Rett Syndrome Testing

Introduction

Rett syndrome testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is Rett syndrome

Definition

Rett syndrome, or classic Rett syndrome, is an X-linked brain development disorder that typically affects females. Atypical Rett syndrome may be more mild or severe than classic Rett syndrome.

Prevalence

Rett syndrome affects about 1 in 8,500 females by age 15. Males are rarely affected with less than 100 overall affected patients reported.¹

Symptoms

Girls with Rett syndrome may not show signs at birth or during infancy, but by the age of 6 to 18 months they begin to lose their motor and language skills, which eventually stabilizes.¹

Signs and symptoms of Rett syndrome usually include ¹,²

• intellectual disability or developmental delay
• specific hand movements, like hand “wringing” and clapping for no reason
• loss of speech

¹ References:
² References:
• problems with sleep
• seizures
• growth failure
• autistic behaviors, and
• gait abnormalities, either impaired or complete absence of ability.

Cause

Rett syndrome is caused by genetic changes (mutations) in the MECP2 gene, located on the X chromosome. Females have two X chromosomes and males have one X chromosome and one Y chromosome.\textsuperscript{1}

Inheritance

Rett syndrome is an X-linked condition. A female who is found to be a MECP2 mutation carrier has a 50% chance to pass the mutation to her children. Approximately 99% of cases of Rett syndrome are the result of a new genetic change (de novo) in the affected person and are not inherited from a carrier parent.\textsuperscript{1-3} Cases of minimally affected or unaffected female carriers of MECP2 mutations have been reported.\textsuperscript{1-4}

Cases of MECP2 mutations in only the germline (egg or sperm) of parents of affected people have been reported.\textsuperscript{1-3} In one study, prenatal diagnosis was offered to nine couples who had a previous child with Rett syndrome due to a known de novo MECP2 mutation.\textsuperscript{3} One of the nine pregnancies was found to have the same MECP2 mutation as in the affected sibling.\textsuperscript{3} Since germline mosaicism cannot be predicted or ruled out in families who have a child with Rett syndrome, prenatal diagnosis may be offered.

If a mutation of unclear significance is found in an affected person, testing both the mother and the father may be appropriate to help to determine whether the mutation is actually causing the disease.\textsuperscript{1}

Diagnosis

Classic Rett syndrome is generally diagnosed by established clinical diagnostic criteria.\textsuperscript{1,2} Diagnostic criteria have also been suggested for atypical Rett syndrome, but diagnostic criteria are imperfect for reliably diagnosing Rett syndrome.\textsuperscript{1,2}

Genetic testing may be useful to confirm a diagnosis (particularly when unclear based on clinical criteria) and to identify the mutation for genetic counseling purposes.

MECP2 mutation

The presence of a mutation in the MECP2 gene alone does not diagnose Rett syndrome. MECP2 mutations may cause conditions other than Rett syndrome.\textsuperscript{1} Conversely, some people who meet the clinical diagnostic criteria for Rett syndrome do not have an identifiable MECP2 mutation.\textsuperscript{1}
When a male has a MECP2 mutation, he has no second normal copy of the gene to help lessen the effect of the mutation. This mutation can cause a severe disease called neonatal encephalopathy and these boys usually die before 2 years of age. Surviving males generally have an abnormal gait or truncal movements, severe speech delay, and intellectual disability.

Diagnostic criteria

Typical or classic Rett (RTT)

- A period of regression followed by recovery or stabilization*
- All main criteria and all exclusion criteria
- Supportive criteria are not required, although often present in typical RTT

Atypical or variant Rett

- A period of regression followed by recovery or stabilization*
- At least 2 out of the 4 main criteria
- 5 out of 11 supportive criteria

Main criteria

- Partial or complete loss of acquired purposeful hand skills.
- Partial or complete loss of acquired spoken language or language skills**
- Gait abnormalities: impaired (dyspraxic) or absence of ability.
- Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms

Exclusion criteria for typical Rett

- Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems***
- Grossly abnormal psychomotor development in first 6 months of life#

Supportive criteria for atypical RTT

- 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 - “eye pointing”

“*Because MECP2 mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of “possible” RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6–12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite RTT. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned.*

“**Loss of acquired language is based on best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language.”

“***There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction.”

“#Grossly abnormal to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met. Mild generalized hypotonia or other previously reported subtle developmental alterations16 during the first six months of life is common in RTT and do not constitute an exclusionary criterion.”

“##If an individual has or ever had a clinical feature listed it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and ≥2 main criteria but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of “probably atypical RTT” may be given. Individuals who fall into this category should be reassessed as they age and the diagnosis revised accordingly.”5

Treatment

Treatment for Rett syndrome is based on the symptoms and usually involves therapies to help with movement and communication.1 Medications can control difficult behavior and seizures, when present.1

People with Rett syndrome are at risk for an irregular heart rhythm (arrhythmia). They may need heart monitoring and should avoid certain drugs that are known to affect the heart rhythm.1
Test information

Introduction

Testing for Rett syndrome may include MECP2 sequencing, deletion/duplication analysis, or known familial mutation analysis.

Sequence analysis

MECP2 sequencing identifies an MECP2 gene mutation in about 80% of people with classic Rett syndrome and 40% of people with atypical Rett syndrome.¹

Deletion/duplication analysis

When MECP2 gene sequencing is normal, deletion and duplication analysis can be performed to look for other types of gene mutations. About 8% of people with classic Rett syndrome and 3% of people with atypical Rett syndrome have an MECP2 gene deletion.¹

Known familial mutation analysis

If a pathogenic MECP2 mutation is found in an affected person, then other family members may be offered testing.¹ Prenatal testing is available when the MECP2 mutation in the family is known.¹

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Rett syndrome testing.

National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE) released evidence-based guidelines entitled *Autism spectrum disorder in under 19s: recognition, referral and diagnosis* in 2011 (updated in 2017). These guidelines state that Rett syndrome should be considered as a type of developmental regression. Genetic testing for such conditions should be considered on an individual basis.⁴

American Academy of Pediatrics

The consensus guideline from the American Academy of Pediatrics (2014)⁶ on the clinical genetic evaluation of a child with intellectual disability (ID) or global developmental delays (DD) and the American College of Medical Genetics (ACMG)⁷ 2013 Practice Guidelines for identifying the etiology of autism spectrum disorders state that:
“If the diagnosis is unknown and no clinical diagnosis is strongly suspected, begin with a stepwise evaluation including: chromosome microarray, specific metabolic testing, and Fragile X syndrome testing. If no diagnosis is established and the patient is female, then MECP2 sequencing, deletion, and duplication testing is appropriate.”

Criteria

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Requests for Rett syndrome testing are reviewed using these criteria.

MECP2 Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of MECP2, and
  - MECP2 mutation identified in 1st degree biologic relative, OR
- Prenatal Testing for At-Risk Pregnancies:
  - MECP2 mutation identified in a previous child of either parent.

MECP2 Sequencing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous MECP2 sequencing, and
  - No known MECP2 mutation in family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member meets clinical diagnostic criteria for classic Rett syndrome, atypical Rett syndrome, or has probable Rett syndrome, or
  - Member meets all of the following:
    - Female with a formal diagnosis of autism, and
    - Previous Fragile X testing has been performed and is negative, and
• Previous chromosome microarray has been performed and is negative, and
  o Genetic testing is necessary because there is uncertainty in clinical diagnosis

MECP2 Deletion/Duplication Analysis

• Previous testing:
  o No previous deletion/duplication analysis of MECP2, and
  o No mutations detected in full sequencing of MECP2.

References

Introduction

These references are cited in this guideline.


