Test Specific Guidelines

Rett Syndrome Genetic Testing

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Introduction

Rett syndrome genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Genomic Unity MECP2 Analysis	0234U
MECP2 Deletion and Duplication Analysis	81304
MECP2 Known Familial Mutation Analysis	81303
MECP2 Sequencing	81302

What Is Rett Syndrome?

Definition

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

Prevalence

Rett syndrome affects about 1:10,000 to 1:23,000 female births worldwide. Males are rarely affected.[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]

regression and then stabilization of both language and motor milestones

intellectual disability or developmental delay stereotypic hand movements, like hand wringing, clapping, and mouthing

loss of speech

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.[1]

MECP2 sequencing identifies a MECP2 gene mutation in the majority of individuals with classic Rett syndrome.[1]

When MECP2 gene sequencing is normal, deletion and duplication analysis can be performed to look for other types of gene mutations.[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.[1-3] Cases of minimally affected or unaffected female carriers of MECP2 mutations have been reported.[1-4]

Cases of MECP2 mutations in only the germline (egg or sperm) of parents of affected people have been reported.[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.[3] One of the nine pregnancies was found to have the same MECP2 mutation as in the affected sibling.[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.[1]

Diagnosis

Classic Rett syndrome is generally diagnosed by established clinical diagnostic criteria.[1,2] Diagnostic criteria have also been suggested for atypical, or variant, Rett syndrome, but diagnostic criteria are imperfect for reliably diagnosing Rett syndrome.[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.[1] Conversely, some people who meet the clinical diagnostic criteria for Rett syndrome do not have an identifiable MECP2 mutation.[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.[1] Surviving males generally have an abnormal gait or truncal movements, severe speech delay, and intellectual disability; pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome; or syndromic/nonsyndromic intellectual disability.[1,2]

Diagnostic Criteria

Typical or classic Rett (RTT)[5]

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[5]

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[5]

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[5]

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 or variant RTT## [5]

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 alterations[1,6] 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]

Management

Treatment for Rett syndrome is based on the symptoms and usually involves therapies to help with movement and communication.[1,7] Medications can control difficult behavior and seizures, when present.[1]

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

Survival

"Despite the difficulties with symptoms, many individuals with Rett syndrome continue to live well into middle age and beyond. Because the disorder is rare, very little is known about long-term prognosis and life expectancy. While there are women in their 40s and 50s with the disorder, currently it is not possible to make reliable estimates about life expectancy beyond age 40."[8]

Test Information

Introduction

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

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small

pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

Introduction

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

American Academy of Pediatrics

The consensus guideline from the American Academy of Pediatrics (AAP, 2020) on the clinical genetic evaluation of a child with autism spectrum disorder stated to follow a stepwise evaluation including: chromosome microarray, specific metabolic testing, and Fragile X syndrome testing. If no diagnosis is established and "the patient is a girl, consider evaluation for Rett syndrome, MECP2 testing."[9] This approach was previously supported in a consensus guideline from the American Academy of Pediatrics (AAP, 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 and Genomics (ACMG, 2013)[10] Practice Guidelines for identifying the etiology of autism spectrum disorders.

National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE, 2017) released evidence-based guidelines titled *Autism spectrum disorder in under 19s: recognition, referral and diagnosis*. These guidelines stated 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]

Selected Relevant Publication

An expert authored reviewed stated:[1]

In females, a diagnosis of a MECP2 disorder should be considered when she has features of classic Rett syndrome or variant Rett syndrome as previously delineated in the "diagnosis" section. This diagnosis may also be considered in females with mild learning disability. This form is mild and non-progressive with the affected females usually being diagnosed with molecular testing after the diagnosis of a first-degree relative who is more significantly affected.

"The diagnosis of a MECP2 disorder is usually established in a female proband with suggestive findings and a heterozygous pathogenic variant in MECP2 identified by molecular genetic testing."

In males, a diagnosis of MECP2 disorder should be considered when he has "severe neonatal encephalopathy; pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome; or syndromic/nonsyndromic intellectual disability."

"The diagnosis of a MECP2 disorder is established in a male proband with suggestive findings and a hemizygous pathogenic variant in MECP2 identified by molecular genetic testing."

Criteria

Introduction

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 that would detect the familial mutation, and

MECP2 mutation identified in 1st degree biologic relative and the member is at-risk for the mutation based on the inheritance pattern, OR

Prenatal Testing for At-Risk Pregnancies:

MECP2 mutation identified in a previous child of either parent and the pregnancy is at-risk for the mutation based on the inheritance pattern, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

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

Genetic testing is necessary because there is uncertainty in clinical diagnosis, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

MECP2 Deletion/Duplication Analysis

Previous testing:

No previous deletion/duplication analysis of MECP2, and

No mutations detected in full sequencing of MECP2, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Introduction

These references are cited in this guideline.

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