

MECP2 Gene Analysis in Rett Syndrome, Atypical Rett Syndrome and Progressive Neurodevelopmental Syndrome in Males

Clinical Features:

Rett syndrome is a progressive, neuro-developmental disorder that affects approximately 1 in 10,000 females. Classic Rett syndrome is diagnosed based on a defined set of clinical criteria and characterized by apparently normal development in the first 6-18 months, followed by an arrest in development and subsequent regression in language and motor skills. Frequent symptoms include loss of speech and purposeful hand use, stereotypic hand movements, ataxia, microcephaly, and seizures. “Atypical” Rett syndrome can be milder or more severe than typical Rett syndrome and is diagnosed when some but not all clinical criteria for Rett syndrome are present. The milder form may include mental retardation, mild learning disabilities and/or autism. Variants in the MECP2 gene have been found to cause Rett syndrome and “atypical” Rett syndrome in females. In males, MECP2 variants are not as common and responsible for a broad spectrum of neurodevelopmental phenotypes, ranging from severe neonatal encephalopathy to a variety of neuropsychiatric features or mild mental retardation.^{1,12} Rarely, males with a progressive neurodevelopmental syndrome, including mental retardation, spasticity, speech and social problems, have been found to have a duplication or triplication of the MECP2 gene.^{2,3}

Genetics:

X-linked dominant, most cases are due to de novo variants

Test Methods:

Analysis is performed by bi-directional sequencing of the 4 exons and the exon/intron splice sites of the MECP2 gene. In females, where sequencing cannot detect large deletions, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. ExonArrayDx is also offered to detect a MECP2 duplication in affected males (MECP2 duplication syndrome). Variants are confirmed by repeat analysis using sequencing, restriction fragment analysis, or quantitative PCR as appropriate.

Test Sensitivity:

DNA sequencing is expected to identify a pathogenic variant in the MECP2 gene in 60% to almost 90% of females with Rett syndrome. In addition, approximately 7-10% of female Rett patients have a deletion involving one or more exons of MECP2, which can be detected by ExonArrayDx deletion/duplication analysis.^{4,5} This assay is also suitable to identify duplication or triplication of the MECP2 gene, which has been reported in males with severe neuro-developmental delay.² Overall, 1.3-1.7% of males with mental retardation were found to have a

disease-causing MECP2 duplication/triplication or MECP2 variants identifiable by sequencing.¹² MECP2 variants identifiable by sequencing have been also reported in patients with atypical Rett syndrome,⁶ Angelman syndrome-like features,⁷ mental retardation with seizures, or mild learning disabilities.^{8,9} Among all patients with non-syndromic autism or autism spectrum disorders, MECP2 variant account for 3-13% of female cases.^{10,11}

References:

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