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Tatton-Brown-Rahman Syndrome

Synonym: *DNMT3A* Overgrowth Syndrome

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Summary

Clinical characteristics

Tatton-Brown-Rahman syndrome (TBRS) is an overgrowth / intellectual disability syndrome characterized by length/height and/or head circumference ≥2 standard deviations above the mean for age and sex, obesity / increased weight, intellectual disability that ranges from mild to severe, joint hypermobility, hypotonia, behavioral/psychiatric issues, kyphoscoliosis, and seizures. Individuals with TBRS have subtle dysmorphic features, including a round face with coarse features, thick horizontal low-set eyebrows, narrow (as measured vertically) palpebral fissures, and prominent upper central incisors. The facial gestalt is most easily recognizable in the teenage years. TBRS may be associated with an increased risk of developing acute myeloid leukemia. There are less clear associations with aortic root dilatation and increased risk of other hematologic and solid tumors.

Diagnosis/testing

The diagnosis of TBRS is established in a proband with suggestive findings and a heterozygous pathogenic variant in *DNMT3A* identified by molecular genetic testing

Management

Treatment of manifestations: Treatments are primarily supportive and based on symptoms. Developmental delay / intellectual disability, behavioral/psychiatric diagnoses, epilepsy, joint hypermobility, kyphoscoliosis, sleep apnea, cryptorchidism, and acute leukemia are all treated in the standardized fashion.

Surveillance: Monitoring of growth parameters, developmental progress, behavior, mobility, and self-help skills at each visit. Assessment for new neurologic manifestations, seizures, and signs and symptoms of sleep apnea and hematologic malignancies at each visit. Low threshold for complete blood count with differential and

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further investigations in those who have concerning signs and symptoms of hematologic malignancy; there are no consensus guidelines regarding screening for hematologic malignancy in individuals with TBRS.

Genetic counseling

TBRS is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, individuals diagnosed with TBRS have the disorder as the result of a *DNMT3A* pathogenic variant inherited from a parent. Each child of an individual with TBRS has a 50% chance of inheriting the *DNMT3A* pathogenic variant. Once the *DNMT3A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Tatton-Brown-Rahman syndrome (TBRS) have been published.

Suggestive Findings

TBRS **should be considered** in individuals with the following clinical findings and family history.

Clinical findings

- Generalized overgrowth (length/height and/or head circumference ≥2 standard deviations above the mean for age and sex) [Tatton-Brown et al 2017]
- Mild-to-severe developmental delay (DD) or intellectual disability (ID)

AND

- Any of the following features presenting in infancy or childhood/adolescence:
  - Dysmorphic facial features (See Clinical Characteristics.)
  - Joint hypermobility
  - Hypotonia
  - Kyphoscoliosis
  - Seizures, including variable afebrile seizure types
  - Cryptorchidism
  - Behavior problems, most commonly autism spectrum disorder, although a variety of behavioral issues have been described (See Clinical Characteristics.)
  - Acute myeloid leukemia and possibly other hematologic malignancies

Family history. Because TBRS is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e. a single occurrence in a family). However, there are individual reports of familial cases, including inheritance from an unaffected mosaic parent [Xin et al 2017, Balci et al 2020] and inheritance from an affected parent [Lemire et al 2017], suggesting rare autosomal dominant inheritance.

Establishing the Diagnosis

The diagnosis of TBRS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *DNMT3A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *DNMT3A* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of TBRS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of TBRS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** If a person presents with the characteristic TBRS phenotype and facial gestalt, a clinician experienced with the condition may decide to undertake sequence analysis of *DNMT3A* as a first-line test to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **An overgrowth and/or intellectual disability multigene panel.** Most clinicians are more likely to choose an overgrowth and/or intellectual disability multigene panel that includes *DNMT3A* and other genes of interest (see Differential Diagnosis) to identify the genetic cause of the condition. An advantage of a gene panel approach over more agnostic sequencing methods (see Option 2) is that a gene panel approach limits identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by intellectual disability or the clinician is unfamiliar with the TBRS phenotype, then **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Tatton-Brown-Rahman Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
DNMT3A	Sequence analysis [4]	>90% [5]
	Gene-targeted deletion/duplication analysis [6]	<10% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. One additional individual with a contiguous gene deletion (not included in these calculations) has been reported; see Genetically Related Disorders [Okamoto et al 2016].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and from Tatton-Brown et al [2018]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Tatton-Brown et al [2018]

