Understanding Rett Syndrome

Fast Facts

Rett syndrome is a rare and severe neurological disorder that **primarily affects girls**[1]

Caused by mutations in a gene located on the X chromosome, Rett syndrome affects **1 in 10,000 to 1 in 15,000** newborn girls worldwide[1]

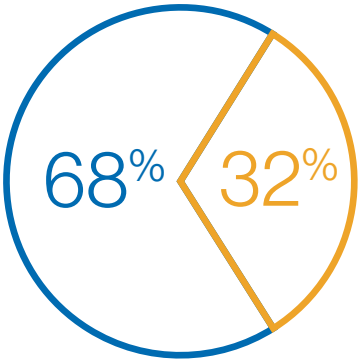
Approximately **15,000** girls and women in the US and **350,000** worldwide have the disorder[2]

Median age at diagnosis for classic Rett syndrome is approximately[3]

2.7 years old

There are two types of Rett syndrome:

Classic Rett syndrome features a single common mutation[1,4]



Atypical Rett syndrome is a "catch-all" term for a variety of less common MECP2 mutations and non-MECP2 mutation variants that have distinct patterns of symptoms[5]

There are no approved treatments[2]

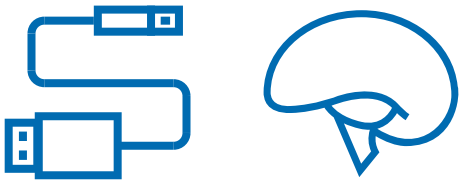
Rett Syndrome: One Disease, Many Consequences

Rett syndrome can cause certain dysfunctions in brain regions responsible for cognitive, sensory, emotional, motor, and autonomic function. Approximately half of affected individuals cannot walk; those who do walk typically have a wide-based and unsteady gait that worsens with age.[1] Diagnosis is challenging because the disease is rare, and its symptoms are similar to those of other disorders such as autism.[1,2,6,7]

Rett Syndrome: a Genetic Disorder

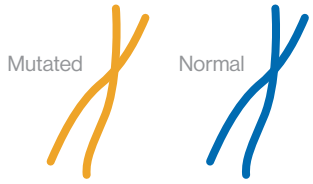
90 - 95%

of Rett syndrome cases are caused by a spontaneous genetic mutation **affecting a single gene located on the X chromosome**, methyl CpG-binding protein 2 (MECP2).[1,5]

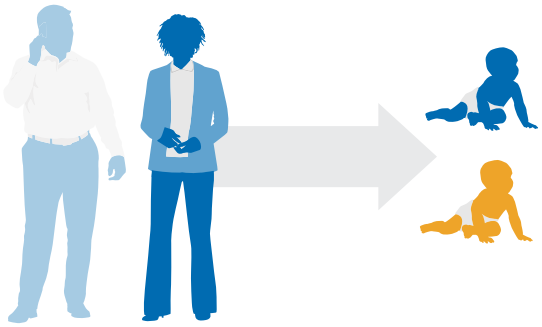


MECP2 MeCP2 protein

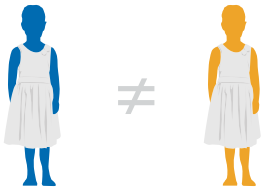
MECP2 encodes the MeCP2 protein, critical for normal function of nerve cells and therefore brain development.[8]



Because females have two X chromosomes, those with Rett usually have one mutated copy of the gene and one normal copy, resulting in a reduction—but not complete absence—of functional MeCP2 protein.[1]



Despite being a genetic disease, **Rett syndrome is rarely inherited**: affected individuals usually do not have a family history of Rett syndrome.[5]

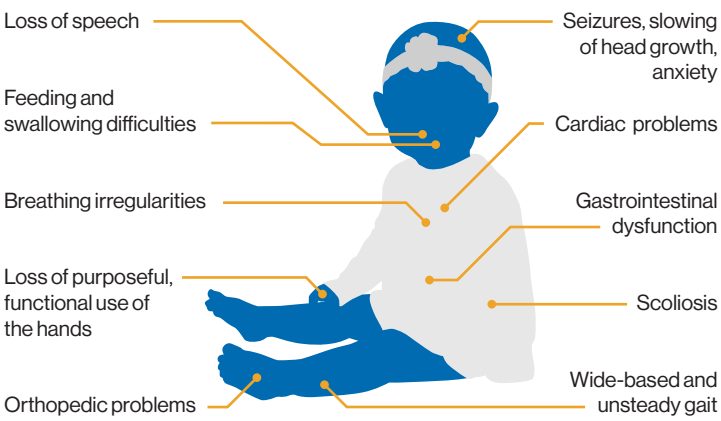


Two girls of the same age with the same mutation can appear significantly different because the course and severity of Rett syndrome is determined by the location, type, and severity of the MECP2 mutation and whether the affected X chromosome is dominant over the second, unaffected X chromosome.[5]

