polygenicity from GWAS provides insights into the genetic architecture of complex traits. *PLOS Comput Biol.* 17(10):e1009483. 10.1371/journal.pcbi.1009483 [PubMed: 34673766]
- Jurj AL, Wen W, Li H-L, Zheng W, Yang G, Xiang Y-B, Gao Y-T, Shu X-O. 2006. Spousal correlations for lifestyle factors and selected diseases in Chinese couples. *Ann Epidemiol.* 16(4):285–291. [PubMed: 16257231]

- Kim H, Grueneberg A, Vazquez AI, Hsu S, de los Campos G. 2017. Will Big Data Close the Missing Heritability Gap? *Genetics*. 207(3):1135–1145. 10.1534/genetics.117.300271 [PubMed: 28893854]
- Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, et al. 2005. Complement Factor H Polymorphism in Age-Related Macular Degeneration. *Science*. 308(5720):385–389. 10.1126/science.1109557 [PubMed: 15761122]
- Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, Willer CJ, Jackson AU, Vedantam S, Raychaudhuri S, et al. 2010. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature*. 467(7317):832–838. 10.1038/nature09410 [PubMed: 20881960]
- Lello L, Avery SG, Tellier L, Vazquez AI, de los Campos G, Hsu SDH. 2018. Accurate Genomic Prediction of Human Height. *Genetics*. 210(2):477–497. 10.1534/genetics.118.301267 [PubMed: 30150289]
- Lello L, Raben TG, Hsu SDH. 2020. Sibling validation of polygenic risk scores and complex trait prediction. *Sci Rep*. 10(1):13190. 10.1038/s41598-020-69927-7 [PubMed: 32764582]
- Lettre G, Jackson AU, Gieger C, Schumacher FR, Berndt SI, Sanna S, Eyheramendy S, Voight BF, Butler JL, Guiducci C, et al. 2008. Identification of ten loci associated with height highlights new biological pathways in human growth. *Nat Genet*. 40(5):584–591. 10.1038/ng.125 [PubMed: 18391950]
- Lewis CM, Vassos E. 2020. Polygenic risk scores: from research tools to clinical instruments. *Genome Med*. 12(1):44. 10.1186/s13073-020-00742-5 [PubMed: 32423490]
- Li B, Ritchie MD. 2021. From GWAS to Gene: Transcriptome-Wide Association Studies and Other Methods to Functionally Understand GWAS Discoveries. *Front Genet* [Internet]. [accessed 2023 Mar 4] 12. <https://www.frontiersin.org/articles/10.3389/fgene.2021.713230>
- Loos RJF. 2020. 15 years of genome-wide association studies and no signs of slowing down. *Nat Commun*. 11(1):5900. 10.1038/s41467-020-19653-5 [PubMed: 33214558]
- Lu T, Forgetta V, Wu H, Perry JRB, Ong KK, Greenwood CMT, Timpson NJ, Manousaki D, Richards JB. 2021. A Polygenic Risk Score to Predict Future Adult Short Stature Among Children. *J Clin Endocrinol Metab*. 106(7):1918–1928. 10.1210/clinem/dgab215 [PubMed: 33788949]
- Lu Z, Gopalan S, Yuan D, Conti DV, Pasianic B, Gusev A, Mancuso N. 2022. Multi-ancestry fine-mapping improves precision to identify causal genes in transcriptome-wide association studies. *Am J Hum Genet*. 109(8):1388–1404. 10.1016/j.ajhg.2022.07.002 [PubMed: 35931050]
- Luo S 2017. Assortative mating and couple similarity: Patterns, mechanisms, and consequences. *Soc Personal Psychol Compass*. 11(8):e12337.
