Rett syndrome

What is Rett syndrome?
Rett syndrome is a neurological and developmental genetic disorder that occurs mostly in females. Infants with Rett syndrome seem to grow and develop normally at first, but then they stop developing and even lose skills in different stages of the disease over a lifetime.

Rett syndrome was first reported by Dr. Andreas Rett in 1966. Rett syndrome is a complex neurological and developmental disorder in which early growth and development appear normal at first, but then the infant stops developing and affected children even lose skills and abilities.1 Rett syndrome occurs mostly in females.

Over time, the effects of Rett syndrome can lead to cognitive, sensory, emotional, motor, cardiac, and such autonomic (pronounced aw-tuh-NOM-ik) nervous system problems as difficulties with digestion or breathing.2


What are the types & phases of Rett syndrome?
There are two main types of Rett syndrome: classic and atypical.1 The two types may differ by their symptoms or by the specific gene mutation.

The majority of Rett syndrome patients have the classic form, which typically develops in four phases. Health care providers and researchers, relying on consensus criteria, view the progression of classic Rett syndrome as the following phases:

Early Onset Phase. In this phase, development stalls or stops completely. Sometimes, the syndrome takes hold at such a subtle pace that parents and health care providers do not notice it at first. Researchers once thought that this phase began around 6 months of age. However, after analyzing videotapes of Rett individuals taken from birth, they now know4 that some infants with Rett syndrome only seem to develop normally. In fact, these infants show problems with very early development. In one study,5 all of the infants with Rett syndrome showed problems with body movements from birth through age 6 months. Another 42%5 showed stereotyped hand movements during this time period.

Rapid Destructive Phase. The child loses skills (regresses) quickly. Purposeful hand movements and speech are usually the first skills lost. Breathing problems and stereotypic hand movements such as wringing (clasping or squeezing), washing (a movement that resembles washing the hands), and clapping or tapping also tend to start during this stage.

Plateau Phase. The child's regression slows and other problems may seem to lessen, or there may even be improvement in some areas. Seizures and movement problems are common at this stage. Many people with Rett syndrome spend most of their lives in this stage.

Late Motor Deterioration Phase. Individuals in this stage may become stiff or lose muscle tone; some become immobile. Scoliosis (an abnormal curvature of the spine) may be present and even become severe enough to require bracing or surgery. Stereotypic hand movements and breathing problems seem to become less common.

There are currently five known variants of atypical Rett syndrome, defined by characteristic symptoms, age at which the symptoms present, or genetic makeup. Forms of atypical Rett syndrome that have been identified to date include:
• Congenital (pronounced kuhn-JEN-i-tl) Rett Syndrome (Rolando Variant)6
• Early-Onset Rett Syndrome (Hanefeld Variant)
• Late-Childhood Rett Syndrome
• Forme Fruste Rett Syndrome
• Preserved-Speech Variant of Rett Syndrome (Zappella Variant)


What are the symptoms of Rett syndrome?

The first symptom of Rett syndrome is usually the loss of muscle tone, called hypotonia (pronounced hahy-poh-T-H-nee-uh). With hypotonia, an infant's arms and legs will appear “floppy.”2

Although hypotonia and other symptoms of Rett syndrome often present themselves in stages, some typical symptoms can occur at any stage. Symptoms may vary among patients and range from mild to severe.3

Typical Symptoms (may occur at any stage) can include:
• Loss of ability to grasp and intentionally touch things
• Loss of ability to speak (Initially, a child may stop saying words or phrases that he or she once said; later, the child may make sounds, but not say any purposeful words.)
• Severe problems with balance or coordination, leading to loss of the ability to walk. (These problems may start out as clumsiness and trouble walking. About 60%4 of those with Rett syndrome are still able to walk later in life; others may become unable to sit up or walk or may become immobile.)
• Mechanical, repetitive hand movements, such as hand wringing, hand washing, or grasping
• Complications with breathing, including hyperventilation and breath holding when awake
• Anxiety and social-behavioral problems
• Intellectual disability

