MECP2 Gene Analysis in Rett Syndrome and Other MECP2-Related Disorders

Clinical Features:

Rett syndrome is a progressive, neurodevelopmental disorder that affects approximately 1 in 10,000 females.[1,2] Classic Rett syndrome is diagnosed based on a defined set of clinical criteria and is 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.[1,2] 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.[1,2] The milder form may include intellectual disability, mild learning disablilities and/or autism.

In males, MECP2 variants are responsible for a broad spectrum of neurodevelopmental phenotypes, ranging from severe neonatal encephalopathy to syndromic and nonsyndromic forms of intellectual disability.[1] Rarely, males with a progressive neurodevelopmental syndrome including intellectual disability, spasticity, speech delay, and social problems have been found to have a duplication or triplication of the MECP2 gene.[1]

Genetics:

The MECP2 gene is located on chromosome Xq28 and encodes the methylCpG binding protein 2 transcriptional repressor, which binds and thereby silences other genes that are controlled via methylation of CpG islands.[3] Thus, the loss of MECP2 function impairs the normal control mechanisms for gene transcription.

Most variants in the MECP2 gene are missense or nonsense variants, frameshifts, or large deletions. Eight recurrent pathogenic variants account for more than half of cases.[4] Up to 10% of female patients have a deletion including one or more exons of MECP2 and sometimes a neighboring gene (IRAK1).[4] Studies of genotype-phenotype correlation suggest that certain variants (R133C, R294X, C-terminal truncations) are associated with a less severe phenotype, while other variants (R168X, R270X, R255X, large gene deletions) are more likely to be associated with a severe clinical presentation.[5,6]

The majority of MECP2 variants are de novo, although inheritance from an unaffected parent with gonadal mosaicism has been reported.[1] In rare cases, a pathogenic MECP2 variant may be inherited from a mother with highly skewed X-chromosome inactivation who has no features of Rett syndrome or only mild learning disabilities.[1]

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the MECP2 gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

DNA sequencing is expected to identify a pathogenic variant in the MECP2 gene in up to 90% of females with classic Rett syndrome, with a lower detection rate in females with atypical Rett syndrome.[1,4] Rarely, males with intellectual disability are found to have a MECP2 duplication/triplication or a pathogenic MECP2 variant identifiable by sequencing.[1] MECP2 variants identifiable by sequencing have been also reported in males and females with atypical Rett syndrome, Angelman syndrome-like features, autism, and/or mild learning disabilities.[1]

References:
1. Kaur et al. MECP2 Disorders. 2001 Oct 3 [Updated 2019 Sep 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. (Available from: https://www.ncbi.nlm.nih.gov/books/NBK1497/) (PMID: 20301670)
2. Neul et al. Rett syndrome: revised diagnostic criteria and nomenclature. Annals Neurol 2010 Dec 68(6):944-50 (PMID: 21154482)
3. Lombardi et al. MECP2 disorders: from the clinic to mice and back. J of Clin Invest. 2015 Aug 03 125(8):2914-23 (PMID: 26237041).
4. Percy et al. Rett syndrome: North American database. J of Child Neurol. 2007 Dec 22(12):1338-41 (PMID: 18174548).
5. Bebbington et al. Investigating genotype-phenotype relationships in Rett syndrome using an international data set. Neurol. 2008 70(11):868-75 (PMID: 18332345).
6. Neul et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurol. 2008 70(16):1313-21 (PMID: 1833758)