Genetics of Size at Birth

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Size at birth is strongly related to a number of maternal factors including parity, length of gestation, mother's adult size, and mother's own birth weight (1). The importance of genetic factors has come from studies of monozygous and dizygous twins, where estimates of heritability of birth weight range from 30 to 70% (2,3). Ounsted et al. (4), however, reported that there may be a stronger relationship between the birth weight of the mother and that of the offspring, particularly in infants born with a low birth weight, and that these relationships may vary with parity. These data suggest that not only fetal genes but also genes that regulate the maternal uterine environment could be important in determining size at birth.

MATERNAL UTERINE ENVIRONMENT

— Size at birth is the strongest determinant of perinatal survival (5), yet in most populations, mean birth weight is slightly lower than optimal for offspring survival (6). Thus, it would appear that all fetal growth is subject to some degree of restraint by the maternal uterine environment (7), perhaps reflecting the importance to the mother of restricting the nutritional demands of the fetus if it would threaten her survival in times of poor nutrition. Although maternal undernutrition may (8) or may not (9) be a less common determinant of birth weight in contemporary populations, restraint of fetal growth is still evident, particularly in first pregnancies. First babies have a lower birth weight and tend to be thinner than subsequent babies, with a preserved head circumference and length, suggesting reduced adiposity. Postnatally, these babies demonstrate rapid catch-up growth (1). Such a growth pattern is evident in infants whose intrauterine environment has been affected by poor placental function, secondary to maternal hypertension and preeclampsia, but a similar pattern is also evident in uncomplicated pregnancies, where it is predicted by maternal factors such as maternal smoking and the mother's own low birth weight (1).

Ounsted et al. (4) were the first to report a strong association between birth weight of offspring and maternal birth weight in their study of small growth-restrained infants. Thus, restraint of fetal growth may be inherited through the maternal line. There may be a close relationship between restraint of fetal growth and the risk of preeclampsia, which is also more common in first pregnancies. In a recent study of over 4,000 pregnancies in Cambridge (U.K.), we noted that mothers' first pregnancies were associated with lower birth weight in the offspring (mean difference between first and subsequent pregnancies, 130 g; $P < 0.0001$) and an increased risk of pregnancy-induced hypertension (odds ratio, 4.3; 95% CI 2.5–7.3; $P < 0.0001$). A mother's risk of preeclampsia has also been related to her own low birth weight (10).

Size at birth can also be affected by maternal blood glucose levels. This is most clearly seen in infants of diabetic mothers, where increased glucose transfer to the fetus results in β-cell hyperplasia, increased insulin secretion, and greater fetal adiposity. More subtle variation in maternal glucose levels can also affect size at birth, as demonstrated in a study of mothers and offspring with rare genetic defects of the glucokinase gene (11), and more recent reports that common variation in the glucokinase gene promoter also relates to size at birth (12). In our own studies of over 4,000 normal pregnancies, a continuous relationship is observed between maternal glucose levels and the birth weight of the offspring (Fig. 1). Interestingly, such variation in maternal glucose levels may be partly transmitted through the maternal line, as risk of gestational diabetes is also related to low maternal birth weight (13).

The association between a mother's birth weight and the birth weight of her offspring is likely to be complex and could relate to in utero programming of fetal metabolism and epigenetic or genetic effects. Variation in the mitochondrial genome is an important candidate, since this is exclusively transmitted through the maternal line. The mitochondrial DNA 16189 variant has been reported by our group to be associated with thinner offspring at birth (14). Infants with this variant showed increased postnatal weight gain, suggesting that the effect may be mediated through the maternal uterine environment, although the mechanism is unclear and these observations have yet to be confirmed in other populations.

