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National Institute of Neurological Disorders and Stroke

Rett Syndrome Fact Sheet

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What is Rett syndrome?

Rett syndrome is a childhood neurodevelopmental disorder characterized by normal early development followed by loss of purposeful use of the hands, distinctive hand movements, slowed brain and head growth, gait abnormalities, seizures, and mental retardation. It affects females almost exclusively.

The disorder was identified by Dr. Andreas Rett, an Austrian physician who first described it in a journal article in 1966. It was not until after a second article about the disorder was published in 1983 that the disorder was generally recognized.

The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child to child. Before the symptoms begin, however, the child appears to grow and develop normally. Then, gradually, mental and physical symptoms appear. Hypotonia (loss of muscle tone) is usually the first symptom. As the syndrome progresses, the child loses purposeful use of her hands and the ability to speak. Other early symptoms may include problems crawling or walking and diminished eye contact. The loss of functional use of the hands is followed by compulsive hand movements such as wringing and washing. The onset of this period of regression is sometimes sudden.

Another symptom, apraxia — the inability to perform motor functions — is perhaps the most severely disabling feature of Rett syndrome, interfering with every body movement, including eye gaze and speech.

Individuals with Rett syndrome often exhibit autistic-like behaviors in the early stages. Other symptoms may include toe walking; sleep problems; wide-based gait; teeth grinding and difficulty chewing; slowed growth; seizures; cognitive disabilities; and breathing difficulties while awake such as hyperventilation, apnea (breath holding), and air swallowing.

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What are the stages of the disorder?

There are four stages of Rett syndrome. Stage I, called **early onset**, generally begins between 6 and 18 months of age. Quite frequently, this stage is overlooked because symptoms of the disorder may be somewhat vague, and parents and doctors may not notice the subtle slowing of development at first. The infant may begin to show less eye contact and have reduced interest in toys. There may be delays in gross motor skills such as sitting or crawling. Hand-wringing and decreasing head growth may occur, but not enough to draw attention. This stage usually lasts for a few months but can persist for more than a year.

Stage II, or the **rapid destructive** stage, usually begins between ages 1 and 4 and may last for weeks or months. This stage may have either a rapid or a gradual onset as purposeful hand skills and spoken language are lost. The characteristic hand movements begin to emerge during this stage and often include wringing, washing, clapping, or tapping, as well as repeatedly moving the hands to the mouth. Hands are sometimes clasped behind the back or held at the sides, with random touching, grasping, and releasing. The movements persist while the child is awake but disappear during sleep. Breathing irregularities such as episodes of apnea and hyperventilation may occur, although breathing is usually normal during sleep. Some girls also display autistic-like symptoms such as loss of social interaction and communication. General irritability and sleep irregularities may be seen. Gait patterns are unsteady and initiating motor movements can be difficult. Slowing of head growth is usually noticed during this stage.

Stage III, also called the **plateau** or **pseudo-stationary** stage, usually begins between ages 2 and 10 and can last for years. Apraxia, motor problems, and seizures are prominent during this stage. However, there may be improvement in behavior, with less irritability, crying, and autistic-like features. An individual in stage III may show more interest in her surroundings, and her alertness, attention span, and communication skills may improve. Many girls remain in this stage for most of their lives.

The last stage, stage IV — called the **late motor deterioration** stage — can last for years or decades and is characterized by reduced mobility. Muscle weakness, rigidity (stiffness), spasticity, dystonia (increased muscle tone with abnormal posturing of extremity or trunk), and scoliosis (curvature of the spine) are other prominent features. Girls who were previously able to walk may stop walking. Generally, there is no decline in cognition, communication, or hand skills in stage IV. Repetitive hand movements may decrease, and eye gaze usually improves.

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What causes Rett syndrome?

Rett syndrome is caused by mutations (structural alterations or defects) in the MECP2 (pronounced *meck-pea-two*) gene, which is found on the X chromosome (see section on "Who gets Rett syndrome" for a discussion of the importance of the involvement of the X chromosome). Scientists identified the gene — which is believed to control the functions of several other genes — in 1999. The MECP2 gene contains instructions for the synthesis of a protein called methyl cytosine binding protein 2 (MeCP2), which acts as one of the many biochemical switches that tell other genes when to turn off and stop producing their own unique proteins. Because the MECP2 gene does not function properly in those with Rett syndrome, insufficient amounts or structurally abnormal forms of the protein are formed. The absence or malfunction of the protein is thought to cause other genes to be abnormally expressed, but this hypothesis has not yet been confirmed.

