Tatton Brown Rahman Syndrome
Fact Sheet

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 largely 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 or moderate disability.
- **Facial Features:** Thick, lowset, horizontal eyebrows, large front teeth, and narrow eye openings are subtle yet distinctive characteristics of people with TBRS. Facial features typically become more recognizable in the teenage years.

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 450 people known to have been diagnosed as of 2025. 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 recognizable facial features, some individuals additionally present with **autism, joint hypermobility, low muscle tone, kyphoscoliosis, seizures, behavioral and mental health disorders, heart defects, hearing and vision concerns, sleep apnea, early puberty, and blood disorders. There is also evidence to suggest patients have an increased risk of developing cancer, mainly thought to be leukemia.**

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 and for **families to participate in the Tatton Brown Rahman Syndrome (TBRS) and DNMT3A Patient Registry.**

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 or deletions in DNMT3A, the location of the mutation in the gene is not the same for all individuals, with most patients having a unique mutation or deletion of their own.

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. Some individuals may have inherited the *DNMT3A* variant from a parent who has TBRS or does not have TBRS. In the latter case, 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.

Clinical Information

Doctors familiar with TBRS recommend meeting with the following clinicians:

- **Cardiologist:** Recent findings show that over half of individuals with TBRS are affected by cardiac conditions, such as valve abnormalities, cardiomyopathy, or aortic root dilation—all of which may develop or worsen over time. It is important for families to discuss cardiac monitoring with their care team, including establishing a baseline echocardiogram and scheduling regular follow-ups to track any changes related to the heart valves, aorta, or heart muscle.
- **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
- **Neurologist:** Registry findings suggest that more than half of patients have experienced a seizure, and a large portion of the population presents with neurological conditions. Assessment and surveillance of these conditions are strongly recommended.
- **Hematologist/Oncologist:** A low threshold should be adopted for investigation of potential symptoms of leukemia and other blood conditions/cancers.
- **Dermatologist:** Skin checks are recommended due to the presence of melanoma cases in children and young adults. Abnormal skin biopsies have also been seen in some children.
- **An orthopedic physician, audiologist, ophthalmologist, urologist, pulmonologist, dentist, psychiatrist, or behavioral therapist** should be consulted if specific issues arise.

Cardiac

While not all TBRS patients have a heart condition, these conditions have been seen in a large portion of the population. Over half of individuals in the TBRS and *DNMT3A* Patient Registry have been diagnosed with a heart condition or structural abnormality. Among the most serious concerns is aortic root dilation, which can be progressive and may lead to life-threatening complications such as dissection or rupture. Other reported heart issues include atrial or ventricular septal defects, patent ductus arteriosus (PDA), mitral valve abnormalities, cardiomyopathy, and arrhythmias.

Routine cardiac evaluations—including baseline and follow-up echocardiograms—are recommended starting in childhood. Referral to a cardiologist should be considered for all individuals with TBRS. For more details and the most up-to-date guidance, *please see detailed cardiac information in the **Appendix 1,** attached.*

Blood Disorders and Cancer Risk

Because DNMT3A plays a key role in regulating cell growth and DNA methylation, individuals with TBRS may have an increased risk for certain cancers. More research is needed into this subject, but surveillance is recommended for these conditions. At least eight individuals with TBRS have been diagnosed with blood cancers such as acute myeloid leukemia (AML), lymphoma, and other hematologic malignancies. These cancers have occurred in both children and adults. Some individuals have also developed solid tumors, including melanoma, central nervous system tumors, and other rare cancers. Skin checks and awareness of symptoms such as persistent fevers, unusual bruising, or frequent infections are recommended.

There are currently no formal screening guidelines, but families may consider discussing symptom monitoring and occasional baseline blood testing (such as a Complete Blood Count, or CBC) with their healthcare team. For a more detailed summary of reported cases and surveillance tips, please *see detailed hematology/oncology information in **Appendix 2,** attached.*

Resources

Website: www.tbrsyndrome.org **Email:** info@tbrsyndrome.org

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

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

Registry: https://tbrsregistry.iamrare.org/

Ostrowski PJ, Tatton-Brown K. Tatton-Brown-Rahman Syndrome. 2022 Jun 30. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK581652/

Totten V et al. Arterial aneurysm and dissection: toward the evolving phenotype of Tatton-Brown-Rahman syndrome. J Med Genet. 2024 Aug 29, 61(9): 870-877.