Another potential mechanism whereby the restraint of fetal growth could be transmitted through the maternal line is in the inheritance of exclusively maternally expressed genes, where paternal alleles are silenced by imprinting. Imprinting results in silencing of either the maternal or paternal copy of a gene and, therefore, exclusive expression of the allele inherited from one or other of the parents (15). Haig (16) pointed out the inherent conflict between the mother's need to limit the nutritional demands of the fetus and the father's interests in promoting fetal growth, to optimize the chance of perinatal survival. This led to the hypothesis that imprinted genes evolved to reflect the competing interests of the mother and father. Many imprinted genes regulate fetal growth. In animal models, genes expressed exclusively from the paternal allele tend to promote fetal growth, such as *IGF2*, which encodes the growth promoter IGF-II. In contrast, genes expressed exclusively from the maternal allele tend to reduce fetal growth, such as *IGF2R*, which encodes the

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Abbreviations: VNTR, variable number of tandem repeats.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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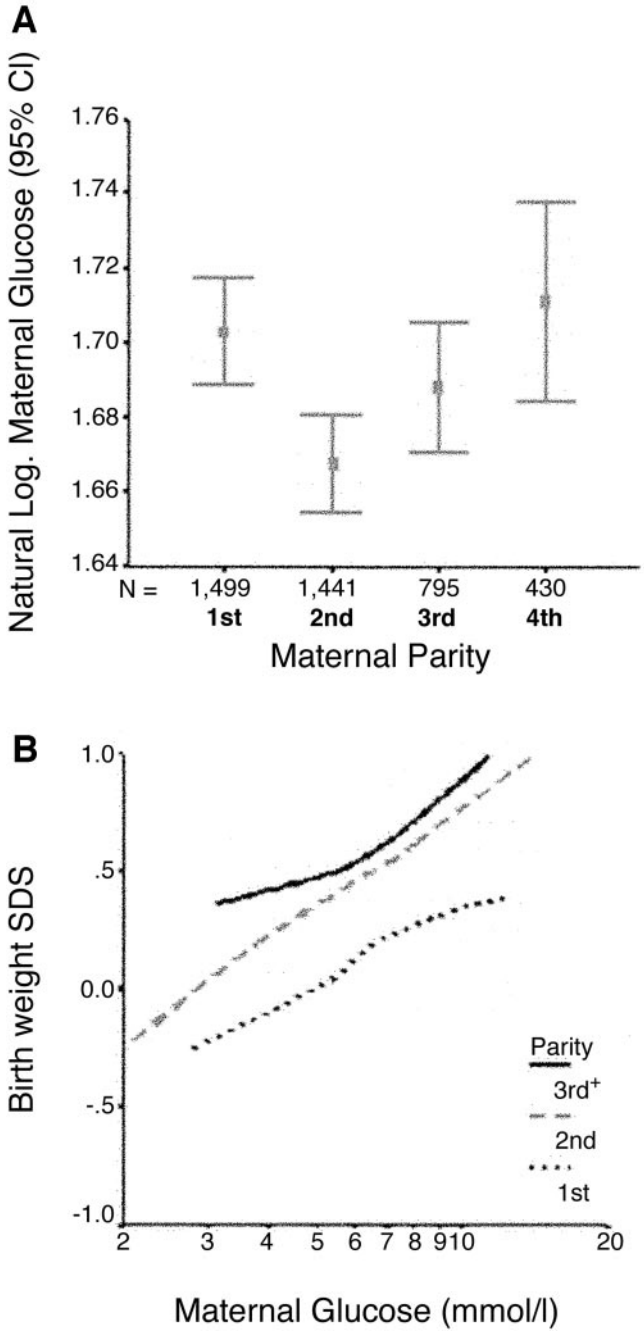

Figure 1—*Maternal glucose levels (post–oral glucose at 28 weeks' gestation)* (n = *4,166) by parity* (A) *and relationship with birth weight* (B).

non-signaling type 2 IGF receptor (17). The extent to which such observations are relevant to human fetal growth is uncertain, as, although *IGF2* is paternally expressed in humans, there is only variable imprinting of *IGF2R*.

