Rett Syndrome

U.S. DEPARTMENT OF HEALTHAND
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What is Rett syndrome?

Rett syndrome is a rare neurological and developmental disorder that almost exclusively affects girls.

Children with Rett syndrome have a general progression of developmental and physical features over time that scientists refer to as the temporal profile. In the temporal profile for Rett syndrome, infants appear to have normal early development for the first several months of life. However, there may be subtle signs of the disorder that initially go unnoticed such as loss of muscle tone (hypotonia), difficulty feeding, and jerkiness in arm and leg movements. Then, typically between ages 6-18 months, the child's development stalls and is followed by loss or regression of earlier gained skills. In particular, the child loses the ability to socialize, language to communicate, purposeful hand use, and ability to crawl or walk. This regression can occur suddenly or over a period of weeks or months. Some of the early symptoms of Rett syndrome are similar to those of autism spectrum disorder and children are sometimes misdiagnosed with that disorder. Usually between 3 and 5 years of age, the symptoms begin to stabilize, and the child develops better social contact, communication, and eye gaze.

The social interactions will continue to improve into adulthood; however, over the course of decades, motor function and movement gradually declines and muscles become increasingly weak, stiff, and inflexible.

Another characteristic feature of Rett syndrome is the development of stereotypic hand movements. These repetitive movements often appear around the time of the regression. Common types of hand movements are hand wringing, clapping, tapping, or repeatedly bringing the hands to the mouth. These repetitive hand movements eventually decrease or stop altogether in adulthood.

There is currently no cure for Rett syndrome. Treatments focus on managing the symptoms, improving mobility and communication, and supporting children and their families through efforts that include physical, occupational, and speech therapy.

What are the symptoms of Rett syndrome?

Symptoms and symptom severity vary among individuals. The typical symptoms of Rett syndrome include:

- **Slowed growth**. Brain development slows after birth, and a smaller than normal head size is usually one of the first symptoms. As the child gets older, slowed growth in weight, height, and other body parts such as the hands and feet become more obvious.
- **Loss of movement.** Early signs include decreased ability to crawl or walk and control hand movements. In those children

who eventually gain the ability to walk, the walking is impaired. Most children develop severe balance and coordination problems.

- **Abnormal hand movements**. Once children lose hand control (such as the ability to grasp objects and intentionally touch things) they typically start repetitive, pointless hand movements such as wringing, squeezing, clapping, mouthing, or rubbing.
- **Communication difficulties.** Problems maintaining prolonged eye contact or speaking are early signs of Rett syndrome. Children may lose the ability to speak or make purposeful sounds.
- **Seizures.** Most children with Rett syndrome will develop seizures.
- **Intellectual disabilities.** Rett syndrome causes cognitive impairment. Since many children with the syndrome cannot complete standard IQ tests, it is difficult to determine the extent of the cognitive impairment.
- **Breathing difficulties**. Children may experience respiratory problems including rapid breathing (hyperventilation), holding their breath while awake, and air swallowing. These problems tend to disappear during sleep.
- **Behavioral problems**. As children with Rett syndrome age they can become increasingly irritable and agitated. Children may begin crying for no apparent reason. These outbursts can last for hours and are especially common during the period of regression (6 to 18 months).

- **Scoliosis**. Scoliosis is a sideways curvature of the spine. Many children with Rett syndrome develop scoliosis. It typically begins between 4 and 11 years of age and worsens as the child gets older. Progression of scoliosis slows or stops after puberty. Some individuals may need back surgery.
- **Gastrointestinal problems**. Children with Rett syndrome have a variety of gastrointestinal problems such as heartburn and severe constipation.
- **Other problems**. Individuals with Rett syndrome may grind their teeth, have sleep problems, have difficulty chewing and swallowing, and have small hands and feet that that often feel cold. They may also have abnormal heart rhythms.

What causes Rett syndrome?

Nearly all cases of Rett syndrome are caused by a mutation in the *MECP2* gene. This gene contains instructions to produce a protein (MeCP2), which is found throughout the entire body but with highest levels in the brain. MeCP2, which is essential for the normal function of nerve cells, acts as a biochemical switch—it can either turn off several other genes to keep them from making proteins when they are not needed or activate them when those proteins are necessary.

Because the *MECP2* gene does not function properly in individuals with Rett syndrome,

insufficient amounts or structurally abnormal forms of the protein are produced and can cause other genes in the body to be abnormally expressed.

Not everyone who has Rett syndrome has a mutation in the *MECP2* gene. Mutations in the *CDKL5* and *FOXG1* genes have been identified in individuals who have atypical Rett syndrome. Scientists believe the remaining cases may be caused by partial gene deletions, mutations in other parts of one of these genes, and additional genes that have not yet been identified, along with other possible causes.

Is Rett syndrome inherited?

