Informative parent-offspring transmissions shed light on the genetics of fetal growth and deepen understanding of its links with adult traits

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Genome-wide association studies have identified several genetic variants in the maternal and fetal genomes associated with birth weight and other early growth traits, but have been limited by the paucity of large-scale family-based cohorts which would enable the resolution of informative genetic transmissions between parents and their offspring. A new study by Juliusdottir and colleagues uses extensive large-scale pedigree data from the Icelandic population, to identify genetic effects on birth weight that differ according to parental origin, and demarcate distinct contributions from the maternal intrauterine environment and offspring genetics on fetal growth.

Fetal growth is a complex trait that is influenced directly by the fetal genome and indirectly by the maternal genome through the intrauterine environment. Large scale observational epidemiological studies have shown that measures of fetal growth like birth weight are positively correlated with adult anthropometric traits like height, but that lower birth weight is associated with higher cardiometabolic risk[1,2]. Uncertainty exists as to the mechanisms underlying these associations, with alternative theories emphasizing the importance of genetics[3], the long-term effects of the intrauterine environment[1], or confounding by incompletely measured socio-economic factors[4]. A new study by Juliusdottir et al sheds considerable light on the aetiology of early life growth, its relationship with the maternal and fetal genomes, and explanations for its correlation with later life traits and diseases[5].

Juliusdottir et al. performed a large genome-wide association study (GWAS) meta-analysis of birth weight, combining information from the Icelandic birth registry with publicly available GWAS summary statistics from the Early Growth Genetics (EGG) Consortium and UK Biobank Studies[6]. The increased sample size enabled the authors to identify novel genetic variants associated with birth weight, with the vast majority of previously identified loci[6] replicating at nominal levels of significance. There was no evidence for paternal specific loci affecting offspring birth weight: as expected, the six loci identified in their paternal GWAS of offspring birth weight were correlated with variants acting directly through the fetal genome.

Birth weight, though readily available, is a relatively crude measure of fetal growth, so valuable additions to this study were GWAS of birth length and ponderal index (birth weight / length cubed, an indicator of neonatal adiposity). Of the seven loci associated with ponderal index, one (*EPAS1*) was also associated with length suggesting general effects on fetal growth, while signals at the remaining six loci were stronger when birth weight was adjusted for length cubed, consistent with effects on

non-skeletal growth. Interestingly, the fetal birth weight-raising allele at the strongest of these (*LINC00880*) has been associated previously with higher neonatal skinfold thickness and higher umbilical cord leptin levels[7] suggesting a role in neonatal adiposity and adipocyte function.

The importance of pedigree information

Previous large-scale GWAS of birth weight have been conducted using unrelated individuals[6,8-9]. Consequently, these studies have been limited in terms of their ability to correctly partition genetic effects into maternal and fetal sources of variation, and identify parent of origin effects, despite the application of clever statistical methods designed to utilize the limited pedigree information contained within the cohorts[10]. In contrast, the extensive pedigree information on the Icelandic participants in the deCODE genetics research program, allowed Juliusdottir et al. to generate phased haplotype data for offspring and assign parent-of-origin information to each offspring haplotype. This meant the authors could analyze the relationships between fetal growth traits and alleles transmitted from either the mother or the father, along with maternal non-transmitted alleles (which may influence growth via the intrauterine environment), to investigate which combination of alleles best explained the association (**Figure 1**). After estimating effect sizes, the authors used a Gaussian mixture model to cluster the variants into one of eight prespecified clusters according to their pattern of maternal and fetal genetic effects. Although this procedure is descriptive rather than a formal statistical test, their results suggest the existence of parent of origin effects at 22 loci, including at some not previously known to be imprinted. These results imply strongly that parent of origin effects are important for explaining variation in perinatal phenotypes like birth weight, and hint that the phenomenon may be more common in the human genome than previously appreciated[11].

