

Explanations for males with MECP2-related disorders

1. Males with Rett syndrome and Klinefelter syndrome: There have been rare males reported with the typical history of classic Rett syndrome. These males have also had an unrelated genetic disorder known as Klinefelter syndrome. In Klinefelter syndrome, males have two copies of the X chromosome and one copy of the Y chromosome; thus, they have an extra chromosome giving them a chromosomal designation of 47,XXY. Klinefelter syndrome is relatively common, appearing in roughly 1 in 500 males. Thus, it is not unexpected that occasionally an individual will have both Klinefelter syndrome and a mutation in the MECP2 gene as two unrelated events. Because these males have two copies of the X chromosome and undergo the same process of X inactivation that is seen in females, these males present with a clinical presentation that is very consistent with the classic Rett syndrome presentation. These males, will in addition to having the clinical features of Rett syndrome, also have features of Klinefelter syndrome, including underdevelopment of the genitalia and underproduction of sex hormones.
2. Mosaicism as a cause of Rett syndrome in males: Mosaicism basically is a term defining a mixture of two different populations of cells. There have been very rare reports of males with Rett syndrome on the basis of mosaicism. These males have a mixture of two cell types. They have some cells with one X chromosome with one MECP2 gene that is functioning normally. In other cells of the body they have one X chromosome with a MECP2 gene that has a mutation that is affecting the function of the MECP2 gene. Depending on the percentage of the mixture of these two cell types, these males will have clinical features similar to females with classic Rett syndrome. This mosaicism occurs by a mutation that occurs after conception but early in embryologic development. The timing of the occurrence of this mutation will determine the percentage of cells affected by the mutation.
It should be noted that basically, at the cellular level, all females are mosaic for the function of the MECP2 gene.
3. MECP2-related severe neonatal encephalopathy: Males that have one of the mutations that are typically seen in Rett syndrome usually present with earlier onset and more severe symptoms than females. Again, this is because this mutation in the MECP2 gene is affecting all the cells in the male. Most of these males present with early onset breathing problems, early onset feeding problems, and early onset seizures. Without aggressive medical care most of these males with typical MECP2 gene mutations pass away in the first year of life. However, with aggressive medical intervention, these males can survive into late childhood. They frequently require significant medical support, including nutritional and breathing support.
4. Males with MECP2 mutations and milder presentations (MECP2-related disorders): With increased sequencing of the MECP2 gene, males are being identified with mutations in the MECP2 gene outside of the regions of the gene that are usually associated with classic Rett syndrome in females. These mutations in the MECP2 gene may present with a male with intellectual disability or milder learning problems and behavioral problems, but not classic or atypical Rett syndrome. Some of these mutations, when seen in females, may present with no clinical features or very mild clinical features. It is thought that these mutations in certain regions of the MECP2 gene do not cause significant disruption of the function of the MECP2 gene, and, thus, result in milder symptoms.