Rett UK
25 years closer to the cure

Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2

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"Rett syndrome is a devastating disease. Think about what it takes to function normally: You have to be coordinated, you must be able to think, you have to be able to communicate, and you need to move smoothly and with balance. The symptoms of other neurological diseases affect some of these functions but Rett syndrome affects them all.

Dr. Huda Zoghbi

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Abstract

Rett syndrome[1] (RTT, MIM 312750) is a progressive neurodevelopmental disorder and one of 15,000 (ref. 2). Patients with classic RTT appear to develop normally until 6–18 months of age, then gradually lose speech and purposeful hand use, and develop microcephaly, seizures, autism, ataxia, intermittent hyperventilation and stereotypic hand movements[3]. After initial regression, the condition stabilizes and patients usually survive into adulthood. As RTT occurs almost exclusively in females, it has been proposed that RTT is caused by an X-linked dominant mutation with lethality in hemizygous males[3, 4, 5, 6, 7, 8]. Previous exclusion mapping studies using RTT families mapped the locus to Xq28 (refs 6,9,10,11). Using a systematic gene screening approach, we have identified mutations in the gene (*MECP2*) encoding X-linked methyl-CpG-binding protein 2 (MeCP2) as the cause of some cases of RTT. MeCP2 selectively binds CpG dinucleotides in the mammalian genome and mediates transcriptional repression through interaction with histone deacetylase and the corepressor SIN3A (refs 12,13). In 5 of 21 sporadic patients, we found 3 *de novo* missense mutations in the region encoding the highly conserved methyl-binding domain (MBD) as well as a *de novo* frameshift and a *de novo* nonsense mutation, both of which disrupt the transcription repression domain (TRD). In two affected half-sisters of a RTT family, we found segregation of an additional missense mutation not detected in their obligate carrier mother. This suggests that the mother is a germline mosaic for this mutation. Our study reports the first disease-causing mutations in RTT and points to abnormal epigenetic regulation as the mechanism underlying the pathogenesis of RTT.