Clinical Characteristics

Clinical Description

The cardinal features of Tatton-Brown-Rahman syndrome (TBRS) are overgrowth and mild-to-severe intellectual disability. Other common features include joint hypermobility, obesity / increased weight, hypotonia, behavioral/psychiatric problems, kyphoscoliosis, and seizures. To date, more than 90 individuals with a pathogenic variant in *DNMT3A* have been reported [Tatton-Brown et al 2014, Tlemsani et al 2016, Kosaki et al 2017, Lemire et al 2017, Shen et al 2017, Xin et al 2017, Tatton-Brown et al 2018, Sweeney et al 2019, Balci et al 2020, Hage et al 2020, Tenorio et al 2020, Yokoi et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports and the authors' personal communications with the families.

Table 2. Select Features of Tatton-Brown-Rahman Syndrome

Feature	% of Persons w/Feature	Comment
Intellectual disability	100%	Most often in mild-to-moderate range
Overgrowth [1]	>80%	• Tall stature (height ≥2 SD above mean) in ~70% • Macrocephaly (head circumference ≥2 SD above mean) in ~50%
Joint hypermobility	~75%	
Overweight [2]	~65%	
Hypotonia	~55%	
Behavioral/psychiatric issues	~50%	Most commonly autism spectrum disorder
Kyphoscoliosis	~30%	
Seizures	~20%	
Cryptorchidism	~20% of males	
Cardiovascular disease	~10%	Most commonly congenital heart disease, although aortic root dilatation also observed
Ventriculomegaly	<10%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Chiari malformation	<10%	
Malignant tumors	~5%	Most commonly acute myeloid leukemia [3]

SD = standard deviation(s)
1. Defined as length/height and/or head circumference ≥2 SD above the mean for age and sex
2. Defined as weight ≥2 SD above the mean for age and sex
3. This figure is an estimate based on cases reported to date; the precise risk remains unknown.

Growth. Overgrowth is present in more than 80% of affected individuals. However, clinical variability is seen among affected individuals and the absence of overgrowth does not preclude a diagnosis of TBRS.

- Tall stature (height ≥2 standard deviations [SD] above the mean for age and sex) is present in about 70% of individuals. Height ranges from 0.3 SD below to 6 SD above the mean.
- Macrocephaly (head circumference ≥2 SD above the mean for age and sex) is present in around 50% of affected individuals. Head circumference ranges from 1.2 SD below to 8.0 SD above the mean.
- About 65% of affected individuals are overweight or obese (weight ≥2 SD above the mean for age and sex). Weight ranges from 1.1 SD below to 4.5 SD above the mean.

There is relatively little information about birth measurements, although overgrowth typically is present from early childhood. In those for whom measurements were available, mean birth weight was 1.3 SD above the mean (range: 1.1 SD below to 4.0 SD above mean), mean birth head circumference was 2.3 SD above the mean (range: 0.6 to 6.5 SD above mean), and mean birth length was 1.6 SD above the mean (range: 0.0 to 4.4 SD above mean) [Tatton-Brown et al 2018].

Developmental delay (DD) and intellectual disability (ID). All affected individuals reported to date have some degree of developmental delay and/or intellectual disability, ranging from mild to severe. While the specific severity is not reported for all known individuals, most of those who are described in detail (n=83) had intellectual disability in the mild-to-moderate range.

- **Mild ID** (23/83, 28%). Children attend mainstream school and need some extra help – for example, a statement of educational needs (see Management) – but would be expected to live independently as adults and may have their own family.
- **Moderate ID** (48/83, 58%). Children develop speech and may be able to attend mainstream school with a high level of support, but more likely will attend a school or be in a program for individuals with special educational needs. While unlikely to live completely independently as adults, they may live in sheltered accommodation or with some additional support.
- **Severe ID** (12/83, 14%). Individuals require special education during schooling and are likely to require considerable support in adulthood.

