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Mouse *Mecp2*knockouts and Rett syndrome

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Rett syndrome, an inherited neurological disorder, is one of the most common causes of mental retardation in females. Babies with Rett syndrome develop normally until 6-18 months, at which point they show a reduction in brain size and become prone to seizures and autism. The syndrome is caused by a mutation in the *MECP2* gene, which maps to the X chromosome. Females with one intact copy of the gene survive until adulthood, despite the neurological symptoms. Male embryos that carry the mutation die during development. The *MECP2* gene encodes the methyl-CpG-binding protein 2, which binds to methylated sites in the genome and represses transcription of adjacent genes.

Two groups, one led by Adrian Bird of the University of Edinburgh, and the other by Rudolf Jaenisch of the Whitehead Institute for Biomedical Research, Massachusetts, report in March *Nature Genetics* that mice having mutations in the *Mecp2* gene - the equivalent of the human *MECP2* gene in humans - have neurological symptoms that resemble Rett syndrome (*Nat Genet* 2001, **27:**322-326; 327-331).

Both groups generated *Mecp2*-null mice using gene targeting techniques in mouse embryonic stem cells to delete key *Mecp2* exons. The Jaenisch group deleted exon 3, which encodes most of the methyl-CpG-binding domain, whereas the Bird group deleted exons 3 and 4. Both groups also generated mice in which the *Mecp2* deletion was trigged only in the embryonic brain using Cre-*loxP* technology. In either case, the only abnormalities were found in the brain, suggesting that Mecp2 is not essential outside the central nervous system. This is surprising given the widespread expression of Mecp2 and its role as a general repressor of transcription.

The mutant brains showed substantial reduction in weight and neuronal cell size, features characteristic of Rett syndrome. When the Jaenisch group triggered the *Mecp2* deletion at an even later stage and only in post-mitotic neurons, the phenotype was similar. This result may indicate that Rett syndrome is not caused by abnormal brain development but rather by the absence of continuous MECP2 function in mature neurons.

References

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