Genetics of Early Growth Traits

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Introduction

For decades, researchers have accumulated strong evidence of associations between in utero and early growth and health throughout life. Recently, studies investigating the genetic variation associated with early growth have brought these lifelong health links into focus, both in terms of individual genetic loci associated with early growth traits and later health outcomes, and when comparing the genome-wide association landscape between traits using genetic correlation analyses(1). In addition, genetic studies can be informative for uncovering key biological pathways and in determining the causal effects of genetic and environmental exposures. Here, we review major advances of the past two years, and highlight areas where studies should place additional focus in the near future.

Studies of birth weight taking maternal genotype into account

Over the last decade, studies of increasing size and diversity have investigated the genetic underpinnings of birth weight. In the last two years, a major advance is in our ability to estimate, for a genome-wide set of SNPs, the direct fetal effects on birth weight and the independent maternal genetic effects that act indirectly via the uterine environment. This advance was made possible by (i) aggregation of genome-wide association studies (GWAS) with maternal genotypes and offspring birth weight(2) in addition to studies with own (fetal) genotype and own birth weight, and (ii) the development of a new genome-wide method to estimate independent maternal and fetal effects on birth weight in the absence of large numbers of genotyped mother-child pairs(3). The most recent GWAS of birth weight estimated independent maternal and fetal effects at 190 genome-wide significant loci(4). Variance in birth weight explained by these loci showed a greater fetal than maternal component, with more than three-quarters of the variance attributable to direct fetal genotype effects. While causal genes and underlying functional variants remain largely unknown, there was a strong overlap of fetal genetic loci with the genetics of childhood and adult height, and enrichment for imprinted genes and those involved in IGF-1 and insulin signaling.

Many identified loci showed evidence of independent contributions from both mother and fetus: of the 138 lead SNPs that could be confidently classified as having maternal and/or fetal effects, 30% showed evidence of both a direct fetal and an indirect maternal effect. For one-third of those, the maternal and fetal effects were in opposite directions. Examples of loci with opposite maternal and fetal effects on

birth weight include those at established glycemic trait loci, such as *G6PC2, ADCY5* and *CDKAL1.* At those loci, fetal insulin is a likely mediator, given the paradigm maternal and fetal birth weight effects of rare mutations in the glucokinase gene(5). However, for most loci, the underlying mechanism is unknown, and current evidence suggests that fetal growth attributable to fetal effects at most birth weight-associated loci is not insulin-mediated(6).

Early growth traits assessed by longitudinal approaches

Recent genetic studies have included postnatal longitudinal approaches to discovering novel loci. Many longitudinal studies have focused on changes in adiposity and BMI. For example, two studies investigating early life adiposity found similar associations at the *LEPR* locus prior to age 5 years, with different genetic loci influencing later childhood and adult BMI(7,8). In a separate study, application of a genetic risk score (GRS) based on adult BMI to a pediatric cohort showed similar patterns of association from infancy to later childhood: the adult BMI-derived GRS was not associated with birth weight, but became increasingly associated with BMI across childhood(9). However, a study of normal variation in childhood BMI assessed between the ages of 2 and 10 years old observed a genetic correlation with both birth weight and adult BMI(10). Collectively, these studies suggest that, although some loci influence weight from birth through to adulthood, the mechanisms influencing body mass shift during early childhood, after which they remain relatively constant throughout adolescence and into adulthood. Additionally, there is some evidence that BMI-associated variants may have varying effects across adulthood, as reported in a candidate study of the association of 282 variants with BMI at age 20 and change in BMI during adulthood in the Japanese(11).

In addition to 25 loci associated with childhood BMI(10), assessing obesity as a dichotomous trait [with cases defined as having BMI ≥95th percentile and controls being consistently <50th percentile] in youth aged 2-18 years revealed a novel locus and fine-mapped many previously reported loci primarily due to the inclusion of African, North/South American, and East Asian samples(12). Still, the largest genetic studies of BMI continue to be carried out in European-only samples, such as the recent GIANT study, which reported 941 nearly independent loci for adult BMI(13). While several small studies of childhood and adult BMI have been published in non-European samples (e.g.(14–16)), future studies including large sample sizes from diverse ancestral backgrounds will yield additional discoveries.