Although Rett syndrome is a genetic disorder, less than 1 percent of recorded cases is inherited from a parent. Most cases are spontaneous (also known as *de novo*), which means the mutation occurs randomly, usually in the father's sperm before fertilization. However, in some families of individuals affected by Rett syndrome, there are other female family members who have a mutation of their *MECP2* gene but who do not show clinical symptoms. These females are known as "asymptomatic female carriers."

Prenatal genetic testing can identify the *MECP2* gene mutation. Genetic testing is also available for sisters of girls with Rett syndrome who have an identified *MECP2* mutation to determine if they are asymptomatic carriers of the disorder, an extremely rare possibility.

Who gets Rett syndrome?

The *MECP2* gene is found on a person's X chromosome, one of the two sex chromosomes. Girls have two X chromosomes, but only one is active in any given cell. In a girl with Rett syndrome only a portion of the cells in the nervous system will use the defective gene. Some of the child's brain cells will use the healthy gene and express normal amounts of the MeCP2 protein.

The severity of Rett syndrome in girls is in part a function of the percentage of their cells that have an activated normal copy of the *MECP2* gene. If the X chromosome carrying the defective gene is turned off in a large proportion of cells, the symptoms will be mild. If the defective gene is turned on in a large percentage of cells the onset of the disorder may occur earlier and the symptoms may be more severe. Other factors may determine the severity of symptoms in Rett syndrome, including what type of genetic mutation and where in the *MECP2* gene the mutation has occurred, the number of cells with the defective gene, and other gene changes, currently being discovered, that may alter the severity.

The story is different for boys with an *MECP2* mutation. Because boys have only one X chromosome (and one Y chromosome) they lack a backup copy that could compensate for the defective one. Boys who inherit the mutation typically experience severe problems at birth and may die shortly thereafter.

Depending on the type and position of the *MECP2* mutation, they typically have global developmental delays, motor problems, abnormal movements, pulmonary dysfunction, and seizures that are difficult to control.

The boys with an *MECP2* mutation who survive into childhood and are diagnosed with the male counterpart to classic Rett syndrome usually have two populations of X chromosomes. The non-mutated *MECP2* copy on one of their populations of X chromosomes allows them to survive. One such instance is associated with Klinefelter syndrome, in which an extra sex chromosome is present. The other example is associated with somatic mosaicism, which occurs after conception and results in two populations of chromosomes. In both instances, these males have two populations of X chromosomes, one with a normal gene and one with an abnormal gene.

How is Rett syndrome diagnosed?

Doctors clinically diagnose Rett syndrome by observing signs and symptoms during the child's early growth and development and conducting ongoing evaluations of the child's physical and neurological status. Scientists have developed a genetic test, which involves searching for the *MECP2* mutation on the child's X chromosome, to complement the clinical diagnosis.

A diagnosis of Rett syndrome should be confirmed by a pediatric neurologist, clinical geneticist, or developmental pediatrician.

The physician will use a highly specific set of guidelines that are divided into three types of clinical criteria: main, supportive, and exclusion.

- **Main criteria**. The main diagnostic criteria are partial or complete loss of ability to control hand movements, partial or complete loss of ability to speak, problems walking (including an unsteady, wide or absent gait), and repetitive hand movements such as wringing, squeezing, clapping, or rubbing.
- **Supportive criteria.** These criteria are not required for a diagnosis of Rett syndrome but may occur in some individuals. These symptoms—which vary in severity from child to child—may not be observed in very young girls but may develop with age. Supportive criteria include breathing difficulties, teeth-grinding, abnormal sleep patterns, abnormal muscle tone, poor circulation of the lower extremities with cold and bluish-red feet and legs, scoliosis, slowed growth, small hands and feet in relation to height, inappropriate laughter or screaming episodes, reduced response to pain, and intense use of eyes to communicate ("eye pointing").

  A child with supportive criteria but none of the main criteria does not have Rett syndrome. Supportive criteria must be used in the diagnosis of atypical or variant Rett syndrome. The diagnosis of atypical or variant Rett syndrome is based on meeting two of the four main criteria and at least five of the 11 supportive criteria. Atypical or variant Rett syndrome represents about 15 percent of the overall population with Rett syndrome.

- **Exclusion criteria**. Several specific conditions (exclusion criteria) enable physicians to rule out a Rett syndrome diagnosis. Children with any one of the following criteria do not have Rett syndrome: brain injury due to trauma (either at or after birth), a metabolic disorder that affects the brain, a neurological disorder resulting from severe infection, or abnormal development of motor functions in the first 6 months of life.

How is Rett syndrome treated?

There is no cure for Rett syndrome. Treatment for the disorder focuses on managing the symptoms and providing support through a multidisciplinary approach. These options may include:

- **Medication**. There are several different medications that can help symptoms ranging from reflux to abnormal breathing to constipation to motor difficulties as well as anticonvulsant drugs to control seizures. Additionally, children should be monitored for scoliosis and possible heart rhythm abnormalities.
- **Occupational and physical therapy**. Occupational therapy can help children develop skills needed for performing self-directed activities (such as dressing and feeding), while physical therapy and hydrotherapy (using aquatic activity for pain relief and treatment) may prolong mobility.

