

## The Rett Syndrome Gene Silences Many Other Genes

Rett syndrome is a common cause of mental retardation in females, with an incidence of 1 per 10,000. It is characterized by normal development until 6 to 18 months of age when there is regression, including loss of speech, hand-wringing, seizures, autism, ataxia, hyperventilation, and, often, growth retardation. The phenotype is very characteristic; however, most cases are sporadic and it is never observed in males. The hypothesis was that it was an X-linked dominant disorder, lethal in hemizygous males. Familial cases had been localized and linked to the tip of the long arm of the X chromosome in the Xq28 region. Amir et al have reported finding mutations in the *MECP2* gene in 6 sporadic cases and 1 familial case of Rett syndrome. The responsible gene, *MECP2*, encodes a methyl-CpG-binding protein that selectively binds CpG dinucleotides and mediates transcription from a variety of genes by repressing the interaction with histone deacetylases. Thus, the Rett syndrome gene is probably a key player in silencing other genes. In other words, the gene normally plays a role in assembling transcription silencing complexes. However, if these complexes are not working at a specific stage in development, then the genes will continue to make proteins that apparently clog up normal processes and lead to the intellectual degeneration of affected females. The recognition of the *MECP2* gene as being responsible for Rett syndrome is the first time a human disease has been determined to be caused by a defect in a protein that involves DNA methylation and, thus, when the protein is absent or not working, leads to abnormal chromatin packaging and abnormal gene expression. Interestingly, the gene is particularly expressed in the brain, and thus it would appear that the brain is particularly sensitive to an excess of transcribed proteins. Undoubtedly, there will be other such genes but it is a real

breakthrough in understanding abnormalities in developmental time-specific processes.

Willard HF, et al. *Nat Genet* 1999;23:127-128.

Amir RE, et al. *Nat Genet* 1999;23:185-188.

**Editor's comment:** *The Human Genome Project is revealing many genes with no previously described homologies, as well as demonstrating many new, previously unknown processes. It is reassuring to have the gene responsible for a common syndrome defined, but surprising to find it affects many other genes in a specific developmental way. In the process of a child's development, there must be many other episodes of switching on and off. Interestingly, the mouse model for MECP2 deficiency also is X-linked and affected males do not develop at all since it leads to male lethality. Because the human cases are mostly sporadic, the effect of male lethality has not been observed. It seems quite possible that if affected girls could be recognized in the newborn period, some type of therapy could be developed.*

Judith G. Hall, OC, MD

**2nd Editor's comment:** *These articles describe a novel pathogenetic mechanism for genetic disease in humans. If the speculation proves correct, Rett syndrome results from at least partial failure of a global process that keeps transcription in check. As Amir, Willard, and their colleagues emphasize, much more work will be needed to prove the theory, and it will likely turn out to be much more complicated than outlined here. Nevertheless, it is an exciting development in medical genetics.*

William A. Horton, MD

## Chromosome 7p Maternal Duplication With Features of Silver-Russell Syndrome

Maternally uniparental disomy of chromosome 7 is present in about 10% of Silver-Russell syndrome (SRS) individuals, suggesting there is a gene or genes that are imprinted on chromosome 7. Growth-related genes on chromosome 7, including *GRB10* (a growth factor receptor-bound protein), *EGFR* (epidermal growth factor receptor), and *IGFBP1* (insulin-like growth factor-binding protein 1), have all been suggested as candidate genes. However, molecular analysis of a duplication present in both mother and daughter who have SRS shows that it includes *GRB10* and *IGFBP1* (but not *EGFR*), suggesting that one or both of these are the culprits involved in the phenotypic effects.

a result of small duplications or undetected trisomy. Investigations of these possibilities may reveal the nature of the genetic abnormalities underlying this disorder.

Joyce CA, et al. *Hum Genet* 1999;105:273-280.

**Editor's comment:** *SRS is a very common cause of intrauterine growth retardation and subsequent short stature. Its etiology is undoubtedly heterogeneous and is beginning to be unraveled. This article contributes significantly to that task.*

Judith G. Hall, OC, MD

The authors summarize:

We have characterized a duplication of 7p12.1-p13 in a mother and daughter who both show features associated with SRS. It seems likely that a gene or genes contained within this region are responsible for at least some of the SRS features and that, in our patients, duplication of additional contiguous genes has resulted in a slightly atypical SRS phenotype. In contrast to current thinking, which favors the involvement of imprinted genes, we hypothesize that SRS may be caused by the inheritance of an additional copy of chromosome 7 material, either as

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