A subsequent publication reported more detailed cognitive and behavioral profiles of a smaller cohort (n=18, age 7-33 years) [Lane et al 2020]. The mean General Conceptual Ability score was 53 (range: 39-76). Nonverbal and spatial reasoning were more significantly impaired than verbal reasoning.

Behavior problems. The behavior problems seen in individuals with TBRS are most commonly associated with autism spectrum disorder.

- In a series of 18 individuals with a confirmed molecular diagnosis, autistic traits were present in the majority, and eight (44%) fulfilled the ADOS-2 criteria for a formal diagnosis of autism [Lane et al 2020].
- The prevalence of autistic traits was lower in older individuals, suggesting that symptoms may improve with age, but this is based on cross-sectional assessment of a relatively small cohort rather than long-term observation.

Other behavior problems reported in a smaller proportion of affected individuals include [Tatton-Brown et al 2018, Tenorio et al 2020]:

- Anxiety
- Aggression
- Psychotic disorders
- Bipolar disorder
- Obsessive behaviors
- Compulsive eating

Musculoskeletal features. Generalized joint hypermobility is a common feature of TBRS. It can be associated with musculoskeletal pain and joint instability; joint dislocations are rare. Kyphoscoliosis is present in about 30% of affected individuals [Tatton-Brown et al 2018]. Widely spaced toes are a commonly reported feature, although the exact prevalence is unknown [Tatton-Brown et al 2018].

Hypotonia is present in a majority of individuals with TBRS [Tatton-Brown et al 2018] and may require physical therapy.

Epilepsy. Seizures are present in around 20% of people with TBRS [Tatton-Brown et al 2018]. Both febrile and afebrile seizures have been reported. There is limited information regarding the specific types of seizures, age of seizure onset, or whether specific anti-seizure medications are more effective than others in individuals with TBRS.

Neuroimaging. No specific or consistent imaging abnormalities are known to be characteristic of TBRS. Individual abnormalities detected on brain MRI have included ventriculomegaly and Chiari malformation [Kosaki et al 2017, Tatton-Brown et al 2018].

Genitourinary abnormalities. Cryptorchidism is present in about 20% of males with TBRS [Tatton-Brown et al 2018]. Other genitourinary abnormalities reported in a few individuals with TBRS include vesicoureteral reflux and hypospadias [Tatton-Brown et al 2018, Tenorio et al 2020].

Malignant tumors. There is evidence that the spectrum of germline *DNMT3A* pathogenic variants found in individuals with TBRS is similar to that found in sporadic, nonsyndromic malignancies [Shen et al 2017]. However, data are insufficient to determine the precise risk of malignancy to a given individual with TBRS. To date, hematologic malignancies have been reported in eight individuals with TBRS, suggesting a risk on the order of about 4% [Hollink et al 2017, Ferris et al 2022] (see Genotype-Phenotype Correlations and Cancer and Benign Tumors).

- The most common malignancy is acute myeloid leukemia (AML; 4/8 individuals); cases of lymphoid malignancy and myelodysplastic syndrome have also been reported.
- The median age at diagnosis is 9.6 years (range: age 2.5-12 years), with the cases of AML diagnosed between ages nine and 20 years.
- Limited information exists regarding lifetime cancer risk in individuals with TBRS, as the majority of individuals identified to date who have developed cancer are children or young adults.

Single case reports of a specific cancer in an individual with TBRS have been published; however, in the absence of further known cases, it is not clear whether these tumors are specifically associated with TBRS or are rare co-occurrences. The tumors are as follows:

- Neuroblastoma [Tenorio et al 2020]
- Medulloblastoma [Sweeney et al 2019]
- Benign glioma [Tenorio et al 2020]
- Acromegaly as a result of a pituitary adenoma [Hage et al 2020]

- Ganglioneuroblastoma and T-cell lymphoblastic lymphoma [Balci et al 2020]; this individual also had a truncating pathogenic variant in *CLTC*.

