

## Parental Imprinting and Fetal Growth

Insulin-like growth factor 2 (IGF-2) has long been implicated as an important fetal growth factor. Three recent reports now suggest that this effect is primarily due to expression of the paternally derived IGF-2 gene (called *Igf2* to distinguish it from the gene product IGF-2).

DeChiara et al used gene targeting to disrupt *Igf2* in embryonic stem cells that were employed to generate mice chimeric for the mutation. Once mice heterozygous for the mutation were established through breeding, transmission of the mutated gene was followed through several generations. The investigators found that when it was transmitted through the mother, there was no effect on the size of the offspring receiving the mutation. However, when transmitted through the father, the progeny receiving the nonfunctional *Igf2* genes were growth-deficient and approximately 60% of normal size. Thus, among heterozygotes for the *Igf2* mutation, only those receiving it from the father were growth-deficient. Using mRNA assays that distinguished between expression of the normal and mutated *Igf2* genes, they further demonstrated that the maternal *Igf2* allele was silent except in the choroid plexus and leptomeninges, where both alleles were expressed. They concluded that the maternal *Igf2* allele is imprinted and therefore inactive in most tissues.

Beckwith-Wiedemann syndrome (BWS) is a fetal overgrowth syndrome in which tumors often arise. The constitutional karyotype is usually normal in the syndrome; however, in several instances DNA studies have demonstrated loss of the maternal contribution of genes that map to chromosome 11p15.5 in the tumors. This has been of considerable interest because it is the chromosomal site to which *Igf2* maps in humans. Suspecting possible uniparental disomy for genes mapping to this region (both sets of genes come from 1 parent rather than 1 set from each parent), Henry and coworkers determined the parental source of several 11p15.5-mapped genes in 21 sporadic cases of BWS with normal karyotypes. The parental source could be determined for at least 1 gene in 8 instances. Three of these 8 had only paternal genes and therefore displayed paternal disomy.

The third report extends this story further. *Igf2* maps to distal chromosome 7 in the mouse. Ferguson-Smith et al introduced cells from very early mouse embryos that carried duplications of either the paternal or maternal distal chromosome 7 into normal mouse blastocysts. The phenotype of the chimeric mice that were generated differed substantially depending upon the

source of the 7p duplication. If the paternal duplication of distal 7 was present, the mice were substantially larger than control mice. In contrast, no size difference was noted when the maternal duplication for distal 7 was present. Comparison of mRNA levels for *Igf2* showed increased *Igf2* expression associated with the paternal distal 7 duplication but very low levels of *Igf2* expression in the mice harboring the maternal distal 7 duplication.

DeChiara TM, Robertson EJ, Efstratiadis A. Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* 1991;64:849-859.

Henry I, Bonaiti-Pellie C, Chehense V, et al. Uniparental paternal disomy in a genetic cancer-predisposing syndrome. *Nature* 1991;351:665-667.

Ferguson-Smith AC, Cattanach BM, Barton SC, et al. Embryological and molecular investigations of parental imprinting on mouse chromosome 7. *Nature* 1991;351:667-670.

**Editor's comment:** *It is often held that maternal factors contribute more to fetal size than do paternal ones if for no other reason than that the fetus resides in the mother and is exposed to a host of maternally determined physical and chemical factors. However, these 3 investigations, utilizing completely different methods, strongly support the view that at least certain aspects of fetal growth are influenced more by the father than by the mother. The active *Igf2* gene appears to be the one inherited from the father, whereas the maternally derived *Igf2* gene is inactive in most tissues due to imprinting.*

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