Rett Syndrome and *MECP2*-Related Disorders

Indications for Ordering

- Confirm clinical diagnosis of Rett syndrome or *MECP2*-related disorder
- Determine cause of severe neonatal encephalopathy or intellectual disability in males
- Rule out *MECP2* variant in individuals with clinical features of Angelman syndrome who lack a molecular abnormality involving 15q11.2-13

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of the *MECP2* coding region (exons 1-4) and intron/exon boundaries
- Multiplex ligation-dependent probe amplification to detect large deletions/duplications in *MECP2* coding regions (exons 1-4)

Tests to Consider

Testing strategy

Consultation with a genetic counselor is recommended to plan the optimal *MECP2* genetic testing sequence

- Sequencing
  - Consider for **females** with
    - Classic or atypical Rett syndrome
    - Nonspecific intellectual disability
    - Autism
    - Clinically suspected, but molecularly unconfirmed, Angelman syndrome
  - Consider for **males** with
    - Unexplained neonatal encephalopathy
    - Nonspecific intellectual disability
    - Phenotype of Rett syndrome (classic or atypical)
    - Manic-depressive psychosis, pyramidal signs, Parkinsonian and macroorchidism (PPM-X syndrome)
    - Clinically suspected, but molecularly unconfirmed, Angelman syndrome
- Deletion/duplication
  - Consider for **females** when suspicion for classic or atypical Rett syndrome remains despite negative *MECP2* sequencing result
  - Consider for **males** with suspected *MECP2* duplication syndrome
    - Severe developmental delay/intellectual disability and a history of recurrent infections, swallowing dysfunction, hypotonia, spasticity, limited speech, and limited ambulation

Primary tests

Rett Syndrome (*MECP2*), Sequencing and Deletion/Duplication 0051614

- Preferred initial test for females with a phenotype of classic or atypical Rett syndrome
- Detects up to 95% of *MECP2* pathogenic variants

Rett Syndrome (*MECP2*), Full Gene Sequencing 0051378

- Acceptable first-tier diagnostic test for females with a phenotype of classic or atypical Rett syndrome

Related tests

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

CDKL5-Related Disorders (*CDKL5*) Sequencing and Deletion/Duplication 2004935

- May be useful for individuals with early-onset seizures and intellectual disability when *MECP2* full-gene analysis fails to detect a pathogenic variant

Disease Overview

Rett syndrome

Incidence

- 1/10,000-15,000 female births

Clinical diagnostic criteria (Neul, 2010)

- Required for classic (typical) Rett syndrome
  - Period of regression followed by recovery or stabilization
  - All main criteria
  - Supportive criteria are not required, although are often present in classic Rett
- Required for atypical Rett
  - Period of regression followed by recovery or stabilization
  - At least 2 of the 4 main criteria
  - 5 of 11 supportive criteria
- Main criteria
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language
  - Gait abnormalities (impaired or absence of ability)
  - Stereotypic hand movements (wringing/squeezing, clapping/tapping, washing/rubbing, and mouthing of hands)
- Supportive criteria
  - Breathing disturbances when awake
  - Bruxism when awake
  - Impaired sleep pattern
  - Abnormal muscle tone
  - Peripheral vasomotor disturbances
  - Scoliosis/kyphosis
  - Growth retardation
  - Small, cold hands and feet
  - Inappropriate laughing/screaming spells
  - Diminished response to pain
  - Intense eye communication

Clinical phenotype – highly variable

Influenced by the patient's sex, age, the specific *MECP2* variant and, in females, the X-inactivation pattern

MECP2 duplication syndrome

Incidence

- 1-2% of males with severe neonatal encephalopathy or moderate to severe intellectual disability
- Female carriers tend to be asymptomatic

Clinical phenotype – suspected in males with

- Severe intellectual disability
- Limited/lack of speech
- Early-onset hypotonia
- Progressive spasticity
- Seizures
- Recurrent respiratory infections
- Limited/lack of ambulation

Genetics

Gene – *MECP2*

Inheritance – X-linked dominant

- 99.5% of cases are sporadic

Penetrance

- Nearly 100% in females
- Female variant carriers may be asymptomatic as a result of highly skewed X-inactivation
- Disruption of *MECP2* in males is usually lethal

Variants – >350 are known

- Sequence variants
  - Classic Rett syndrome – detected in ~80% of affected individuals
  - Atypical Rett syndrome – detected in ~40% of affected individuals
  - Majority of *MECP2* sequence variants occur in exon 4
- Deletions/duplications
  - Large deletions most commonly involve exon 3 and/or exon 4 of *MECP2*
  - Large deletions account for ~8% of classic Rett syndrome and ~3% of atypical Rett syndrome
  - Males with whole-gene duplications are clinically affected

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - Classic Rett syndrome
    - Sequencing – ~80% (Fukuda, 2005; Li, 2007)
    - Deletions/duplications – ~8-10% (Archer, 2006; Li, 2007)
  - Atypical Rett
    - Sequencing – ~40% (Fukada, 2005; Li, 2007)
    - Deletions/duplications – ~3% (Archer, 2006)
- Analytical sensitivity
  - Sequencing – 99%
  - Deletions/duplications – 90%
- Analytical specificity
  - Sequencing – 99%
  - Deletions/duplications – 98%

Results

- Positive – pathogenic variant identified
  - Diagnosis confirmed
- Negative – no pathogenic variant identified
  - Possibility of an *MECP2*-related disorder is decreased, but not excluded
- Inconclusive – gene variant detected
  - Unknown whether variant is pathogenic or benign

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not detected
  - Breakpoints of large deletions/duplications
  - Regulatory region and deep intronic variants

References

- Archer HL, Whatley SD, et al. Gross rearrangements of the MECP2 gene are found in both classical and atypical Rett syndrome patients. J Med Genet. 2006;43(5):451-456
- Fukuda T, Yamashita Y, et al. Methyl-CpG binding protein 2 gene (MECP2) variations in Japanese patients with Rett syndrome: pathological mutations and polymorphisms. Brain Dev. 2005;27(3):211-217
- Li MR, Pan H, et al. MECP2 and CDKL5 gene mutation analysis in Chinese patients with Rett syndrome. J Hum Genet. 2007;52(1):38-47
- Neul JL, Kaufmann WE, et al. Rett syndrome: revised diagnostic criteria and nomenclature**.** Ann Neurol. 2010;68(6):944-950