Seventy to 80 percent of girls given a diagnosis of Rett syndrome have the MECP2 genetic mutation detected by current diagnostic techniques. Scientists believe the remaining 20 to 30

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percent of cases may be caused by partial gene deletions, by mutations in other parts of the gene, or by genes that have not yet been identified; thus, they continue to search for other mutations.

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Is Rett syndrome inherited?

Although Rett syndrome is a genetic disorder — resulting from a faulty gene or genes — less than 1 percent of recorded cases are inherited or passed from one generation to the next. Most cases are sporadic, which means the mutation occurs randomly, mostly during spermatogenesis, and is not inherited.

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Who gets Rett syndrome?

Rett syndrome affects one in every 10,000 to 15,000 live female births. It occurs in all racial and ethnic groups worldwide. Prenatal testing is available for families with an affected daughter who has an identified MECP2 mutation. Since the disorder occurs spontaneously in most affected individuals, however, the risk of a family having a second child with the disorder is less than 1 percent.

Genetic testing is also available for sisters of girls with Rett syndrome and an identified MECP2 mutation to determine if they are asymptomatic carriers of the disorder, which is an extremely rare possibility.

Girls have two X chromosomes, but only one is active in any given cell. This means that in a child with Rett syndrome only about half the cells in the nervous system will use the defective gene. Some of the child's brain cells use the healthy gene and express normal amounts of the proteins.

The story is different for boys who have an MECP2 mutation known to cause Rett syndrome in girls. Because boys have only one X chromosome they lack a back-up copy that could compensate for the defective one, and they have no protection from the harmful effects of the disorder. Boys with such a defect die shortly after birth.

Different types of mutations in the MECP2 gene can cause mental retardation in boys.

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How is Rett syndrome diagnosed?

Doctors 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. Recently, scientists developed a genetic test to confirm the clinical diagnosis of this disorder; the test involves searching for the MECP2 mutation on the child's X chromosome. Given what we know about the genes involved in Rett syndrome, such tests are able to confirm a clinical diagnosis in up to 80 percent of all cases.

Some children who have Rett syndrome-like characteristics or MECP2 genetic mutations do not fulfill the diagnostic criteria for the syndrome as defined below. These persons are described as having "atypical" or "variant" Rett syndrome. Atypical cases account for about 15 percent of the total number of diagnosed cases.

A pediatric neurologist or developmental pediatrician should be consulted to confirm the clinical diagnosis of Rett syndrome. The physician will use a highly specific set of guidelines that are

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divided into three types of clinical criteria: **essential**, **supportive**, and **exclusion**. The presence of any of the exclusion criteria negates a diagnosis of "classic" or "typical" Rett syndrome.

Examples of **essential** diagnostic criteria or symptoms include having apparently normal development until between the ages of 6 and 18 months and having normal head circumference at birth followed by a slowing of the rate of head growth with age (between 3 months and 4 years). Other essential diagnostic criteria include severely impaired expressive language, repetitive hand movements, shaking of the torso, and toe-walking or an unsteady, wide-based, stiff-legged gait.

Supportive criteria are not required for a diagnosis of Rett syndrome but may occur in some patients. In addition, these symptoms — which vary in severity from child to child — may not be observed in very young girls but may develop with age. A child with supportive criteria but none of the essential criteria does **not** have Rett syndrome. Supportive criteria include breathing difficulties; electroencephalogram (EEG) abnormalities; seizures; muscle rigidity, spasticity, and/or joint contracture which worsen with age; scoliosis; teeth-grinding; small feet in relation to height; growth retardation; decreased body fat and muscle mass (although there may be a tendency toward obesity in some affected adults); abnormal sleep patterns, irritability, or agitation; chewing and/or swallowing difficulties; poor circulation of the lower extremities with cold and bluish-red feet and legs; decreased mobility with age; and constipation.