Zebrauskiene D et al. Aortic disease and cardiomyopathy in patients with a novel DNMT3A gene variant causing TBRS. Clin Epigenet. 2024, 16(76).

Disclaimer: The TBRS Community provides this information to support informed clinical decision-making. This fact sheet is not a substitute for medical advice, and we do not provide recommendations for specific treatment. Please consult a qualified healthcare professional for individual medical care.

Updated: *June 2025*

Tatton Brown Rahman Syndrome (TBRS) Cardiac Care and Surveillance Fact Sheet

Background

Tatton Brown Rahman Syndrome (TBRS) is still a relatively new genetic condition, and research is ongoing. The surveillance recommendations published in GeneReviews in 2022 will need ongoing updates as new findings emerge. This fact sheet provides clinicians and families with the most current information by incorporating unpublished data from our TBRS and *DNMT3A* Patient Registry (with over 200 participants) and the latest published research.

Overview of TBRS and Cardiac Concerns

TBRS is a genetic condition caused by pathogenic variants in the *DNMT3A* gene. TBRS is associated with overgrowth, intellectual disability, joint hypermobility, hypotonia, obesity, behavioral/psychiatric problems, kyphoscoliosis, seizures, and a variety of other clinical features.

Cardiac Phenotype in TBRS

Individuals with TBRS may exhibit various cardiovascular manifestations, with aortic root dilation being a significant concern reported in multiple cases. Congenital heart defects, including atrial septal defects (ASD), ventricular septal defects (VSD), and patent ductus arteriosus (PDA), have also been observed, though their frequency is still being studied. Less commonly, individual cases of mitral valve prolapse, dilated cardiomyopathy, and arrhythmias have been reported. The increasingly recognized cardiac involvement among individuals with TBRS highlights the need for routine cardiac surveillance.

> **About 54% of the 200 patients in the TBRS and DNMT3A Patient Registry have been diagnosed with a heart condition or structural abnormality.**

Recent research has identified **aortic root dilation** as a significant concern in some individuals with TBRS. These studies have identified more than 15 cases of aortic dilation or dissection in individuals with TBRS, encompassing pediatric and adult patients. **The cases span from childhood to middle adulthood, and some patients experience rapid progression of aortic dilation.** The aortic root dilation is of varying degrees of severity and can be associated with other cardiovascular issues, including mitral valve abnormalities and arrhythmias. Dissection and rupture are potentially life-threatening complications, and emergency surgery for aortic dissection has been documented.

Key Takeaways for Clinicians

- Routine cardiovascular surveillance is essential for individuals with TBRS.
- Aortic root dilation can be progressive, emphasizing the need for regular echocardiograms starting in childhood.
- Referral to a cardiologist should be considered for all TBRS patients.
- TBRS is still a newly identified condition, and more data are needed to develop formal surveillance guidelines. The TBRS Community continues to collect and analyze data through its Patient Registry to support further research and clinical recommendations.

Surveillance Recommendations

The last updated surveillance guidelines for TBRS were published in GeneReviews in 2022 (**prior to the aortic dilation findings**) and can be found here: https://www.ncbi.nlm.nih.gov/books/NBK581652

The cardiac recommendations from GeneReview suggest (please see GeneReviews for complete information):

- **Recommended Cardiac Evaluations Following Initial Diagnosis:** Baseline echocardiogram to assess structural heart defects and aortic dilation
- ***Ongoing Surveillance Recommendations:*** Echocardiogram to assess aortic root indices: Ongoing surveillance to be determined by size of aortic root, advice of cardiologist, health care framework, and data from longitudinal studies

Recent Findings on Aortic Dilation in TBRS

Recent studies have identified 15 cases of aortic dilation or dissection in individuals with TBRS. Cases include both children and adults, with some experiencing rapid progression over time. Below is a summary:

Age of individual (years)	Description of aortic root dilation	Progressive (yes/no)
40	Near-complete ascending aortic dissection requiring emergency surgery	not known
16	Aortic dilation detected post-genetic diagnosis	Yes: rapid progression
10	Aortic root dilation detected during workup for severe pectus excavatum	Yes
39	Aortic root dilation at 44 mm requiring surgery	Yes
14	Mild aortic dilation with mitral regurgitation	not known
10	Aortic dilation	No
30	Aortic root dilation at 49 mm, with a history of mitral leaflet billowing	not known
16	Aortic root dilation with mitral regurgitation	not known
30	Aortic root dilation at 57 mm, requiring surgery	not known
34	Aortic root dilation diagnosed in adolescence at 35 mm	Yes
38	Diagnosed with aortic root dilation at 41 mm	not known
27 & father of unknown age	Father and son with *DNMT3A* variant; both had aortic dilation, mitral valve prolapse, and arrhythmia	not known
49	Ruptured iliac aneurysm requiring emergency stenting; subsequent complications	Yes
6	Enlarged aortic valve, progressed from 24 mm to 29 mm by age 10	Yes

Citations

Ostrowski PJ, Tatton-Brown K. Tatton-Brown-Rahman Syndrome. 2022 Jun 30. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.

Totten V, Teixido-Tura G, Lopez-Grondona F et al. Arterial aneurysm and dissection: toward the evolving phenotype of Tatton-Brown-Rahman syndrome. J Med Genet. 2024 Aug 29;61(9):870-877.

Zebrauskiene D, Sadauskiene E, Dapkunas J et al. Aortic disease and cardiomyopathy in patients with a novel DNMT3A gene variant causing TBRS. Clin Epigenet 16, 76 (2024).

Tatton Brown Rahman Syndrome (TBRS) Blood and Cancer Fact Sheet

Overview

Tatton Brown Rahman Syndrome (TBRS), caused by pathogenic variants in the *DNMT3A* gene, is associated with overgrowth, intellectual disability, hypotonia, obesity, increased risk of malignancy, cardiac disorders, seizures, and other features. Because *DNMT3A* plays a key role in regulating cell growth and DNA methylation, researchers believe it may also contribute to an increased risk of developing certain cancers.

Tatton-Brown-Rahman Syndrome (TBRS) is still a relatively new genetic condition, and research is ongoing. The surveillance recommendations published in GeneReviews in 2022, will need ongoing updates as new findings emerge. This fact sheet is designed to provide clinicians and families with the most current information by incorporating unpublished data from our TBRS and *DNMT3A* Patient Registry (with over 200 participants) and the latest published research. As we continue to gather insights, we will update this reference sheet.

While it will take many more years and larger studies to fully understand cancer risk in TBRS, early findings suggest the importance of cancer surveillance—particularly for blood cancers like leukemia and solid tumors.

What We Know About Cancer Risk in TBRS

- **Leukemia and Other Blood Cancers:** Research has shown that individuals with TBRS may be at increased risk for **acute myeloid leukemia (AML), lymphoma,** and other hematologic malignancies. To date, at least 8 cases of hematologic cancer have been reported in individuals with TBRS. These cancers have appeared in both children and adults, with a **median age of diagnosis around ten years.**
- **Melanoma and Other Solid Tumors:** A recent publication reported the first known case of melanoma in an adult with TBRS, with genetic evidence suggesting that *DNMT3A* deficiency contributed to tumor development. Two additional melanoma cases have been reported in the TBRS Community, but are not published in the literature. There have also been rare reports of central nervous system and peripheral tumors.

Key Takeaways for Families and Clinicians

- **Know the signs and symptoms of leukemia:** These include persistent fevers, fatigue, easy bruising, unusual bleeding (like nosebleeds or petechiae), pallor, swollen lymph nodes, or frequent infections.
- **Skin exams should be part of routine care.** Families should regularly check for new or changing moles or skin lesions, and a dermatologist may be helpful for ongoing surveillance.
- **No formal guidelines exist yet.** Surveillance decisions should be discussed with your medical team and may depend on age, personal and family history, and advice from specialists. As there is no good screening test for blood cancers, and there is no generally agreed-upon routine monitoring. Having a blood test called a complete blood cell count (CBC) done once when you

are healthy and not having symptoms could be helpful to establish your normal baseline values. If any symptoms concerning a blood cancer occur, blood tests, including a CBC, should be done immediately. Some experts have suggested doing CBCs yearly, but no consensus has been reached.