In addition, a person with Rett syndrome may experience one or more of the following associated problems:
• Scoliosis (pronounced skoh-lee-oh-sis), or curvature of the spine from side to side. (Approximately 80% of girls with Rett syndrome have scoliosis. In some cases, the curving of the spine can become so severe that the girls require surgery. For some, bracing relieves the problem, prevents it from getting worse, or delays or eliminates the need for surgery.)
• Seizures (These may involve the whole body, or they may be staring spells with no movement.)
• Constipation and gastroesophageal (pronounced gas-stro-ih-sof-uh-JEE-uh) reflux
• Discomfort in the abdomen or gallbladder problems, such as gallstones
• Cardiac or heart problems, usually problems with heart rhythm. (Some persons with Rett syndrome may have abnormally long pauses between heartbeats, as measured by an electrocardiogram, or they may experience other types of arrhythmia [pronounced uh-RITH-me-uh].)
• Trouble feeding oneself, swallowing, and chewing food. (In some cases, too, in spite of healthy appetites, girls with Rett syndrome do not gain weight or have trouble maintaining a healthy weight. As a result, some girls with Rett syndrome rely on feeding tubes.)
• Disrupted sleep patterns at night (during childhood) and increased sleep (after age 5). (Some researchers suggest that problems with sleep are among the earliest symptoms of Rett syndrome and can appear between 1 and 2 months of age. Such problems can lead to sudden death during sleep.)

• Excessive saliva and drooling

• Poor circulation in hands and legs

• Walking on toes or the balls of feet

• Walking with a wide gait (ataxia)

• Grinding the teeth (bruxism)

Symptoms can vary from person to person and from one stage to the next. Symptoms may also improve in the “Plateau Phase”


How many people are affected by or at risk of Rett syndrome?

Current estimates suggest that Rett syndrome occurs in one out of every 10,000 to 15,000 girls born and affects 1 in 10,000 to 22,000 females in the U.S.

What causes Rett syndrome?

Most cases of Rett syndrome are caused by a change (also called a mutation) in a single gene. In 1999, NICHD-supported scientists discovered that most classic Rett syndrome cases are caused by a mutation within the Methylcytosine-binding protein 2 (MECP2) gene. The MECP2 gene is located on the X chromosome. Between 90% and 95% of girls with Rett syndrome have a mutation in the MECP2 gene. Among families with a child affected by Rett syndrome the chance of having a second child with the syndrome is less than 1%.4

Eight mutations in the MECP2 gene represent the most prevalent causes of Rett syndrome. The development and severity of Rett syndrome symptoms depend on the location and type of the mutation on the MECP2 gene.5

The MECP2 gene makes a protein that is necessary for the development of the nervous system, especially the brain. The mutation causes the gene to either make insufficient amounts of this protein or to make a damaged protein that the body cannot use. In either case, if there is not enough of the working protein for the brain to develop normally, Rett syndrome develops.
Researchers are still trying to understand exactly how the brain uses this protein, called MeCP2, and how problems with this protein cause the typical features of Rett syndrome.

Mutations on two other genes can cause some of the atypical variants of Rett syndrome: Congenital Rett syndrome (Rolando variant) is associated with mutations of the FOXG1 gene, and CDKL5 mutations are linked with the early-onset, or Hanefeld, variant. Males affected by these types of mutations can survive infancy. Males can also have a duplication of a normal MECP2 gene and survive, but are severely affected. Too much MeCP2 protein is as bad for development as too little.

**Is Rett syndrome passed from one generation to the next?**

In 99.9% of cases, the genetic change that causes Rett syndrome is spontaneous, meaning it happens randomly. Such random mutations are usually not inherited or passed from one generation to the next. However, in a very small percentage of families—about 1%—Rett mutations are inherited and passed on by female carriers.

Why do mostly females and so few boys have Rett syndrome?

Two types of chromosomes determine the sex of an embryo: the X and the Y chromosomes. Girls have two X chromosomes, and boys have one X and one Y chromosome.

Because the mutated gene that causes Rett syndrome is located on the X chromosome, females have twice the opportunity to develop a mutation in one of their X chromosomes. Females with Rett syndrome usually have one mutated X chromosome and one normal X chromosome. Only one X chromosome in a given cell remains active throughout life and cells randomly determine which X chromosome will remain active. If the cells have an active mutated gene more often than the normal gene, the symptoms of Rett syndrome will be more severe. This random process allows most females with Rett syndrome to survive infancy.

Because most boys have only one X chromosome, when this gene is mutated to cause Rett syndrome the detrimental effects are not softened by the presence of a second, normal X chromosome. As a result, many males with Rett syndrome are stillborn or do not live past infancy.

