MECP2-RELATED DISORDERS

CARRIER TESTING

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What are *MECP2*-related disorders?

***MECP2* (pronounced "mek-pee-2") is a gene. Genes are present in every cell of the body. They carry the instructions for making proteins that control how each cell functions. The *MECP2* gene instructs cells to make a protein that is found throughout the body but is especially important for brain development.**[1]

When there is a defect in the *MECP2* gene, normal brain development may be disrupted, which can lead to physical, behavioral, and intellectual disabilities. Some disorders linked with *MECP2* defects include[2]:

- Classic Rett syndrome in females.
- Variant Rett syndrome in females.
- Learning disabilities in females.
- Severe neonatal encephalopathy in males — a disorder that typically leads to death before 2 years of age.
- PPM-X syndrome (also known as X-linked mental retardation) in males. This condition gets its name from the conditions it causes, which include manic-depressive psychosis (most commonly bipolar disorder), parkinsonism (a pattern of movement abnormalities), pyramidal signs (these indicate damage to the nerve paths connecting the brain and spinal cord), and macroorchidism (enlarged testes).

What is Rett syndrome?

Rett syndrome is a disorder that starts in early childhood and causes abnormal brain development. It mainly occurs in girls. One in 8,500 to 1 in 15,000 females are affected by Rett syndrome.[2-4]

The age of onset and severity of problems linked to Rett syndrome differ from child to child.[3] Most girls with the classic form of Rett syndrome have normal or nearly normal growth and development for the first 6 to 18 months of life, but then they start to lose muscle tone, they lose their ability to speak, and their rate of growth slows.[2-4]

A key feature of Rett syndrome is the loss of normal, purposeful use of the hands. Affected children will repeatedly wring, "wash," clap, or pat their hands.[2-4] These are called stereotypical hand movements. Additional symptoms of Rett syndrome may include the following[2-4]:

- Loss of the ability to speak
- Decreased ability to make eye contact with other people
- Seizures
- Breathing problems
- Autism-like behaviors
- Fits of screaming and crying
- Tremors
- Small head size (microcephaly)

Over time, muscle and movement problems may increase, but behavior, alertness, attention span, eye contact, and speaking ability tend to improve.[3]

Some girls are diagnosed with an "atypical" type of Rett syndrome, called variant Rett syndrome, that differs from the classic type described above. These atypical forms of Rett syndrome range from a mild type in which the ability to speak is not lost to a severe type in which a child never has a period of normal development.[2,4]

Rett syndrome in boys is rare. Most boys born with the defect that causes Rett syndrome die shortly after birth.[3] Those who do survive may have brain damage and learning disabilities.[2-4]

Currently, there is no cure for Rett syndrome. Most females with the disorder live to be middle aged or older, but since the disorder is so rare, not much is known about the long-term outlook and life expectancy for people with Rett sydrome.[2,3]

What causes *MECP2*-related disorders?

MECP2-related disorders are caused by defects in the *MECP2* gene. Genes can undergo abnormal changes (mutations) that may lead to cells not working properly. Mutations in the *MECP2* gene disrupt the way nerve cells in the brain work.

- More than 300 mutations have been identified in females with Rett syndrome. Many of these same mutations are responsible for severe neonatal encephalopathy in males. The mutations either change the structure of the protein produced by *MECP2* or reduce the amount of protein that is produced.[1]
- In most cases, *MECP2* mutations are de novo.[2-4] This means the gene mutation occurs for the first time in

the affected child instead of being passed from parent to child (inherited).

How are *MECP2*-related disorders diagnosed?

Rett syndrome is diagnosed by observing certain symptoms during a child's early growth and development. Specific guidelines have been provided to help doctors and other medical specialists diagnose Rett syndrome. Genetic testing can be performed to help confirm or establish a diagnosis of Rett syndrome.

Although there are no specific guidelines for diagnosing the other disorders linked with *MECP2* defects, genetic testing can be a helpful tool in diagnosing those conditions.

What is *MECP2* full gene sequencing?

MECP2 full gene sequencing is a procedure that reads the instructions (DNA) that make up the *MECP2* gene. This is a way to identify the presence of an altered *MECP2* gene in a person's cells, helping a doctor confirm the diagnosis of *MCEP2*-related disorders.

The test can be performed on:

- A sample of blood.
- Cells obtained by swabbing the inside of the mouth (buccal swab).
- Prenatal samples of amniotic fluid (the watery substance that surrounds a developing baby) or the chorionic villi (a small piece of tissue taken from the placenta).

When might *MECP2* full gene sequencing be recommended?

Your doctor or genetic counselor may recommend *MECP2* full gene sequencing when there is a need to[2]:

- Confirm a diagnosis in a child who has symptoms of a *MECP2*-related disorder.
- Test for the presence of a *MECP2* mutation in the sisters of girls with Rett syndrome.
- Test for the presence of a *MECP2* mutation in a developing baby if a risk has been identified.

What possible results of full gene sequencing can be reported, and what might they mean?

- **Negative:** After scanning the *MECP2* gene, no mutations were found. It is possible that the signs and symptoms seen in the child are caused by genetic changes that the test is not capable of detecting, or they may be due to other genetic or non-genetic factors.
- **Positive:** After scanning the *MECP2* gene, a mutation was found. Along with the child's signs and symptoms, a positive genetic test result may confirm the diagnosis of a *MECP2*-related disorder (including classic or variant Rett syndrome).
- **Variant of unknown significance:** After scanning the *MECP2* gene, a change was found that has not been reported before in the *MECP2* gene. It is not clear if the change plays a role in the development of a *MECP2*-related disorder.

Full gene sequencing test results should be combined with clinical findings and reviewed by a heath professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for *MECP2-related disorders*, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at **www.nsgc.org**.

Other information resources include:

- Brain Resources and Information Network (BRAIN)
  Telephone: 800-352-9424
  Home page: **www.ninds.nih.gov**
- International Rett Syndrome Foundation
  Telephone: 513-874-3020
  Home page: **www.rettsyndrome.org**
- Easter Seals
  Telephone: 800-221-6827, 312-726-6200
  Home page: **www.easterseals.com**

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

References

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