Birth weight symposium

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Nick Mann

Introduction to the Birth weight symposium

What factors determine birth weight and do they have any biological significance for the future health and welfare of the individual? These are important questions for all paediatricians and four groups of experts have been approached to independently give their thoughts on key areas. The aim was for concise pithy comments and opinions, so the length of the articles was rigourously controlled. Firstly, are there genetic factors that contribute to birth weight, secondly does maternal nutrition determine size, then are there social influences on birth weight? Is birth weight of biological significance for the individual or the species? Patrick Cartlidge, Senior Lecturer in child health in Cardiff, kindly refereed this symposium. Please feedback your views and comments to the rapid response section of the journal website at www.archdischild.com.

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Genetic factors contributing to birth weight

L B Johnston, A J L Clark, M O Savage

Epidemiological studies suggest that genetic factors account for 30-80% of birth weight variance

The genetic influence on birth size has been recognised for many years, but only recently have some of the specific genes and chromosomal loci involved been identified. This article outlines the evidence for a genetic influence on birth size and reviews our current understanding of the specific genetic factors involved.

WHAT IS THE EVIDENCE THAT GENES INFLUENCE BIRTH WEIGHT?

Epidemiological studies estimate that environmental influences account for about 25% birth weight variance and genetic influences account for 38–80% birth weight variance.[1–3] There is considerable variability in the estimates of the fetal and parental components of these genetic influences from 18 to 69.4% and from 3 to 20% variance of birth weight respectively. Overall there is strong evidence that genetic factors play a significant role in determining birth size.

> "Thus there is evidence of strong familial trends in birth size."

Familial trends in birth weight have also been observed. There is significant correlation between parental birth weights and birth weight in index cases using multiple regression analysis (mothers 0.19–0.20; fathers 0.12–0.16).[4 5] Maternal and paternal birth weights were significantly lower in families with two small for gestational age (SGA) births (index child below 10th centile) compared with families with no SGA births in the Scandinavian SGA study.[5] The odds ratio calculated for having an SGA mother and SGA father in families with two SGA births were 1.74 and 2.49. A mother born SGA is 2.5 (white) or 2.7 (African American) times more likely to have an SGA child than a mother of normal birth weight, and this increased to 10.2 and 10.1 if there was also a low birthweight sibling.[6] A study of cousins in which the correlation between birth weights was greater if the mothers were sisters ($r = 0.135$) than if the fathers were brothers ($r = 0.015$) suggests that there is greater influence of maternal than paternal birth size.[7] Thus there is evidence of strong familial trends in birth size.

WHICH GENETIC FACTORS INFLUENCE BIRTH WEIGHT?

Birth size is the result of fetal growth. The fetal experience is unique and influenced by parental, placental, and fetal factors. Furthermore, it is likely that there are complex interactions between genetic and environmental factors of parental, placental, and fetal origin.

Parental genes

Parental genetic influences are likely to be polygenic, but the exact genes involved and how they act is not fully understood. Glucokinase provides an elegant example of the effect of a parental genetic variant and also shows the interaction between parental and fetal genotypes. Mutations in this gene have been found to cause maturity onset diabetes of the young type 2.[8] Hattersley and colleagues investigated the influence of glucokinase gene defects on birth size in 58 offspring where one parent was known to be affected.[9] If a mother had a glucokinase mutation, the birth weight was increased by a mean 601 g as a result of maternal hyperglycaemia in pregnancy. If a fetus had inherited a glucokinase mutation, the birth weight was decreased by 533 g, equivalent to a fall from the 50th to the 25th birth weight centile. An affected mother resulted in a rise from the 50th to the 85th centile in an unaffected child, or the 25th to the 50th centile in an affected child.

Placental genes

The placenta is critically involved in transporting nutrition and acting as a barrier to infection and maternal corticosteroids. In most cases, it is genetically identical with the fetus, but in 1–2% of conceptuses confined placental mosaicism is observed, in which a cytogenetic abnormality is detected in the placenta and not the fetus.[10 11] Up to 20% of idiopathic SGA term deliveries have confined placental mosaicism.[11 12] How mosaicism affects fetal growth

Abbreviations: IGF, insulin-like growth factor; SGA, small for gestational age dehydrogenase.

is not known, but presumably it is related to an alteration of placental function.

Fetal genes

Insight into the genes that may be involved in human fetal growth has been provided by studies on human and animal fetal physiology. In particular, mouse gene knockout studies have clearly shown that insulin-like growth factor (IGF)-I, IGF-II, IGF receptor type 1, insulin, insulin receptor, and insulin receptor substrate 1 are all critical for normal fetal growth.[13–16]

In humans, the first single gene defect in a short SGA subject was found in the IGF-I gene.[17] A homozygous deletion of exons 4 and 5 of the IGF-I gene resulted in undetectable levels of serum IGF-I, extreme intrauterine growth retardation, severe postnatal growth failure, deafness, and moderate learning difficulties. This case shows that, in man, an IGF-I gene defect can be compatible with life whereas there is high mortality in the knockout mice as a result of respiratory muscle weakness.[13 14]

Studies of the insulin gene in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) subcohort of 758 term singletons found a significant association of the insulin variable number tandem repeat class III genotype and longer length, weight, and head circumference at birth in children who did not change weight centile from birth to 2 years.[18] Children homozygous for the class III allele showed a 200 g increase in birth weight. There was no association of genotype with birth size in the group as a whole, which the authors argued was due to the effect of environmental factors.

Detailed genetic studies have been performed in children with Silver-Russell syndrome, but no consistent cytogenetic abnormalities have been found. However, it has been shown that 10% of these children have inherited two copies of the maternal chromosome 7 and no paternal copy (uniparental disomy; mUPD7).[19–21] This suggests that there may be a recessive gene defect if there is isodisomy—that is, two copies of the same chromosome are inherited—or an imprinted paternally expressed gene if there is heterodisomy—that is, both maternal chromosomes 7 are inherited—in this region. There are several good candidate genes in the two regions of interest (7p12–13 and 7q32) that are homologous to imprinted regions in the mouse genome. Molecular studies have not yet found the causative defect(s).

CONCLUSIONS

Epidemiological studies have shown that genetic factors account for 38–80% birth weight variance. There is growing evidence supporting the roles of certain candidate genes in influencing size at birth. Many more genetic influences remain to be discovered. Furthermore, an understanding of how these factors interact will be necessary before this knowledge can be fully exploited.

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