Insights into height growth from genetic studies

In recent years, it has become clear that the genetic determinants of size at birth and height throughout childhood are correlated, with positive genetic correlations beginning with birth length and childhood height to final adult stature(4). Additionally, there is an enrichment of GWAS signals for adult height in DNAseI hypersensitivity sites in human embryonic stem cells(17), showing that these signals may act in early development, with an impact on growth throughout the life course. However, the correlation between the genetic determinants of birth weight and height is weaker during puberty(4), which may be explained by the impact of differences in the timing of puberty on height growth. Still, these findings suggest that many of the same genetic determinants of body length, in contrast to BMI, act throughout life.

While few studies have been published recently investigating the genetic determinants of specific height growth phases, the GIANT consortium released a GWAS of adult stature including ~700,000 individuals and reporting 3200 loci associated with the trait(13). This data is providing insights into the mechanisms underlying growth; using expression quantitative trait locus (eQTL) data, 610 genes were prioritized as potentially causal for variation in height, and pathway analysis subsequently identified enrichment for skeletal growth and cartilage and connective tissue development. Further, height-associated GWAS signals were enriched in noncoding regulatory regions in the growth plates of long bones(18), which is intuitively plausible as a key effector tissue for mediating differences in stature. Other studies have noted enrichment in pathways relevant to growth, such as the TGFB and Hedgehog pathways in growth plate development(19), as well as growth hormone regulation(20). A Japanese study subsequently noted in a pathway comparison with the GIANT European study that the biological mechanisms regulating height growth are largely shared across populations(21), indicating that additional genetic insights could be gained by trans-ancestry approaches.

Another axis becoming clear is the relationship between the genetic determinants of height and other skeletal traits, such as bone size, bone mineral density, and osteoarthritis(22,23). These studies suggest that the genetic determinants affecting variation in height also impact other aspects of endochondral ossification and bone biology(24,25), with implications for therapeutic development. Specific loci with potential clinical applications for later health include the *GDF5* locus, associated with early growth, body size, and developmental traits (infant length(26), height at age 10 (UK Biobank(35)), bone size(22), and age at menarche(28)). This locus was originally associated with osteoarthritis in Asian populations(29) and adult height(30). In the past two years, however, additional GWAS and large-scale biobank phenome-wide association studies (PheWAS) have revealed a breadth of health outcomes across the life course associated with the *GDF5* locus, including skeletal site-specific osteoarthritis(23,31), congenital hip dysplasia(32), internal derangement of the knee, monoarthritis, connective tissue disease, and bunions (SAIGE(33)), and knee pain(34). Furthermore, the causal SNP has been identified as well the mechanism by which noncoding variants differentially affect DNA methylation, transcription factor binding, and subsequent *GDF5* expression level, with differential methylation between knee osteoarthritis samples when compared to other skeletal sites and non-osteoarthritis samples(35,36). GDF5 may thus play a role in tissue repair and remodeling(37) and is currently under development as a therapeutic target for osteoarthritis and cartilage regeneration(31,38). For most genetic association loci, much less is known about the causal variants, genes, and mechanisms by which they act, but recent developments in identifying lifelong effects for childhood growth loci such as *GDF5* suggest that in the coming years, additional loci should yield insights of clinical relevance.

Impact of early growth on lifelong health outcomes

In addition to specific loci, GWAS summary results from across the genome can be informative for uncovering the causal relationships between early growth traits and future health outcomes. In the past few years, causal inference methods utilizing genetic variants, collectively termed Mendelian randomization (MR), have begun to investigate these associations. Briefly, to test for a causal relationship between an exposure and outcome of interest, MR uses genetic variants associated with the exposure as proxies (“instruments”) for that exposure. In contrast correlations between the measured exposure and outcome, a genetic association between the exposure instruments and the

outcome of interest is unlikely to be subject to confounding or reverse-causality due to the random shuffling of alleles that occurs between parents and offspring, and can thus provide evidence supportive of causality, subject to various assumptions(39).