We recently identified a common variant in the maternally expressed gene *H19*, which regulates the imprinting and expression of *IGF2* and was associated with size at birth in two independent cohorts (Fig. 2) (18). The *H19* +2992 variant was associated with increased cord blood levels of IGF-II and higher maternal levels of glucose during pregnancy. *H19* is expressed but does not have a protein product. It is thought to regulate imprinting of the exclusively paternally expressed growth promoter *IGF2*. In our observational studies of large normal populations, it was not possible to distinguish whether the birth size association was directly due to inheritance of the maternal allele by the fetus, or indirectly through effects of the mother's genotype on the uterine environment. Data from a study of a placental-specific *igf2* promoter in the mouse (19) indicate how complex such interactions may be. Knockout of this promoter led to an initial compensatory upregulation of placental nutrient transfer, which could also have affected maternal metabolism, but subsequently there was failure of this compensatory process and fetal growth slowed, with a resultant low birth weight (20).

FETAL GENES AND SIZE AT BIRTH

— A series of elegant animal knockout experiments have identified the importance of IGF-I, IGF-II, insulin, and their respective receptors in regulating fetal growth and size at birth (21). Studies of rare mutations in humans support the role of these proteins and receptors in the regulation of human fetal growth. Newborns with defects in pancreatic development or insulin receptor activation show reduced fetal growth and adiposity (22). Individuals born with defects of the *IGF1* gene are small at birth, with a particular reduction in head size (23,24). Intrauterine growth retardation has also been reported in individuals with genetic defects in the IGF type 1 receptor (*IGF1R*) (25). Infants with a reduced or increased copy number of this receptor are reported to show reduced or increased fetal and postnatal growth, respectively (26), indicating that the copy number of *IGF1R* may influence growth in humans. As yet, there have been no reported human cases with severe mutations of *IGF2R*, but variable rates of imprinting and expression of this gene have been reported in relation to size at birth (27). Finally, overexpression of *IGF2* has been shown to result in fetal overgrowth as part of the Beckwith-Wiedemann syndrome (28) and, very recently, Silver-Russell syndrome has been shown to be associated with demethylation of the telomeric imprinting center ICR1 on chromosome 11p15 and resulting over-methylation and underexpression of *IGF2* (29).

Thus, common polymorphisms in genes regulating expression of the genes encoding IGF-I, IGF-II, insulin, and their respective receptors could relate to size at birth. In population studies, cord blood levels of IGF-I, IGF-II, and insulin are positively related to size at birth (30). In contrast, growth hormone levels tend to be higher in babies born small for gestational age, perhaps reflecting the metabolic rather than anabolic role of growth

