Discovery of the Rett syndrome gene and its function*

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Rett syndrome (RTT) is a neurodevelopmental disorder which affects approximately 1/15,000 liveborn females. Normal development for the first 6-18 months of life is followed by progressive neurological deterioration, such as loss of communication skills and purposeful hand use, the appearance of stereotypic hand wringing movements, seizures, acquired microcephaly, and mental retardation. The majority of cases are sporadic, but a few families with multiple affected females related through females suggested a genetic defect, in particular, an X-linked dominant mutation that may be lethal in hemizygous males.

Work on the identification of the RTT gene was done in collaboration with the laboratory of Huda Zoghbi at Baylor College of Medicine. First, the RTT gene was assigned to chromosome band Xq28 by exclusion mapping studies of the few available families. Candidate genes in this region were systematically tested for any changes in individuals affected with RTT, and a number of them were excluded. In 1999, our search was successful: we identified mutations in the MECP2 gene[1] MECP2 encodes a ubiquitously expressed abundant chromosomal protein, methyl-CpG-binding protein 2, which binds specifically to methylated DNA and is thought to inhibit the expression of other genes. Loss of MECP2 function in RTT patients could lead to inappropriate expression or over-expression of those genes in specific tissues. Missense or truncating mutations in the MECP2 gene have now been found in over 70 percent of classic RTT patients, as well as in some altypical RTT patients and in a male with congenital encephalopathy[2]. We have developed a molecular diagnostic test to confirm the clinical diagnosis of RTT. Genotype/phenotype correlations, however, are not straight-forward, they need to take into account the modulating influence of X chromosome inactivation mosaicism. Attempts to discover the targets of MeCP2-mediated gene silencing and their role in RTT pathogenesis are under way by using gene expression microarray technology.

REFERENCES

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