While MR is a potentially powerful tool for determining causal factors that influence health-relevant outcomes, these studies need to be carried out with care, especially when aiming to examine causal relationships between fetal growth and later health outcomes. This is because (i) fetal growth is influenced by both maternal and fetal genetic effects(4,40), and (ii) available instruments are for birth weight, which is a crude proxy for fetal growth. Recently, studies using maternal genetic variants as instruments for in utero environmental exposures that lower birth weight (independent of fetal genetic effects) found no evidence that they are causally associated with adverse cardiometabolic health outcomes in adulthood, contrary to observational epidemiological associations(4,41). Explicit understanding of the precise exposure captured by genetic instruments is crucial for appropriate interpretation of such MR studies. For example, studies using fetal genotype effects on birth weight as instruments for fetal growth have, in contrast, observed associations with later adverse outcomes such as type 2 diabetes(42,43). Such associations may reflect (i) direct effects of an individual's own genotype on their birth weight and on later health, as expected under the fetal insulin hypothesis(44), (ii) direct effects of the individual's genotype on their own later health and correlation with maternal genotype effects on birth weight, as seen recently for blood pressure(4), or (iii) potentially, health effects secondary to fetal growth. However, under such study designs with fetal genotype instruments, it is not possible to separate possibility (iii) from (i) or (ii).

While many studies have used MR to investigate the causal impact of adult stature on health outcomes, very few studies to date have assessed the causal impact of distinct childhood growth phases. One study investigated both childhood height and adult height, and found a separate influence of each on osteosarcoma risk(45). Indeed, in just the past 2 years, large studies taking a broad approach have implicated taller height as a causal factor for many health outcomes(24), whether increasing risk (such as for diagnosis with cancer and death from any cancer(46,47) and specific cancers (ovarian cancer(48); head and neck cancer(49); melanoma(50)), varicose veins(51), atrial fibrillation, venous thromboembolism, intervertebral disc disorder, hip fracture, and vasculitis(47). Taller stature also appears to have protective effects for other traits, in particular coronary artery disease(47,52). These relationships are sometimes complex, such as findings that taller height was causally related to ovarian cancer(47) in the general population, but not among premenopausal *BRCA1/2* carriers(53). These divergent findings could also be due to specific limitations of each study, and further work is needed to gain clarity. Additionally, while very few have been carried out to date, studies are beginning to look at the impact of height on pediatric outcomes, such as ocular biometry at age 6 years(54), and in non-European populations, e.g. on pulmonary traits in Latinos(55).

Future priorities for genetic studies of early growth traits: diversity and mechanism

To date, genetic investigations of birth weight have been performed predominantly in European ancestry samples, but low birth weight and associated adverse outcomes are often higher in non-Europeans, e.g. in South Asian or African ancestry(56); the reasons for these differences are not fully understood. The key priority for future GWAS efforts is to target large studies of other ancestral backgrounds, as these genetic studies will inform about both the heritable and environmental effects on

birth weight. Indeed, a recent study examined birth weight, length, and ponderal index (PI) across geographic regions and found that while the contribution of genetic factors was smaller than environmental factors, genetic variance was similar across geographic regions(57).

Aside from increasing diversity in future genetic studies of birth weight, there are further priorities for data aggregation and analysis that will improve our understanding of mechanisms. First, a limitation of the most recent GWAS of birth weight was that most samples did not have information on gestational age(4), so further large studies with both birth weight and gestational duration data will be necessary to understand which loci primarily influence birth timing vs. fetal growth. While initial indications were that only a few loci influence birth weight through a primary effect on gestational duration(4,58), the extent to which the remaining "growth" loci might in turn influence gestational duration is not known. Second, the integration of epigenetic data will help to inform on mechanisms. For example, DNA methylation may be influenced by environmental exposures, and may in turn influence gene expression. A recent epigenome-wide association study (EWAS) of birth weight in 8825 individuals identified more than 900 differentially-methylated associated sites in neonatal blood(59). Another smaller EWAS (n=301) identified 15 differentially-methylated sites in placenta(60). By integrating such findings with GWAS data, future studies will be able to assess evidence of causal effects, and examination of relevant cells and tissues will also be important(61). Third, longitudinal antenatal studies are needed to gain a clearer understanding of the genetics of fetal growth. Multilevel models can be applied to ultrasound scan data to model fetal growth trajectories (62), and both the heritability of fetal growth measures(63) and the contribution of a fetal genetic score for birth weight to fetal growth are higher in later gestation(64). Applying GWAS to antenatal phenotypes should improve understanding of links between different growth trajectories and pregnancy outcomes.

