Invited Commentary

Invited Commentary: Two Studies of Genetic Control of Birth Weight Where Large Data Sets Were Available

T. H. Beaty

From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

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Physical size at birth (primarily birth weight) is a key predictor of infant mortality and morbidity and may serve as a predictor of risk to chronic disease in adulthood. By use of birth records, it is sometimes possible to accumulate large, even massive, data sets that can permit analyses to separate genetic and environmental factors controlling variation in the complex phenotype, birth weight. Two studies of birth records, one from Norway and one from Lebanon, demonstrate how hospital- or registry-based data sets can be used to address fundamental questions about genetic control. The Medical Birth Registry of Norway has birth certificate data dating back to 1967 and allowed nuclear families to be reconstructed by linking children and their parents. Path models were used to estimate heritability of head circumference, along with birth weight and length for over 100,000 reconstructed families. A hospital-based study of birth records in Beirut, Lebanon, collected information on over 10,000 births, including sufficient numbers of marriages between first and second cousins to estimate inbreeding effects. Both of these studies confirm that birth weight is not simply due to the direct effects of the baby’s genes but is a complex phenotype reflecting the effects of maternal genes and environments.

birth weight; environment; genetics; gestational age

Because physical size at birth (birth weight is most commonly used) is a prime predictor of infant mortality and morbidity and has also been shown to be associated with risk to several major chronic diseases in adulthood (among them diabetes, hypertension, and cardiovascular disease), it is important to understand the extent to which genes control normal variation in birth weight (or more generally physical size at birth). Yet even estimating the proportion of variance in birth weight attributable to genes (commonly termed the “heritability” of a quantitative phenotype) has proven difficult, because there is a complex association between maternal genetic factors and the genes carried by the developing fetus itself (who inherited genes from both the mother and the father). In this issue of the American Journal of Epidemiology, two papers illustrate how very large sets of birth record data can be exploited to address questions of genetic control of physical size at birth, one from Norway (1) and one from Beirut, Lebanon (2).

The Medical Birth Registry of Norway includes birth certificate information collected since 1967 and represents an invaluable data resource because it is possible to link birth records of parents and children within this registry. Lunde et al. (1) reconstructed two-generation families from the Medical Birth Registry of Norway by linking child and parent records on a very large scale (over 100,000 families were available for analysis of birth weight). These reconstructed families provided information sufficient to estimate familial correlations (mother-offspring, father-offspring, and sibling correlations) with extraordinarily small confidence intervals. As with most published studies of birth weight, the sibling correlation for birth weight was very close to 50 percent, which would be expected if the child’s genes exerted complete control over his/her physical size at birth. Clearly, though, more than just the child’s genes are acting, because the correlations between maternal half siblings were too close to those of full siblings, and the
parent-child correlations were too different from the full-sibling correlation to reflect simple additive genetic control by independent genes, commonly referred to as “polygenic” inheritance. The Norwegian group fit a specific causal model that included genetic heritability \( (h^2) \), reflecting the genes in the child), a separate term for variation controlled by maternal genes \( (m^2) \), a common sibship environment (with separate terms for full and maternal half-siblings), and separate residual error components for full and half siblings. Maximum likelihood methods were used to estimate path coefficients under this causal model. The role of fetal genes was consistently greater for measures of physical size (birth weight, birth length, and head circumference) than were corresponding path coefficients for the effects of maternal genes controlling the intrauterine environment or other unspecified factors shared among siblings. The heritability of birth weight \( (h^2 = 31.0 \text{ percent}) \) is due to the direct effects of genes in the developing fetus was smaller than in previous published studies, but no other study can match the size or depth of family data presented here. Maternal genes, on the other hand, always exerted a larger effect on normal variation in the length of pregnancy or gestational age, which also influences physical size at birth.

The second paper by Mumtaz et al. (2) used a large cohort of livebirths drawn from eight hospitals in Beirut, Lebanon, over a 2 year period (2000–2001) to test for an effect of consanguinity (marriage between related individuals) on a standardized measure of birth weight, the fetal growth ratio. The rate of consanguineous matings in Beirut is not terribly high (<10 percent combined), but the size of this study (10,289 consecutive livebirths) provided adequate statistical power to estimate differences in the fetal growth ratio among singleton children of parents who are first cousins and those who are second cousins compared with children of unrelated parents. The literature is consistent in showing that inbred children (offspring of related parents in a consanguineous mating) are at higher risk of birth defects, mental retardation, and other diseases. The effects of inbreeding on birth weight are less clear, and the literature is often inconsistent. The relatively large numbers in this study provide an excellent opportunity to test for differences in the fetal growth ratio, a standardized measure of birth weight. The multiple regression model used here showed no real difference in the fetal growth ratio between offspring of second cousins and those of first cousins, but both inbred groups showed a modest (but statistically significant) decrease in birth weight adjusted for other maternal characteristics (age, education, smoking, and so on). This apparent effect of consanguinity on birth weight cannot reflect any simple effect of recessive genes alone, because it is basically the same for both first and second cousins (which are third- and fifth-degree relatives with a prior probability of sharing alleles identical by descent of 0.0625 and 0.015625, respectively). Nonetheless, this study nicely illustrates how genetic factors (here, inbreeding) can be incorporated into analysis of the numerous factors influencing birth weight, a primary predictor of infant health.

These two studies confirm that numerous genetic factors (including the genes of the infant and the mother, as well as the genetic association between parents) are critical in controlling variation in physical size at birth and, perhaps, its subsequent health consequences. Identifying specific genes that control birth weight (or any measure of physical size at birth) will be more complicated, of course. A recent linkage study yielded intriguing evidence of a quantitative trait locus for birth weight (adjusted for gender and full term vs. premature gestational age) on chromosome 6q in both Mexican-American families from San Antonio, Texas, and European-American families from Ohio (3). This evidence of linkage is based on identical-by-descent sharing of marker alleles between various pairs of relatives and should thus represent genes of the infant, not the mother. The region of strongest evidence (spanning a genetic distance of 16 cM on chromosome 6q) contains several candidate genes that may control growth of the developing fetus. This same study yielded weaker evidence for other chromosomal regions that may also contain genes influencing birth weight (on chromosomes 2, 1, and 9, in decreasing order of strength). A polymorphism in one candidate gene, LRP8, located near a secondary region of linkage on chromosome 1q identified by Arya et al. (3), appeared to influence fetal growth among children born to African-American women when the maternal genotype was analyzed as a risk factor (4). An earlier linkage study in Pima families yielded evidence of linkage to chromosome 11p, which became stronger when “parent-of-origin” was considered (5). This parent-of-origin effect may represent genetic “imprinting,” where the expression of inherited alleles is determined by whether it is inherited from the mother or the father. Thus, in addition to the usual problems of replicating evidence of linkage and/or association across studies, the genotypes of both parents and the child need to be considered (as well as maternal factors that may influence in utero growth) to fully understand how genes control birth weight and other physical size at birth. Approaches such as those used by Infante-Rivard and Weinberg (6) may be preferred. Here, the case-parent trio design was used to show that a common polymorphism (Val34Leu) in the factor XIII gene may be subject to a parent-of-origin effect in controlling risk to intrauterine growth retardation, where paternal transmission increased risk to the child but maternal transmission did not. The overall effects of genes on complex phenotypes such as fetal growth can be estimated from large data resources, such as birth records, but fully understanding their mode of action will require both marker and phenotypic data from children and parents, as well as information on factors such as inbreeding.

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References

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