- **Special equipment and aids**. Some children may require special equipment and aids such as orthotics to maintain normal foot position, braces to treat scoliosis, splints to modify hand movements, and nutritional programs to help maintain adequate weight.
- **Communication therapy**. Communication therapies are advancing quickly. Many special devices—such as picture cards or advanced computer aids that depend on gaze—can help girls make choices and communicate. These devices require special academic, social, vocational, and support services for proper implementation.

What is the outlook for those with Rett syndrome?

Despite the difficulties with symptoms and the need for assisted care throughout life, most individuals with Rett syndrome continue to live well into middle age and beyond. Because the disorder is rare, information on long-term prognosis and life expectancy is just emerging. It is known that there are women in their 40s, 50s, and even 60s with the disorder. The most comprehensive work to date indicates that more than 70 percent of affected individuals will survive to age 45. However, additional longitudinal studies are needed to confirm this finding.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge of the brain and nervous system, and to use that knowledge to reduce the burden of neurological disease. NINDS is a component of the National Institutes of Health, the leading supporter of biomedical research in the world.

NINDS, along with several other NIH Institutes and Centers, supports research on Rett syndrome through grants to medical institutions across the country.

Understanding the cause of this disorder is necessary for developing new therapies to manage specific symptoms, as well as for providing better methods of diagnosis. The discovery of the main Rett syndrome gene (*MECP2*) provides a basis for further genetic studies.

New therapies and treatments

NINDS researchers are currently examining the underlying mechanisms in the brain that contribute to the development and progression of the disorder and how they can be reversed. This research will also help design new therapies for Rett syndrome and other disorders that share similar cellular mechanisms, including autism and some forms of intellectual disability.

Some of the most exciting findings in Rett syndrome research to date are the groundbreaking studies in mice, which revealed that some symptoms of Rett syndrome could be reversed by activating the *MECP2* gene later in life. These studies provide hope that one day this process may work in people with the disorder.

Researchers are investigating how to treat some of the symptoms of Rett syndrome such as breathing problems and communication difficulties. For example, scientists are studying cells in the brain stem, the part of the brain that controls breathing, to determine how abnormalities in this region contribute to Rett syndrome. This is part of ongoing efforts to develop treatments for breathing complications caused by the disorder.

Drug interventions

Researchers are evaluating the ability of several new drugs to reverse symptoms of neurologic dysfunction in mice. Several of these drugs have been successful in animal studies and are now being tested in clinical trials with individuals suffering from Rett syndrome.

Genetics

NINDS researchers are studying the MeCP2 protein to determine how it contributes to Rett syndrome. Scientists are examining mutations in this protein to determine how MeCP2 interprets its genetic environment and how these processes affect the way the protein functions.

The goal is that these studies will provide a better understanding of how the MeCP2 protein works, offer insights into the causes of Rett syndrome, and ultimately provide new opportunities to develop therapeutic strategies for the disorder.

Some research suggests that the specific type of mutation in the *MECP2* gene affects the severity of Rett syndrome symptoms. NIH-funded researchers are studying each mutation that may cause the features of Rett syndrome, and how these mutations might change the symptoms.

One NIH study funded by NINDS, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Office of Rare Diseases Research in the National Center for Advancing Translational Sciences, has been following more than 1,000 individuals with Rett syndrome for more than a decade. The study is looking for biomarkers that will predict which types of symptoms they will develop as they age. Biomarkers are signs that may help diagnose or monitor progression of a disease.

Scientists know that the lack of a properly functioning MeCP2 protein disrupts the function of mature brain cells but they do not know exactly how this occurs. Investigators are trying to find other genetic switches that operate in a similar way to the MeCP2 protein. Once they discover how the protein works and locate similar switches, they may devise therapies that can substitute for the malfunctioning switch.

Another outcome might involve manipulating other biochemical pathways to compensate for the malfunctioning *MECP2* gene, thereby preventing progression of the disorder. Researchers are also trying to identify other genes that may be involved in Rett syndrome. Some studies have helped narrow the search for these genes, but much is still unknown about how these genes may cause or contribute to Rett syndrome.

More information about Rett syndrome research supported by NINDS and other NIH Institutes and Centers can be found using NIH RePORTER (projectreporter.nih.gov), a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications and resources from these projects.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

International Rett Syndrome Foundation/ Rettsyndrome.org
4600 Devitt Drive
Cincinnati, OH 45246
513-874-1298
800-818-7388
www.rettsyndrome.org

Rett Syndrome Research Trust
67 Under Cliff Road
Trumbull, CT 06611
203-445-0041
www.rsrt.org

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National Institutes of Health, DHHS
31 Center Drive, Room 2A32
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Genetic and Rare Diseases Information Center (GARD)
(*See also* National Center for Advancing Translational Sciences)
P.O. Box 8126
Gaithersburg, MD 20898-8126
301-251-4925
888-205-2311
http://rarediseases.nih.gov

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