For childhood and adolescent growth, studies are needed to examine whether specific growth phases or trajectories more closely relate to adverse health outcomes. For instance, pubertal timing is correlated with many health outcomes, and variation in pubertal timing impacts the total amount and velocity of growth during adolescence(65). When dealing with anthropometric traits such as pubertal timing and height growth, BMI should also be taken into account, due to its close relationship with pubertal timing (for instance, in assessing the causal impact of prepubertal BMI and pubertal timing on cardiometabolic outcomes(66)). Furthermore, taking BMI into account as a mediator or confounder can even reverse causal relationships; for example, age at menarche had an inverse direct causal effect on risk of breast cancer independent of BMI while BMI itself had a positive indirect effect(67,68).

Perhaps of most direct societal impact is the increasing understanding that elevated BMI impacts adult health beginning in childhood, with growing numbers of genetic studies also supporting the idea that efforts should be made to reduce childhood obesity rates to improve public health. In the past two years, MR approaches have implicated childhood BMI in risk for asthma(69) and coronary artery disease and type 2 diabetes(70,71), as well as childhood abdominal obesity on plasma triglycerides and other cardiometabolic risk factors(72). Importantly, there is some evidence that the impact of childhood adiposity can be mitigated by weight loss later in life(73). Here, also, there is a need for studies in non-European population groups; standard obesity thresholds are not equally valid across ethnicities, with some ethnic group having higher disease risks at lower BMI thresholds than Europeans(74), and rates of adverse health outcomes, including BMI and cardiometabolic traits, vary by ethnicity(75).

Conclusions

Genetic studies of early growth phenotypes have recently made great progress in identifying underlying genetic loci, and analyses using these loci have begun to illuminate links with lifelong health. To further improve understanding in this field, key future priorities are the examination of growth trajectories through longitudinal study designs and a redoubled effort to study samples of diverse ancestries.

Figure 1

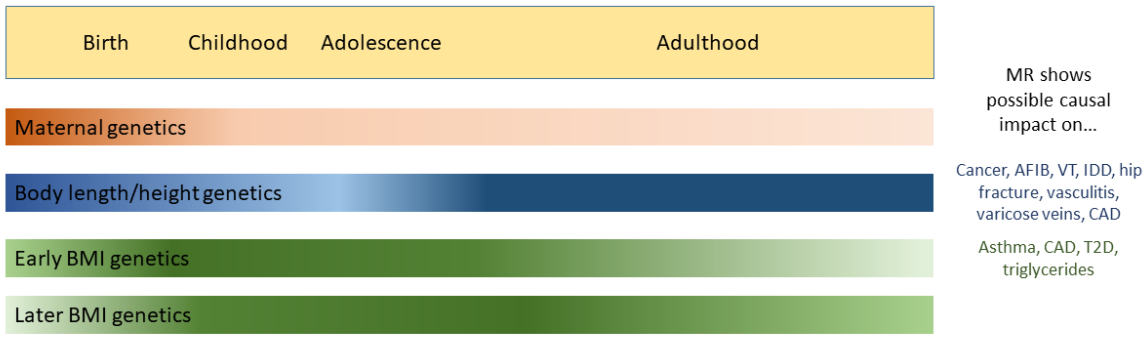

Figure Legend

Figure 1. A schematic of genetic effects on growth traits, with color gradients showing the approximate timing of genetic effects based on current knowledge. Some questions remain, for example the extent to which maternal effects persist to adulthood, and which height variants act during postnatal, but not fetal, growth. In Mendelian randomization (MR) studies, adult height-associated variants have typically been used to create genetic instruments to test causality with health outcomes. For BMI, more work has been done using childhood BMI-associated variants (with some example outcomes shown here). AFIB, Atrial fibrillation. VT, venous thromboembolism. IDD, intervertebral disc disorder. CAD, coronary artery disease.

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