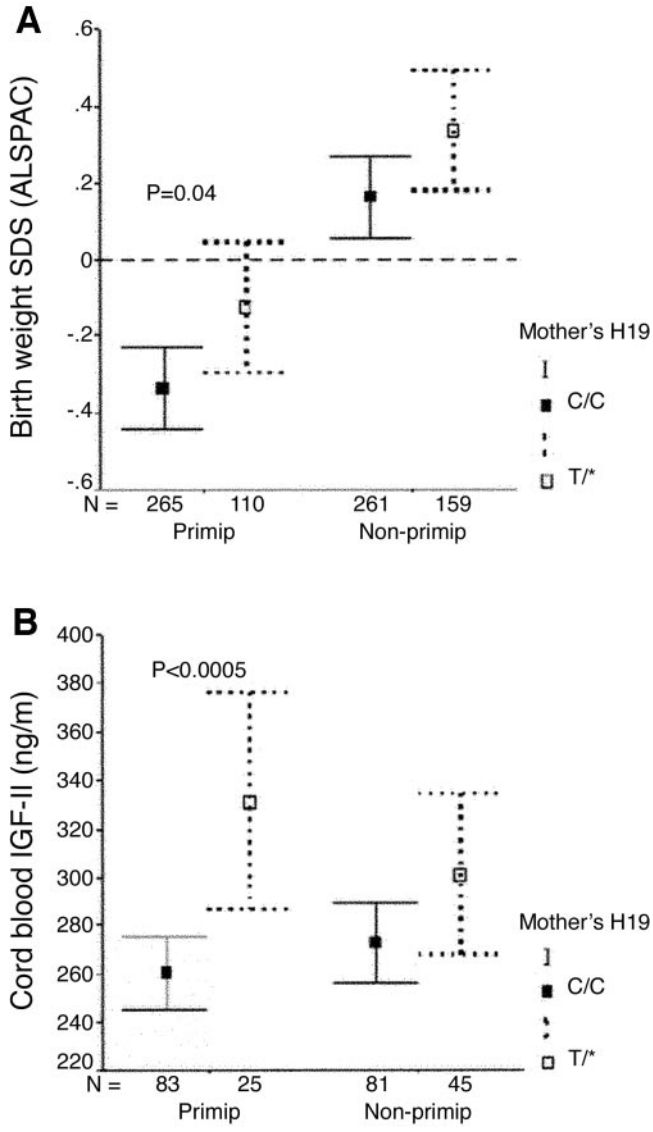

Figure 2—*Birth weight SD score (SDS)* (A) *and cord blood IGF-II levels* (B) *at birth in the ALSPAC cohort, by mother's H19 + 2992 genotype, stratified by birth order ("Primip" = mother's first child; "Non-primip" = second or subsequent child). Data are means (95% CIs). Firstborn infants had lower birth weights than infants of subsequent pregnancies. Associations with mother's genotype (CC vs. T* [CT or TT]) were only seen in first pregnancies. Taken from Petry et al. (18), originally published by Biomed Central Ltd.*

hormone in the perinatal period (31). Higher levels of the soluble form of IGF2R and higher levels of IGF2R relative to IGF-II have been associated with smaller size at birth and placental weight, suggesting that, as in the mouse, IGF2R may have a growth inhibitory function (17, 32).

The extent to which the variations in cord blood hormone concentrations and size at birth are related to common genetic polymorphisms remains uncertain. Polymorphisms of the *IGF1* gene and, in particular, a common *IGF1* promoter CA repeat, have been reported to be associated with size at birth (33,34); however, these associations have not been confirmed in other large population studies (35). Our group has examined the relationship between a common variation in *IGF2* and *IGF2R* and size at birth in large representative birth cohorts. Whereas variation in these genes has been associated with postnatal weight and height gain, we could not find any association with size at birth (36,37).

In contrast, variation in the length of the insulin gene (*INS*) variable number of tandem repeats (VNTR) on chromosome 11, which is thought to regulate transcription of both *INS* and *IGF2* (38,39), has been associated with size at birth. We originally reported an association between the *INS* VNTR class III/III genotype and larger size at birth, particularly in relation to head circumference and, to a lesser extent, birth length and weight (40). We subsequently confirmed these associations with head circumference at birth, by the identification of an association in a second cohort, and by observing the transmission of the parental class III allele, excluding potential confounding by population stratification (41). An association between *INS* VNTR and size at birth was also observed in the Pima Indians of Arizona, but the association was reversed compared with the previous study, and class III/III individuals had lower birth weights (42). Other studies from Finland and the southwest of England have failed to replicate any of these findings (43,44). It is possible that such associations may be confounded by linkage disequilibrium with other genetic variants in this region of chromosome 11, which is rich in imprinted loci that have putative effects on *IGF2* expression and fetal growth. Additional confounding may come from selection of cases, since in our own study the associations were strongest in second and subsequent pregnancies, where the potential confounding effects of the maternal uterine environment and maternal restraint of fetal growth are less evident (41).

The impetus to identify the common genetic regulators of size at birth has increased with the observation that size at birth is an important predictor of adult disease risk (45). The common *IGF1* promoter CA repeat has been reported to be associated with size at birth (33,34); however, this association was not confirmed in a large population study (35). Our own group has looked at common variations in insulin receptor substrate 1 and peroxisome proliferator–activated receptor-γ, since both have been associated with risk of insulin resistance in adult populations. However, we were unable to confirm any association with size at birth (46). Common polymorphism in the G protein β3 subunit gene has been associated with low birth weight in pregnancies without other risks for reduced fetal growth (47). Other common genetic variants reported to be associated with size at birth include variants in angiotensinogen (48), the small heterodimer partner in a cohort of obese children (49); phosphoglucomutase locus 1 in girls (50); and the vitamin D receptor (51), preproneuropeptide Y (52), and acid phosphatase in boys (52a).