- Luo Y, Li X, Wang X, Gazal S, Mercader JM, 23 and Me Research Team, SIGMA Type 2 Diabetes Consortium, Neale BM, Florez JC, Auton A, et al. 2021. Estimating heritability and its enrichment in tissue-specific gene sets in admixed populations. *Hum Mol Genet*. 30(16):1521–1534. 10.1093/hmg/ddab130 [PubMed: 33987664]
- Macgregor S, Cornes BK, Martin NG, Visscher PM. 2006. Bias, precision and heritability of self-reported and clinically measured height in Australian twins. *Hum Genet*. 120(4):571–580. 10.1007/s00439-006-0240-z [PubMed: 16933140]
- Maes HH, Neale M, Kendler KS, Hewitt JK, Silberg JL, Foley D, Meyer J, Rutter M, Simonoff E, Pickles A. 1998. Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychol Med*. 28(6):1389–1401. [PubMed: 9854280]
- Maheshwari HG, Silverman BL, Dupuis J, Baumann G. 1998. Phenotype and Genetic Analysis of a Syndrome Caused by an Inactivating Mutation in the Growth Hormone-Releasing Hormone Receptor: Dwarfism of Sindh I. *J Clin Endocrinol Metab*. 83(11):4065–4074. 10.1210/jcem.83.11.5226 [PubMed: 9814493]
- Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorf LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, et al. 2009. Finding the missing heritability of complex diseases. *Nature*. 461(7265):747–753. 10.1038/nature08494 [PubMed: 19812666]
- Marouli E, Del Greco MF, Astley CM, Yang J, Ahmad S, Berndt SI, Caulfield MJ, Evangelou E, McKnight B, Medina-Gomez C, et al. 2019. Mendelian randomisation analyses find pulmonary

factors mediate the effect of height on coronary artery disease. *Commun Biol.* 2(1):119. 10.1038/s42003-019-0361-2 [PubMed: 30937401]

- Marouli E, Graff M, Medina-Gomez C, Lo KS, Wood AR, Kjaer TR, Fine RS, Lu Y, Schurmann C, Highland HM, et al. 2017. Rare and low-frequency coding variants alter human adult height. *Nature.* 542(7640):186–190. 10.1038/nature21039 [PubMed: 28146470]
- Mascie-Taylor C 1989. Spouse similarity for IQ and personality and convergence. *Behav Genet.* 19(2):223–227. [PubMed: 2719625]
- McLeod JD. 1995. Social and psychological bases of homogamy for common psychiatric disorders. *J Marriage Fam.*:201–214.
- Meyler D, Stimpson JP, Peek MK. 2007. Health concordance within couples: a systematic review. *Soc Sci Med.* 64(11):2297–2310. [PubMed: 17374552]
- Mills MC, Rahal C. 2020. The GWAS Diversity Monitor tracks diversity by disease in real time. *Nat Genet.* 52(3):242–243. 10.1038/s41588-020-0580-y [PubMed: 32139905]
- Mook-Kanamori DO, Beijsterveldt CEM, Steegers EAP, Aulchenko YS, Raat H, Hofman, Eilers PH, Boomsma, Jaddoe VWV. 2012. Heritability Estimates of Body Size in Fetal Life and Early Childhood. *PLOS ONE.* 7(7):e39901. 10.1371/journal.pone.0039901 [PubMed: 22848364]
- Moon J, Hwang IC. 2019. The link between height and cardiovascular disease: To be deciphered. *Cardiology.* 143(3–4):114–115. [PubMed: 31484185]
- N'Diaye A, Chen GK, Palmer CD, Ge B, Tayo B, Mathias RA, Ding J, Nalls MA, Adeyemo A, Adoue V, et al. 2011. Identification, Replication, and Fine-Mapping of Loci Associated with Adult Height in Individuals of African Ancestry. *PLOS Genet.* 7(10):e1002298. 10.1371/journal.pgen.1002298 [PubMed: 21998595]
- Nüesch E, Dale C, Palmer TM, White J, Keating BJ, van Iperen EP, Goel A, Padmanabhan S, Asselbergs FW, EPIC-Netherlands Investigators, et al. 2016. Adult height, coronary heart disease and stroke: a multi-locus Mendelian randomization meta-analysis. *Int J Epidemiol.* 45(6):1927–1937. 10.1093/ije/dyv074 [PubMed: 25979724]
- Nunney L 2018. Size matters: height, cell number and a person's risk of cancer. *Proc R Soc B Biol Sci.* 285(1889):20181743. 10.1098/rspb.2018.1743
- Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ. 2012. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet.* 44(3):302–306. [PubMed: 22344221]
- Owolabi MO, Akpa OM, Made F, Adebamowo SN, Ojo A, Adu D, Motala AA, Mayosi BM, Ovbiagele B, Adebamowo C, et al. 2019. Data Resource Profile: Cardiovascular H3Africa Innovation Resource (CHAIR). *Int J Epidemiol.* 48(2):366–367g. 10.1093/ije/dyy261 [PubMed: 30535409]
