



Tatton Brown Rahman Syndrome (TBRS), also referred to as DNMT3A Overgrowth Syndrome, is a rare genetic disease caused by variants in the *DNMT3A* gene. There is a wide range of medical issues associated with TBRS but most individuals have a few unifying characteristics:

- **Overgrowth** TBRS causes children to grow rapidly, and adults with the syndrome are often above average in height and weight. Head circumference is also often increased in size (this is referred to by doctors as macrocephaly).
- **Intellectual disability** Some individuals have severe cognitive impairment, while others have a mild disability.
- **Facial features** Horizontal eyebrows, large front teeth, and narrow eye openings are subtle yet distinctive characteristics of people with TBRS.

TBRS was first described in 2014, and although doctors continue to identify more individuals affected by the syndrome each year, it remains extremely rare, with around 150 people diagnosed as of 2020. Physicians are still learning about the full spectrum of conditions associated with TBRS. In addition to having the three characteristic features of overgrowth, intellectual disability, and facial features, some individuals additionally present with **autism, heart defects, low muscle tone, joint hypermobility, seizures, behavioral and mental health disorders, and scoliosis.**

There is no cure for TBRS. The needs of individuals with TBRS vary greatly—some are able to live independently with minimal aid, while others require lifelong intensive support and medical care. Because of this variability, it is important to gather a thorough assessment of each person's specific needs.

Doctors familiar with TBRS recommend meeting with the following clinicians:

- **Cardiologist** To screen for heart defects and get a baseline echocardiogram
- **Physical therapist, speech therapist, occupational therapist** For young children, states' Early Intervention programs can screen for eligibility. Older children may access these services through the school district, and adults, through their medical insurance or local adult services programs.
- **Geneticist and genetic counselor** To coordinate care and screenings, and keep families updated on new developments with the diagnosis
- A neurologist, orthopedic physician, psychiatrist, or behavioral therapist should be consulted if specific issues arise.



Leukemia connection

DNMT3A mutations, when acquired in blood cells later on in life (also called somatic mutations), are known to drive the development of leukemia in people *without* TBRS. For this reason, researchers are investigating whether TBRS is linked with an increased risk for leukemia. There is no evidence yet that TBRS causes cancer. If someone with TBRS shows possible signs of leukemia, such as easy, unexplained bruising or fatigue, consult a physician for testing.

The gene

The protein produced by the *DNMT3A* gene is involved in a process called DNA methylation, which helps cells determine which genes are turned on or off. Although all cases of TBRS involve mutations in *DNMT3A*, the location of the mutation in the gene is not the same for all individuals.

It appears that most mutations arise from spontaneous changes in the gene (called *de novo* mutations), rather than mutations inherited from the person's parents. However, some individuals may have inherited the *DNMT3A* variant from a parent who does not have TBRS. This is because the mutation can sometimes occur later in development and therefore be present in only certain types of cells (this is called mosaicism). Individuals with mosaicism could have a mutation in *DNMT3A* in sperm or eggs, also called the germline, and therefore possibly pass it down to their children.

Mutations in *DNMT3A* that cause TBRS are heterozygous, meaning they are only on one of the two copies of the gene that each person has. Because each parent provides one copy of a gene, someone with TBRS has a 50 percent chance of having a child with the genetic mutation. Genetic counseling is important to help clarify the inheritance pattern of TBRS.

Resources

Website

tbrsyndrome.org

Email

tbrsyndrome@gmail.com

Public Facebook page <https://www.facebook.com/dnmt3aovergrowthsyndrome/>

Private Facebook group for families and providers <https://www.facebook.com/groups/705487016188994/>

K. Tatton-Brown et al., "The Tatton-Brown Rahman Syndrome: A clinical study of 55 individuals with *de novo* constitutive *DNMT3A* variants," *Wellcome Open Research*, 3:46, 2018.

The Tatton Brown Rahman Syndrome Community supports individuals with TBRS, families, educators, clinicians, service providers, and researchers. More detailed information is available at tbrsyndrome.org.