

Hemihypertrophy, Uniparental Disomy, and Risk for Cancer Or: Chromosome 11 Uniparental Isodisomy Predisposing to Embryonal Neoplasms

Grundy et al report on a child with hemihypertrophy and congenital adrenal carcinoma in whom Wilms' tumor subsequently developed. It has been known for some time that Wilms' tumor is associated with the inactivation of both alleles of a tumor-suppressor locus on chromosome 11p. Tumor-specific loss of 11p15 sequences also has been demonstrated in adrenal carcinoma. The overgrowth disorder Beckwith-Wiedemann syndrome is associated with the development of Wilms' tumor and other cancers, and it also has been shown to be associated with loss of the same portion of chromosome 11, either through deletion or uniparental disomy (2 copies of chromosome 11p from father). It is always the maternal copy of chromosome 11p that is lost. These results prompted Grundy et al to examine chromosome 11 in this case of hemihypertrophy with Wilms' tumor.

Molecular genetic analysis revealed that the child had a normal-appearing karyotype. However, when restriction fragment length polymorphism (RFLP) analysis was done, it became apparent that he had uniparental paternal isodisomy for chromosome segments 11p13 and 11p15 (ie, both chromosome 11p segments came from the father). This supports the theory that these segments of chromosome 11 are imprinted, ie, they are differentially expressed when inherited from the mother as opposed to the father, and that they play some role in tumorigenesis. (However, because the child had inherited 2 copies of the same chromosome 11, rather than 1 copy from each parent or 2 different chromosomes from the father, it is also possible that the father carried a mutant recessive

tumor-suppressor gene and that the absence of a balancing normal allele in the child has revealed this mutation.) Because the child also had normal kidney and adrenal tissue, the authors conclude that isodisomy cannot represent the final event responsible for oncogenic transformation. Thus, inactivation of an 11p tumor-suppressor locus seems insufficient to cause Wilms' tumor, which they conclude must be a multistep disorder.

The authors comment that their case, with hemihypertrophy and tumors as the only phenotypic abnormality, may or may not represent an incomplete form of Beckwith-Wiedemann syndrome. But it does demonstrate that this type of chromosome 11 aberration can be present without expression of the complete syndrome.

Grundy P, Telzerow P, Paterson MC, et al. *Lancet* 1991;338:1079-1080.

Editor's comment: *In addition to providing further support for the theory of genomic imprinting, this case also shows us that patients with hemihypertrophy may carry uniparental disomy for particular chromosomal segments, and that this can cause loss of tumor suppression and increase the risk of these patients for developing malignant tumors. These observations may provide a means of identifying those patients with hemihypertrophy who are at risk for malignancy.*

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