- Ozaki K, Ohnishi Y, Iida A, Sekine A, Yamada R, Tsunoda T, Sato Hiroshi, Sato Hideyuki, Hori M, Nakamura Y, Tanaka T. 2002. Functional SNPs in the lymphotoxin- α gene that are associated with susceptibility to myocardial infarction. *Nat Genet.* 32(4):650–654. 10.1038/ng1047 [PubMed: 12426569]
- Paajanen TA, Oksala NKJ, Kuukasjärvi P, Karhunen PJ. 2010. Short stature is associated with coronary heart disease: a systematic review of the literature and a meta-analysis. *Eur Heart J.* 31(14):1802–1809. 10.1093/eurheartj/ehq155 [PubMed: 20530501]
- Perkins JM, Subramanian SV, Davey Smith G, Özaltın E. 2016. Adult height, nutrition, and population health. *Nutr Rev.* 74(3):149–165. 10.1093/nutrit/nuv105 [PubMed: 26928678]
- Perola M, Sarnalisto S, Hiekkalinna T, Martin NG, Visscher PM, Montgomery GW, Benyamin B, Harris JR, Boomsma D, Willemsen G, et al. 2007. Combined Genome Scans for Body Stature in 6,602 European Twins: Evidence for Common Caucasian Loci. *PLOS Genet.* 3(6):e97. 10.1371/journal.pgen.0030097 [PubMed: 17559308]
- Pes GM, Ganau A, Tognotti E, Errigo A, Rocchi C, Dore MP. 2018. The association of adult height with the risk of cardiovascular disease and cancer in the population of Sardinia. *PLOS ONE.* 13(4):e0190888. 10.1371/journal.pone.0190888 [PubMed: 29677219]
- Peyrot WJ, Robinson MR, Penninx BW, Wray NR. 2016. Exploring boundaries for the genetic consequences of assortative mating for psychiatric traits. *JAMA Psychiatry.* 73(11):1189–1195. [PubMed: 27732705]

- Polderman TJC, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, Posthuma D. 2015. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet.* 47(7):702–709. 10.1038/ng.3285 [PubMed: 25985137]
- Preece MA. 1996. The Genetic Contribution to Stature. *Horm Res Paediatr.* 45(suppl 2)(Suppl. 2):56–58. 10.1159/000184849
- Price RA, Vandenberg SG. 1980. Spouse similarity in American and Swedish couples. *Behav Genet.* 10(1):59–71. [PubMed: 7191703]
- Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, Muroya K, Binder G, Kirsch S, Winkelmann M, et al. 1997. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nat Genet.* 16(1):54–63. 10.1038/ng0597-54 [PubMed: 9140395]
- Rosen CJ, Ingelfinger JR. 2015. Unraveling the Function of FTO Variants. *N Engl J Med.* 373(10):964–965. 10.1056/NEJMe1508683 [PubMed: 26287747]
- Sanna S, Jackson AU, Nagaraja R, Willer CJ, Chen W-M, Bonnycastle LL, Shen H, Timpson N, Lettre G, Usala G, et al. 2008. Common variants in the GDF5-UQCC region are associated with variation in human height. *Nat Genet.* 40(2):198–203. 10.1038/ng.74 [PubMed: 18193045]
- Schrodi SJ, Mukherjee S, Shan Y, Tromp G, Sninsky JJ, Callear AP, Carter TC, Ye Z, Haines JL, Brilliant MH, et al. 2014. Genetic-based prediction of disease traits: prediction is very difficult, especially about the future†. *Front Genet [Internet].* 5. <https://www.frontiersin.org/articles/10.3389/fgene.2014.00162>
- Shi H, Kichaev G, Pasaniuc B. 2016. Contrasting the Genetic Architecture of 30 Complex Traits from Summary Association Data. *Am J Hum Genet.* 99(1):139–153. 10.1016/j.ajhg.2016.05.013 [PubMed: 27346688]
- Shiang R, Thompson LM, Zhu Y-Z, Church DM, Fielder TJ, Bocian M, Winokur ST, Wasmuth JJ. 1994. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell.* 78(2):335–342. 10.1016/0092-8674(94)90302-6 [PubMed: 7913883]
- Silventoinen K 2003. DETERMINANTS OF VARIATION IN ADULT BODY HEIGHT. *J Biosoc Sci.* 35(2):263–285. 10.1017/S0021932003002633 [PubMed: 12664962]
- Silventoinen K, Jelenkovic A, Yokoyama Y, Sund R, Sugawara M, Tanaka M, Matsumoto S, Bogl LH, Freitas DL, Maia JA, et al. 2019. The CODATwins Project: The Current Status and Recent Findings of Collaborative Project of Development of Anthropometrical Measures in Twins. *Twin Res Hum Genet.* 22(6):800–808. 10.1017/thg.2019.35 [PubMed: 31364586]