Origins of birthweight-disease correlations

Finally, the authors examined associations between birth weight, birth length or gestational duration and polygenic risk scores that proxied various adult traits and diseases. Crucially, the polygenic scores were calculated separately for transmitted and non-transmitted alleles. This enabled the authors to test whether the effect of each polygenic score was through the maternal and/or fetal genome, and to infer through which component of fetal growth such an effect was likely to be mediated. A key finding was that polygenic scores for higher systolic blood pressure were strongly associated with lower birth weight through transmitted alleles (i.e. the fetal genome), with much less evidence for an effect of maternal non-transmitted alleles. This result agrees with a small study that used similar methods[12], but is contrary to larger studies that showed a maternal (but not fetal) genetic score for higher systolic blood pressure was associated with lower offspring birth weight[6,13]. The discrepant findings may partly be explained because those larger studies included large samples (e.g. UK Biobank) that were unable to condition birth weight on gestational duration. Findings from the latest study[5] indicate a maternal effect of blood pressure-raising alleles on shorter gestation, which may in turn associate with lower birth weight, but taken together, their results indicate that the observational association between higher systolic blood pressure and lower birth weight is mediated through pleiotropy in the fetal genome, rather than through maternal genotype influencing growth via the intrauterine environment. Thus the ability to discriminate between transmitted and non-transmitted alleles gives vital insight into observed correlations between early growth phenotypes and adult traits such as cardiometabolic disease.

What next?

Despite the large size of the deCODE cohort, it provides limited power to detect genetic variants showing parent of origin effects. Also deCODE and most large GWAS of fetal growth have been limited to populations of northern-European ancestry. Efforts are already underway to combine the results of this latest GWAS meta-analysis with others, including the large Norwegian HUNT[14] and MoBa[15] cohorts, and several other studies of diverse ancestries. The HUNT and MoBa cohorts include considerable numbers of genotyped mother-offspring pairs and parent-offspring trios, which will enable accurate phasing and the assignment of the parental origin of alleles. This will be critical in order to confirm the parent of origin effects identified in the deCODE study, identify and characterize new genetic loci associated with fetal growth, and properly investigate the relationships between early growth phenotypes and future risk of cardiometabolic disease.

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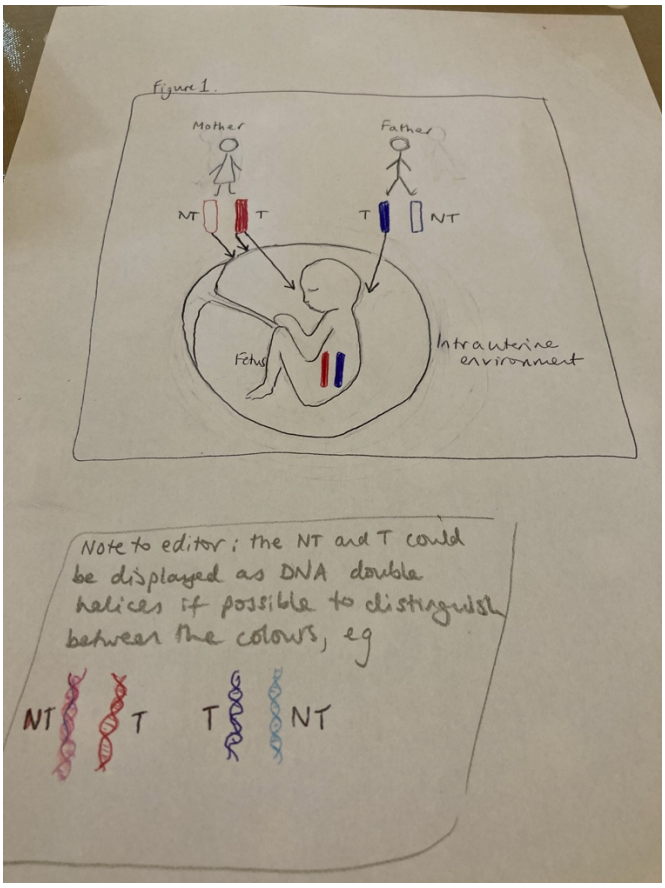

Figure Legend

Figure 1. Schematic diagram showing the different ways maternal and paternally derived alleles can influence fetal growth. Juliusdottir et al. found evidence of effects on fetal growth that differed between maternal and paternal transmitted alleles at 22 loci. Both maternal transmitted and non-transmitted alleles may additionally influence fetal growth via effects on the intrauterine environment. Complex patterns of association can influence fetal growth. For example, the authors showed that the maternal glucose-raising alleles at the known *GLIS3* locus (both transmitted and non-transmitted) were associated with higher birth weight, consistent with their effect on maternal glucose, which crosses the placenta, resulting in increased insulin-mediated growth in the fetus. They also found that the paternal transmitted allele was associated with lower birth weight. *GLIS3* is paternally expressed in human placenta. These results are consistent with a paternal-specific fetal effect (likely due to reduced fetal insulin secretion) acting in the opposite direction to the maternal intrauterine effect. NT, non-transmitted allele; T, transmitted allele.