Further genetic polymorphisms in placental alkaline phosphatase in the fetus (53) and maternal aromatic compound-inducible cytochrome P450 and glutathione-S-transferase genes (54) were associated with modifications of the effects of maternal smoking during pregnancy on offspring birth weight. Other maternal genetic polymorphisms that may influence maternal metabolism and are reported to be associated with size at birth include methlenetetrahydrofolate reductase (55) and G protein β3 subunit (56).

INTERACTION BETWEEN FETAL GENES AND THE MATERNAL UTERINE ENVIRONMENT

— Size at birth is an important determinant of not only offspring perinatal survival but also maternal survival, and it is likely that it has been the subject of intense genetic selection pressure throughout human history. It has been argued that the conflicting interest of the mother and father in restricting and promoting fetal growth, respectively, may be reflected in the evolutionary development of imprinted genes of which over 70% are thought to regulate fetal growth and brain development (15).

We have argued that a thrifty fetal genotype is one that would enhance fetal growth and postnatal weight gain, thus enhancing chances of perinatal survival (57). The *INS* VNTR class III/III genotype would be a good candidate for such a thrifty genotype because it affects size at birth (40,41,58). Preliminary work in our Department from the Cambridge Birth Cohort examining the effects of transmission of class III genotype in three generations confirmed the effects of transmission of class III alleles, particularly from the father, on size at birth and also indicated that in the mothers inheritance of class III from their fathers may be associated with increased glucose levels during pregnancy. But there is considerable overlap. These observations were particularly marked in second and subsequent pregnancies where the effects of maternal constraint of fetal growth are least evident. The data from Innes et al. linking low birth weight with subsequent risk for preeclampsia (10) and gestational diabetes (13) suggest that similar transgenerational effects related to inheritance from the mother may also be associated with subsequent pregnancy effects on birth weight.

From our own studies of common variation in the *H19* gene, we observed that, particularly in first pregnancies, this genotype is associated with not only size at birth but also variation in maternal glucose levels during pregnancy (18). Genetic variation was strongly associated with cord blood IGF-II levels, suggesting that the primary influence was on fetal physiology, whereas variation in the mother's *H19* and *IGF2* gene expression is unlikely to have led directly to lower glucose levels. This leads to the suggestion that expression of imprinted fetal genes in the fetus could influence maternal metabolism. Further evidence to support this hypothesis has come from the study of a knockout mouse model, where lack of fetal expression of the maternally expressed, imprinted gene *p57Kip2* leads to hypertension, proteinuria, thrombocytopenia, decreased anti-thrombin III activity, and increased endothelin levels associated with trophoplastic hyperplasia during late pregnancy in functionally wild-type mothers (59). After birth of the pups, mothers' blood pressure and urine protein levels return to normal. This model shows strong similarities to preeclampsia in humans, a condition associated with the birth of low-weight babies. Evidence for a role for the fetal genome in influencing maternal blood pressure in pregnancy in humans comes from the finding of higher blood pressures in women carrying fetuses with Beckwith-Wiedemann syndrome, where the genetic defect is located within the highly imprinted 11p15.5 chromosomal region (60). The likely mechanisms of such fetal effects on the mother are complex, but recent study of an *igf2* placental promoter-specific knockout mouse show that the fetus can indeed respond to poor nutrition by regulating the nutritional transport from the mother, be it only temporarily (19,20).

CONCLUSIONS

— The complexity of the potential interactions between maternal and fetal genotype should not be unexpected given that the delicate balance between maternal and fetal survival has been essential for the evolutionary development of our species. Genetic selection perhaps primarily but exclusively involving imprinted genes has led to a delicate balance in fetal nutrient demands and maternal restraint of fetal growth. That balance may vary by parity, and it has been argued that as the family size increases, the rising maternal glucose levels may reflect a biological commitment to increased prenatal weight gain, thus enhancing chances of perinatal survival and reducing postnatal demands on the mother. There are now compelling data to suggest that both maternal gestational diabetes and maternal restraint of fetal growth are associated with future risk for type 2 diabetes, and further exploration of these complex interactions between maternal and fetal genotype may help to elucidate the mechanisms underlying those associations.

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