Letters to the Editor

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Genomic Imprinting and the Beckwith-Wiedemann Syndrome

To the Editor:

It has recently been reported in the *Journal* that the gene for the Beckwith-Wiedemann syndrome (BWS) is located at 11p15.5, by demonstrating linkage in inherited cases (Koufos et al. 1989; Ping et al. 1989). In addition, duplications of 11p15 have been demonstrated in some sporadic cases (Waziri et al. 1983; Turleau et al. 1984; Journel et al. 1985; Wales et al. 1986; Henry et al. 1989; authors' unpublished data), and this region of 11p is also involved in some Wilms tumors, since a subset show loss of heterozygosity of alleles at 11p15 but not at 11p13 (Koufos et al. 1989; Reeve et al. 1989).

In inherited cases, the manifestations of BWS are usually only apparent when the mutated gene is inherited from the mother, which led Koufos et al. (1989) to suggest that the paternally transmitted allele at the BWS locus is always functionally inactivated (by imprinting); offspring are then only affected if they inherit a mutation from their mother.

In surveying reported cases of 11p15 duplications in BWS (Waziri et al. 1983; Turleau et al. 1984; Journel et al. 1985; Wales et al. 1986; Henry et al. 1989), together with one case of our own (authors' unpublished data), we have noted that in all six cases where the parental origin of the duplicated material can be ascertained, it is always of paternal origin. This finding is difficult to reconcile with the hypothesis of Koufos et al., since it is hard to explain why the duplication of a functionally inactive allele should have any phenotypic effect. We therefore wish to propose an alternative model, which is consistent both with the recent findings in BWS and with the loss of maternal 11p alleles observed in Wilms tumor (including one case from a BWS patient; Schroeder et al. 1987; Mannens et al. 1988; Williams et al. 1989). We suggest that the BWS locus may indeed be an imprinted gene but that it is one in which at some stage during fetal development the paternal allele is relatively more active than the maternal allele. We propose that in BWS the normal imprinting is overridden, either by inactivation of the maternal allele by mutation or by an increase in the relative activity of the paternal allele by gene duplication. This would effectively fix the gene in a state which is normally only transient and would therefore cause the overgrowth that characterizes the syndrome. In Wilms tumors, the loss of maternal alleles would have a similar effect.

This hypothesis fits well with the consistent loss of maternal alleles observed in Wilms tumor and suggests that the BWS gene may be equivalent to the "transforming" gene postulated in Wilkin's model of imprinting in Wilms tumor (Wilkins 1988).

With the recent definitive mapping of the BWS locus to 11p15.5 (Koufos et al. 1989; Ping et al. 1989), it should now be possible to clone the gene and thereby to test the validity of these various hypotheses.

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Proficiency Testing for Biochemical Genetics Laboratories: The First 10 Rounds of Testing

To the Editor:

The laboratory diagnosis of inherited metabolic disorders has evolved from a highly specialized activity, carried out mostly by a few—predominantly university-affiliated—biochemical geneticists, to a more generally accepted and practiced part of the workup of a patient. Associated with this maturation is the institutionalization of procedures, the licensing of laboratories, directors and personnel, and quality control and proficiency testing. It still is a highly specialized activity with its own set of rules, which sets it clearly apart from classical clinical chemistry, especially in the areas of interpretation of the analytical results (Wadman in press) and of the transmission of the analytical results to the requester (Wright and Warren in press).

The Southeastern Regional Genetics Group (SERGG), covering Maternal and Child Health Region IV plus Louisiana, decided in 1984 to start a pilot project on proficiency testing for biochemical genetics laboratories. Supported by a grant from the genetics branch of the Bureau of Maternal and Child Health, Department of Health and Human Services, the program started in January 1985, with 11 laboratories participating. (Currently, after 13 rounds of testing, 50 laboratories are participating in the program).

The areas surveyed are amino acids, glycosaminoglycans, and organic acids. Each test kit contained (1) a synthetic mixture of amino acids, to be analyzed quantitatively, (2) a plasma sample and a short clinical description of the case, to be analyzed quantitatively, (3) a urine sample and a short clinical description of the case, to be analyzed qualitatively for glycosaminoglycans, and (4) a urine sample and a short clinical description of the case, to be analyzed for organic acids. The laboratories were requested to report back within 2 wk of receiving the test kit, stating their analytical results as well as giving a presumed diagnosis, if the