- Silventoinen K, Kaprio J, Lahelma E, Koskenvuo M. 2000. Relative effect of genetic and environmental factors on body height: differences across birth cohorts among Finnish men and women. *Am J Public Health.* 90(4):627–630. [PubMed: 10754982]
- Silventoinen K, Kaprio J, Lahelma E, Viken RJ, Rose RJ. 2001. Sex Differences in Genetic and Environmental Factors Contributing to Body-Height. *Twin Res Hum Genet.* 4(1):25–29. 10.1375/twin.4.1.25
- Smemo S, Tena JJ, Kim K-H, Gamazon ER, Sakabe NJ, Gómez-Marín C, Aneas I, Credidio FL, Sobreira DR, Wasserman NF. 2014. Obesity-associated variants within FTO form long-range functional connections with IRX3. *Nature.* 507(7492):371–375. [PubMed: 24646999]
- van Soelen ILC, Brouwer RM, van Baal GCM, Schnack HG, Peper JS, Chen L, Kahn RS, Boomsma DI, Pol HEH. 2013. Heritability of volumetric brain changes and height in children entering puberty. *Hum Brain Mapp.* 34(3):713–725. 10.1002/hbm.21468 [PubMed: 22140022]
- Soranzo N, Rivadeneira F, Chinappan-Horsley U, Malkina I, Richards JB, Hammond N, Stolk L, Nica A, Inouye M, Hofman A, et al. 2009. Meta-Analysis of Genome-Wide Scans for Human Adult Stature Identifies Novel Loci and Associations with Measures of Skeletal Frame Size. *PLOS Genet.* 5(4):e1000445. 10.1371/journal.pgen.1000445 [PubMed: 19343178]
- Stimpson JP, Peek MK. 2005. Peer Reviewed: Concordance of Chronic Conditions in Older Mexican American Couples. *Prev Chronic Dis.* 2(3).
- Stulp G, Simons MJP, Grasman S, Pollet TV. 2017. Assortative mating for human height: A meta-analysis. *Am J Hum Biol.* 29(1):e22917. 10.1002/ajhb.22917 [PubMed: 27637175]

- Sugrue LP, Desikan RS. 2019. What Are Polygenic Scores and Why Are They Important? *JAMA*. 321(18):1820–1821. 10.1001/jama.2019.3893 [PubMed: 30958510]
- Tanner JM. 1981. A history of the study of human growth. [place unknown]: Cambridge university press.
- Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, et al. 2001. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet*. 29(4):465–468. 10.1038/ng772 [PubMed: 11704759]
- The “All of Us” Research Program. 2019. *N Engl J Med*. 381(7):668–676. 10.1056/NEJMs1809937 [PubMed: 31412182]
- Torvik FA, Eilertsen EM, Hannigan LJ, Cheesman R, Howe LJ, Magnus P, Reichborn-Kjennerud T, Andreassen OA, Njølstad PR, Havdahl A, Ystrom E. 2022. Modeling assortative mating and genetic similarities between partners, siblings, and in-laws. *Nat Commun*. 13(1):1108. 10.1038/s41467-022-28774-y [PubMed: 35233010]
- Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 2017. 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet*. 101(1):5–22. 10.1016/j.ajhg.2017.06.005 [PubMed: 28686856]
- Vissing H, D’Alessio M, Lee B, Ramirez F, Godfrey M, Hollister DW. 1989. Glycine to serine substitution in the triple helical domain of pro- α 1 (II) collagen results in a lethal perinatal form of short-limbed dwarfism*. *J Biol Chem*. 264(31):18265–18267. 10.1016/S0021-9258(18)51455-1 [PubMed: 2572591]
- Wand H, Lambert SA, Tamburro C, Iacocca MA, O’Sullivan JW, Sillari C, Kullo IJ, Rowley R, Dron JS, Brockman D, et al. 2021. Improving reporting standards for polygenic scores in risk prediction studies. *Nature*. 591(7849):211–219. 10.1038/s41586-021-03243-6 [PubMed: 33692554]
- Wang Y, Tsuo K, Kanai M, Neale BM, Martin AR. 2022. Challenges and Opportunities for Developing More Generalizable Polygenic Risk Scores. *Annu Rev Biomed Data Sci*. 5(1):293–320. 10.1146/annurev-biodatasci-111721-074830 [PubMed: 35576555]
- Watanabe K, Stringer S, Frei O, Umi evi Mirkov M, de Leeuw C, Polderman TJC, van der Sluis S, Andreassen OA, Neale BM, Posthuma D. 2019. A global overview of pleiotropy and genetic architecture in complex traits. *Nat Genet*. 51(9):1339–1348. 10.1038/s41588-019-0481-0 [PubMed: 31427789]
- Weedon MN, Frayling TM. 2008. Reaching new heights: insights into the genetics of human stature. *Trends Genet*. 24(12):595–603. 10.1016/j.tig.2008.09.006 [PubMed: 18950892]
- Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, Freathy RM, Perry JRB, Stevens S, Hall AS, et al. 2008. Genome-wide association analysis identifies 20 loci that influence adult height. *Nat Genet*. 40(5):575–583. 10.1038/ng.121 [PubMed: 18391952]
- Weedon MN, Lettre G, Freathy RM, Lindgren CM, Voight BF, Perry JRB, Elliott KS, Hackett R, Guiducci C, Shields B, et al. 2007. A common variant of HMGA2 is associated with adult and childhood height in the general population. *Nat Genet*. 39(10):1245–1250. 10.1038/ng2121 [PubMed: 17767157]
- Wen W, Cho Y-S, Zheng W, Dorajoo R, Kato N, Qi L, Chen C-H, Delahanty RJ, Okada Y, Tabara Y. 2012. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet*. 44(3):307–311. [PubMed: 22344219]
- Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, Highland HM, Patel YM, Sorokin EP, Avery CL, et al. 2019. Genetic analyses of diverse populations improves discovery for complex traits. *Nature*. 570(7762):514–518. 10.1038/s41586-019-1310-4 [PubMed: 31217584]
- Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, Chu AY, Estrada K, Luan J, Kutalik Z, et al. 2014. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet*. 46(11):1173–1186. 10.1038/ng.3097 [PubMed: 25282103]
- Wray NR, Wijmenga C, Sullivan PF, Yang J, Visscher PM. 2018. Common Disease Is More Complex Than Implied by the Core Gene Omnigenic Model. *Cell*. 173(7):1573–1580. 10.1016/j.cell.2018.05.051 [PubMed: 29906445]

- Yaghootkar H, Bancks MP, Jones SE, McDaid A, Beaumont R, Donnelly L, Wood AR, Campbell A, Tyrrell J, Hocking LJ, et al. 2017. Quantifying the extent to which index event biases influence large genetic association studies. *Hum Mol Genet.* 26(5):1018–1030. 10.1093/hmg/ddw433 [PubMed: 28040731]
- Yang J, Ferreira T, Morris AP, Medland SE, Madden PAF, Heath AC, Martin NG, Montgomery GW, Weedon MN, Loos RJ, et al. 2012. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet.* 44(4):369–375. 10.1038/ng.2213 [PubMed: 22426310]
- Yang J, Lee SH, Goddard ME, Visscher PM. 2011. GCTA: A Tool for Genome-wide Complex Trait Analysis. *Am J Hum Genet.* 88(1):76–82. 10.1016/j.ajhg.2010.11.011 [PubMed: 21167468]
- Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. 2017. Concepts, estimation and interpretation of SNP-based heritability. *Nat Genet.* 49(9):1304–1310. 10.1038/ng.3941 [PubMed: 28854176]
- Yang T-L, Guo Y, Zhang L-S, Tian Q, Yan H, Guo Y-F, Deng H-W. 2010. HMGA2 Is Confirmed To Be Associated with Human Adult Height. *Ann Hum Genet.* 74(1):11–16. 10.1111/j.1469-1809.2009.00555.x [PubMed: 19930247]
- Yano S 2022. Does body height affect vascular function? *Hypertens Res.* 45(2):369–371. 10.1038/s41440-021-00812-0 [PubMed: 34876696]
- Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, Frayling TM, Hirschhorn J, Yang J, Visscher PM, the GIANT Consortium. 2018. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum Mol Genet.* 27(20):3641–3649. 10.1093/hmg/ddy271 [PubMed: 30124842]
- Yengo L, Vedantam S, Marouli E, Sidorenko J, Bartell E, Sakaue S, Graff M, Eliassen AU, Jiang Y, Raghavan S, et al. 2022. A saturated map of common genetic variants associated with human height. *Nature* [Internet]. 10.1038/s41586-022-05275-y
- Yong SY, Raben TG, Lello L, Hsu SDH. 2020. Genetic architecture of complex traits and disease risk predictors. *Sci Rep.* 10(1):12055. 10.1038/s41598-020-68881-8 [PubMed: 32694572]
- Yuan K, Longchamps RJ, Pardiñas AF, Yu M, Chen T-T, Lin S-C, Chen Y, Lam M, Liu R, Xia Y, et al. 2023. Fine-mapping across diverse ancestries drives the discovery of putative causal variants underlying human complex traits and diseases. medRxiv:2023.01.07.23284293. 10.1101/2023.01.07.23284293
- Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, Montgomery GW, Goddard ME, Wray NR, Visscher PM, Yang J. 2016. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet.* 48(5):481–487. 10.1038/ng.3538 [PubMed: 27019110]