Because males only have one X chromosome, those with the MECP2 mutation do not have an unaffected X chromosome to produce MeCP2 protein. Without any MeCP2 protein, most die before or shortly after birth.[5]

Common symptoms of and complications due to Rett syndrome[1,2,5]

- Many Rett syndrome symptoms are difficult or impossible to measure, including changes in cognitive ability or social behavior in **nonverbal patients**.[9]
- Most individuals affected with Rett live into adulthood but **require lifelong, round-the-clock care**.[5]
- Approximately **30% of patients with Rett syndrome** live in group homes or other institutions.[7]
- Mortality is **largely caused by comorbidities** (such as seizures and pneumonia) and death is often sudden.[5,10]



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Researchers Have Established That There Are 4 Basic Stages of Classic Rett Syndrome[1]

Stage 1[1]

Early onset

Onset: Typically 6–18 months of age

Duration: Months to more than a year

Subtle signs may appear: Children may exhibit less eye contact, reduced interest in toys, delays in sitting/crawling, and slow head growth—but these symptoms often go unnoticed by parents and doctors

Stage 2[1]

Rapid deterioration

Onset: Typically 1–4 years of age

Duration: Weeks to months; onset may be rapid or slow

Symptom progression: Children exhibit slow head growth and movement problems, as well as noticeable developmental regression such as loss of hand skills and speech

Hallmark symptoms: Hand wringing or squeezing, clapping, rubbing, washing, or hand to mouth movements appear

Breathing problems and autistic-like symptoms: Some may suffer communication issues and experience difficulties with social interactions

Stage 3[1,11]

Pseudo-stationary (plateau)

Onset: Typically 2–10 years of age

Duration: Years or decades

Movement problems and seizures: Prominent

Neurological symptoms stabilize: Some individuals may show slight improvements, particularly with autistic-like behaviors, hand skills, and walking

Attention span: Children's awareness of surroundings and communication skills may improve

Breathing problems may worsen, abnormal heart rhythm may develop in some children

Plateau phase: Many individuals remain at this stage for much of their lives

Stage 4[1,11]

Late motor deterioration

Onset: Typically around 10 years of age

Duration: Years or decades

Scoliosis develops

Mobility problems worsen: Those able to walk may lose that ability as muscle weakness and stiffness increase

Cognitive, communication, and hand skills: These symptoms usually stabilize, and hallmark hand movements may decrease

References: 1. Rett syndrome fact sheet. National Institute of Neurological Disorders and Stroke. December 30, 2021. Accessed January 6, 2022. https://www.ninds.nih.gov/disorders/patient-caregiver-education/fact-sheets/rett-syndrome-fact-sheet **2.** About Rett syndrome. Rett Syndrome Research Trust. 2022. Accessed January 28, 2022. https://reverserett.org/about-rett-syndrome/ **3.** Tarquinio DC, Hou W, Neul JL, et al. Age of diagnosis in Rett syndrome: patterns of recognition among diagnosticians and risk factors for late diagnosis. *Pediatr Neurol*. Accepted manuscript. Published online February 16, 2015. doi:10.1016/j.pediatrneurol.2015.02.007 **4.** Atypical Rett syndrome. Orpha.net. January 31, 2022. Updated March 2009. Accessed February 1, 2022. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=3095 **5.** Rett syndrome. National Organization for Rare Disorders. 2015. Accessed January 28, 2022. https://rarediseases.org/rare-diseases/rett-syndrome/ **6.** Rett syndrome. Mayo Clinic. October 11, 2018. Accessed January 28, 2022. https://www.mayoclinic.org/diseases-conditions/rett-syndrome/diagnosis-treatment/drc-20377233 **7.** Anderson A, Wong K, Jacoby P, et al. Twenty years of surveillance in Rett syndrome: what does this tell us? *Orphanet J Rare Dis*. 2014;9(87). http://www.ojrd.com/content/9/1/87 **8.** Rett syndrome. Genetic and Rare Disease Information Center. August 4, 2014. Updated February 1, 2021. Accessed January 28, 2022. https://rarediseases.info.nih.gov/diseases/5696/rett-syndrome **9.** Gogliotti RG, Niswender CM. A coordinated attack: Rett syndrome therapeutic development. *Trends Pharmacol Sci*. 2019;40(4):233-236. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6482467/ **10.** Life expectancy. *Rett Syndrome News*. BioNews. 2013-2022. Accessed February 2, 2022. https://rettsyndromenews.com/life-expectancy/ **11.** Stages of Rett syndrome. *Rett Syndrome News*. BioNews. 2013-2022. Accessed February 2, 2022. https://rettsyndromenews.com/stages-of-rett-syndrome/

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