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. Rett syndrome is caused by mutation or deletion in the MECP2 gene located on chromosome Xq28. MECP2 encodes the methylCpG binding protein 2 transcriptional repressor, which binds and thereby silences other genes that are controlled via methylation of CpG islands. Thus, the loss of MECP2 function impairs the normal control mechanisms for gene transcription. As duplication of the MECP2 locus in males is also associated with a progressive neurodevelopmental delay, it appears that the correct gene dosage of MECP2 protein is critical for normal behavior.

To date, more than 200 mutations have been reported in the MECP2 gene, including 7 recurrent mutations that together account for two-thirds of the cases. 5-10% of cases are due to frameshift mutations leading to premature protein truncation at the carboxy-terminal end of the MECP2 protein. Emerging genotype-phenotype correlations suggest that certain mutations may produce a milder phenotype (R133C, R294X, C-terminal truncations) than others (R168X, R270X, R255X, large gene deletions). Approximately 10% of female patients have a partial or whole deletion of the MECP2 gene, including one or more exons of MECP2 and sometimes a neighboring gene (IRAK1). Rare gene duplications were found in males with neurodevelopmental delay. 2,4,5 Of note, a few females with a classic Rett syndrome
phenotype had two different de novo disease-causing mutations in MECP2, presumed to be located on the same allele (in cis). 13

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. 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. 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. MECP2 variants identifiable by sequencing have been also reported in patients with atypical Rett syndrome, Angelman syndrome-like features, mental retardation with seizures, or mild learning disabilities. Among all patients with non-syndromic autism or autism spectrum disorders, MECP2 variant account for 3-13% of female cases.

References:
2. del Gaudio et al. Gene Med 8:784-792, 2006;