In addition to the essential diagnostic criteria, a number of specific conditions enable physicians to rule out a diagnosis of Rett syndrome. These are referred to as **exclusion** criteria. Children with any one of the following criteria do not have Rett syndrome: enlargement of body organs or other signs of storage disease, vision loss due to retinal disorder or optic atrophy, microcephaly at birth, an identifiable metabolic disorder or other inherited degenerative disorder, an acquired neurological disorder resulting from severe infection or head trauma, evidence of growth retardation in utero, or evidence of brain damage acquired after birth.

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Why are some cases more severe than others?

The course and severity of Rett syndrome vary from individual to individual. Some girls have symptoms from birth onward, while others may have late regression or milder symptoms.

Because females have two copies of the X chromosome and need only one working copy for genetic information, they turn off the extra X chromosome in a process called **X inactivation**. This process occurs randomly so that each cell is left with one active X chromosome. The severity of Rett syndrome in girls is in part a function of the percentage of cells with a normal copy of the MECP2 gene after X inactivation takes place: if X inactivation turns off the X chromosome that is carrying the defective gene in a large proportion of cells, the symptoms will be mild, but if a larger percentage of cells have the X chromosome with the normal MECP2 gene turned off, onset of the disorder may occur earlier and the symptoms may be more severe.

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Is treatment available?

There is no cure for Rett syndrome. Treatment for the disorder is symptomatic — focusing on the management of symptoms — and supportive, requiring a multidisciplinary approach. Medication may be needed for breathing irregularities and motor difficulties, and antiepileptic drugs may be used to control seizures. There should be regular monitoring for scoliosis and possible heart abnormalities. Occupational therapy (in which therapists help children develop skills needed for performing self-directed activities — *occupations* — such as dressing, feeding, and practicing arts and crafts), physiotherapy, and hydrotherapy may prolong mobility. Some children may require

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special equipment and aids such as braces to arrest scoliosis, splints to modify hand movements, and nutritional programs to help them maintain adequate weight. Special academic, social, vocational, and support services may also be required in some cases.

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What is the outlook for those with Rett syndrome?

Despite the difficulties with symptoms, most 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 it is estimated that there are many middle-aged women (in their 40s and 50s) with the disorder, not enough women have been studied to make reliable estimates about life expectancy beyond age 40.

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What research is being done?

Within the Federal Government, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Child Health and Human Development (NICHD), two of the National Institutes of Health (NIH), support clinical and basic research on Rett syndrome. 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 Rett syndrome gene in 1999 provides a basis for further genetic studies and enables the use of recently developed animal models such as transgenic mice.

One NINDS-supported study is looking for mutations in the MECP2 gene of individuals with Rett syndrome to find out how the MeCP2 protein functions. Information from this study will increase understanding of the disorder and may lead to new therapies.

Scientists know that lack of a properly functioning MeCP2 protein disturbs the function of mature brain cells but they do not know the exact mechanisms by which this happens. Investigators are also trying to find other genetic mutations that can cause Rett syndrome and 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 be able to devise therapies that can substitute for the malfunctioning switch. Another outcome might involve manipulating other biochemical pathways to compensate for the malfunctioning MECP2 gene, thus preventing progression of the disorder.

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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
<http://www.ninds.nih.gov>

Information also is available from the following organizations:

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International Rett Syndrome Association (IRSA)

9121 Piscataway Road
Suite 2B
Clinton, MD 20735

admin@rettsyndrome.org

<http://www.rettsyndrome.org>

Tel: 301-856-3334 800-818-RETT (7388)

Fax: 301-856-3336

National Institute of Child Health and Human Development (NICHD)

National Institutes of Health, DHHS
31 Center Drive, Rm. 2A32 MSC 2425
Bethesda, MD 20892-2425

<http://www.nichd.nih.gov>

Tel: 301-496-5133

Fax: 301-496-7101

Rett Syndrome Research Foundation (RSRF)

4600 Devitt Drive
Cincinnati, OH 45246

monica@rsrf.org

<http://www.rsrf.org>

Tel: 513-874-3020

Fax: 513-874-2520

Easter Seals

230 West Monroe Street
Suite 1800
Chicago, IL 60606-4802

info@easterseals.com

<http://www.easterseals.com>

Tel: 312-726-6200 800-221-6827

Fax: 312-726-1494

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"Rett Syndrome Fact Sheet," NINDS.

NIH Publication No. 04-4863

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Last updated November 13, 2007