Some boys with Rett syndrome, however, do live past infancy, likely for one of three reasons:

Mosaicism (pronounced moh-ZEY-uh-siz-uhm), a condition in which individual cells within the same person have a different genetic makeup. This means that some of the X chromosome genes in a boy's body have the Rett mutation, and some genes do not have the mutation. When a lower percentage of genes have the Rett syndrome mutation, the symptoms are not as severe.

A boy may have two X chromosomes and one Y chromosome (Klinefelter syndrome). Only one X chromosome will be active in each cell, so if one X carries a mutation in MECP2, the severity of symptoms will depend on how many cells have that the mutant X active in the body.

The genetic mutation is less severe than that of other forms of Rett syndrome mutations.

Duplication of the MECP2 gene can occur in boys and affects intellectual and physical function.


How do health care providers diagnose Rett syndrome?

**Blood test.** Genetic evaluation of a blood sample can identify whether a child has one of the known mutations that cause Rett syndrome. Even if a child has a mutation of the Methylcytosine-binding protein 2 (MECP2) gene (which also occurs in other conditions), the symptoms of Rett syndrome may not always be present, so health care providers also need to evaluate the child's symptoms to confirm a diagnosis.

**Clinical symptoms.** A child must meet the following five necessary criteria to be diagnosed with classic Rett syndrome:

- A pattern of development, regression, then recovery or stabilization
- Partial or complete loss of purposeful hand skills such as grasping with fingers, reaching for things, or touching things on purpose
- Partial or complete loss of spoken language
- Repetitive hand movements, such as wringing the hands, washing, squeezing, clapping, or rubbing
- Gait abnormalities, including walking on toes or with an unsteady, wide-based, stiff-legged gait

A slowing of head growth between 3 months and 4 years of age, leading to acquired microcephaly (pronounced mahy-kroh-SEF-uh-lee), is also characteristic of Rett syndrome and calls for a diagnosis to be considered.

For additional information and a listing of the supportive criteria, visit the International Rett Syndrome Foundation.

Health care providers will also consider whether any of the following conditions are present. The presence of any of the symptoms below would rule out a Rett syndrome diagnosis.

- **Atypical Rett syndrome.** Genetic mutations causing some atypical variants of Rett syndrome have been identified. After a blood test to confirm a child's genetic makeup, a health care provider may diagnose the child with atypical Rett syndrome if the child demonstrates development, followed by regression and then recovery or stabilization. In addition, the health care provider will confirm at least two of the other four main criteria, and five of the 11 supportive criteria before making a diagnosis.

- **Other possible diagnoses.** Sometimes Rett syndrome is misdiagnosed as regressive autism, cerebral palsy, or nonspecific developmental delays.

For some males, the features of Rett syndrome occur with another genetic condition called Klinefelter syndrome, in which a boy has two X chromosomes and one Y chromosome. This means that the boy may have one mutated MECP2 gene and one normal MECP2 gene, reducing the effects of the mutated gene.

What are the treatments for Rett syndrome?
Most people with Rett syndrome benefit from well-designed interventions no matter what their age, but the earlier that treatment begins, the better. With therapy and assistance, people with Rett syndrome can participate in school and community activities.

These treatments, forms of assistance, and options for medication generally aim to slow the loss of abilities, improve or preserve movement, and encourage communication and social contact. A list of treatment options is presented below; the need for these treatments depends on the severity of different symptoms.

Physical therapy/hydrotherapy
- Improves or maintains mobility and balance
- Reduces misshapen back and limbs
- Provides weight-bearing training for patients with scoliosis (an abnormal curvature of the spine)

Occupational therapy
- Improves or maintains use of hands
- Reduces stereotypic hand movements such as wringing, washing (a movement that resembles washing the hands), clapping, rubbing, or tapping
- Teaches self-directed activities like dressing and feeding

Speech-Language Therapy
- Teaches nonverbal communication
- Improves social interaction

Feeding assistance
- Supplements calcium and minerals to strengthen bones and slow scoliosis
- High-calorie, high-fat diet to increase height and weight
- Insertion of a feeding tube if patients accidentally swallow their food into their lungs (aspiration [pronounced as-pu-REY-shuhn])

Physical assistance
- Braces or surgery to correct scoliosis
- Splints to adjust hand movements

Medication
- To reduce breathing problems
- To eliminate problems with abnormal heart rhythm
- To relieve indigestion and constipation
- To control seizures