Suggested Surveillance

These are not clinical recommendations, but areas to consider discussing with your healthcare provider:

Area of Concern	Suggested Screening Tool	Frequency	Notes
Blood cancers	Complete Blood Count (CBC)	Anytime symptoms develop	Have a routine CBC done to establish baseline values
Skin cancer	Skin check (self or clinical)	Monthly self-exams	
Yearly exams by your doctor, early referral to a dermatologist for any concerning lesion	Patients in the TBRS Community report precancerous skin biopsies, melanoma, and other skin cancers, even in early childhood, suggesting skin checks should be done regularly.		
Other solid tumors	Based on symptoms	No routine surveillance guidance exists	Referral as clinically indicated.

Research indicates that TBRS may predispose individuals to both hematologic (blood-based) and solid tumors. As of now:

- At least 8 individuals with TBRS have been diagnosed with hematologic cancers, including acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia (B-ALL), Hodgkin lymphoma, essential thrombocythemia, and T-lymphoblastic leukemia.
- These diagnoses range from early childhood to adulthood, with a median age of diagnosis around 10 years.
- One individual developed chronic multilineage cytopenias, which may represent a cancer predisposition or pre-leukemic condition.
- Three individuals have been reported with melanoma. One of these cases had lymph node metastasis, along with a previous rare tumor (dermatofibrosarcoma protuberans).
- There are also three reported cases of central and peripheral nervous system tumors, including medulloblastoma, pituitary adenoma, and ganglioneuroma.

Table of Published Cancer Cases in TBRS

Case #	Cancer Type	Age at Diagnosis	DNMT3A Variant	Notes	Source
1	Acute Myeloid Leukemia (AML)	12	R882C	NPM1, NF1, MYC mutations; remission after treatment	Ferris et al. 2022
2	B-cell Acute Lymphoblastic Leukemia	9	R882H	Alive; details of mutations unknown	Ferris et al. 2022
3	T-lymphoblastic Leukemia (post GNBL)	6 (GN), 6 (T-ALL)	R882H	Passed away; metastatic ganglioneuroblastoma prior to T-ALL	Balci et al. 2020
4	Chronic multilineage cytopenias	5	Y528X	Possible pre-leukemic condition	Ferris et al. 2022
5	AML	20	I310F	Received allogeneic transplant	Ferris et al. 2022
6	Hodgkin Lymphoma	27	Y735C	Treated with autologous transplant; alive	Ferris et al. 2022
7	Essential Thrombocytosis	34	R882H	Deceased	Ferris et al. 2022
8	AML	15	R882C	Co-mutation PTPN11T73I; alive 8 years later	Ferris et al. 2022
9	AML	12	Y735S	Alive 12 years later	Ferris et al. 2022
10	Melanoma (Stage IIIA)	34	F414fs (germline), R749C (somatic)	Also had prior dermatofibrosarcoma protuberans at age 20	Chen et al. 2023
11	Medulloblastoma	Child	Not specified	CNS tumor	GeneReviews
12	Pituitary adenoma	Child	Not specified	CNS tumor	GeneReviews
13	Ganglioneuroma (with T-ALL)	6	R882H	Reported as part of case #3 above	Balci et al. 2020

**Patient #10 has since passed away at 39 years old from metastatic melanoma.*

Importantly, additional cancers have been reported anecdotally by families in the TBRS Community Facebook group. These have not yet been included in the published literature.

Why Surveillance Matters

Because cancer risk in TBRS is not fully defined, **early detection** through symptom awareness and basic screening may improve outcomes. Several TBRS families have shared personal stories where early recognition led to timely care.

Additional Resources

- TBRS and DNMT3A Patient Registry: tbrsregistry.iamrare.org
- Hematologic malignancy risk: Ferris et al., Blood 2022
- Melanoma case study: Chen et al., Mol Case Stud 2023
- GeneReviews TBRS Entry: NCBI GeneReviews

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