Facial features. While the facial gestalt of TBRS may not be as clinically recognizable as other overgrowth disorders (e.g., Sotos syndrome), common facial features are shared by a significant proportion of affected individuals. The facial features are most characteristic in adolescence and less specific in early childhood or adulthood. They include the following [Tatton-Brown et al 2018]:

- A round face with coarse features (describing some loss of definition of the nose, lips, mouth, and chin because of rounded and heavy features)
- Thick horizontal low-set (i.e., closer than anticipated to the orbit) eyebrows
- Narrow (as measured vertically) palpebral fissures
- Prominent upper central incisors

Other associated features. The following are less common features seen in affected individuals, including features reported in only one affected individual each. It remains to be confirmed whether the feature is specifically associated with TBRS or is a rare co-occurrence.

- **Cardiovascular disease.** Aortic root dilatation has been reported in several individuals with TBRS [Tatton-Brown et al 2018, Tenorio et al 2020, Cecchi et al 2022]. Aortic dissection and sudden cardiac death have not been reported, and it remains to be established whether aortic dilatation is static or progressive. Congenital heart defects (atrial septal defect, ventricular septal defect, persistent ductus arteriosus) are also commonly reported by families (although not yet published as a frequent association in the literature). A longitudinal study is under way to quantify the incidence. Less common cardiovascular features, reported in one affected individual each, include the following [Kosaki et al 2017, Tatton-Brown et al 2018, Cecchi et al 2022]:
  - Mitral valve prolapse
  - Dilated cardiomyopathy
  - Arrhythmia
- **Respiratory abnormalities.** Central sleep apnea has been reported in several individuals with TBRS [Tatton-Brown et al 2018, Balci et al 2020].
- **Dental anomalies** including malocclusion, caries, and double teeth have been reported in individuals with TBRS [Tatton-Brown et al 2018, Paz-Alegría et al 2020].
- **Congenital diaphragmatic hernia** has been described in one affected individual [Balci et al 2020].
- **Autonomic dysfunction** including postural orthostatic hypotension and episodic vasomotor instability in the extremities have been reported in four affected individuals [Balci et al 2020].

Prognosis. Data on whether TBRS alters life span are limited. Since many adults with disabilities have not undergone advanced genetic testing and mutation of *DNMT3A* was first recognized to be associated with a clinical phenotype in 2014 [Tatton-Brown et al 2014], it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Malignancy. As in the case of sporadic, nonsyndromic malignancies (see Cancer and Benign Tumors), the most commonly observed pathogenic variants in individuals with TBRS who develop malignancy (n=8) are missense variants affecting the arginine residue at position 882 (Arg882 or R882), present in five of the eight affected individuals in whom malignancy occurred. This suggests that germline pathogenic variants affecting this residue may be particularly associated with an increased risk of malignancy (see Molecular Genetics).

Psychiatric issues. While there are relatively few reports of psychotic symptoms in individuals with TBRS, when psychotic symptoms have been reported, the majority of individuals (4/5) have pathogenic missense variants

clustering within the methyltransferase domain of *DNMT3A* [Tatton-Brown et al 2018, Tenorio et al 2020] (see Molecular Genetics).

Prevalence

The prevalence of TBRS is unknown. More than 90 cases have been reported in the literature to date [Tatton-Brown et al 2014, Tlemsani et al 2016, Kosaki et al 2017, Lemire et al 2017, Shen et al 2017, Xin et al 2017, Tatton-Brown et al 2018, Sweeney et al 2019, Balci et al 2020, Hage et al 2020, Tenorio et al 2020, Yokoi et al 2020].

Genetically Related (Allelic) Disorders

Larger deletions of 2p23.3. Okamoto et al [2016] described a person with a larger (1.5-Mb) deletion of 2p23.3 that included *DNMT3A* and adjacent genes. The predominant features were those seen in individuals with TBRS.

Heyn-Sproul-Jackson syndrome (OMIM 618724). Heterozygous germline pathogenic variants in *DNMT3A* are also known to be associated with Heyn-Sproul-Jackson syndrome, which is characterized by microcephalic dwarfism and has been described as a reciprocal phenotype to TBRS [Heyn et al 2019]. In contrast to TBRS, which is caused by loss-of-function pathogenic variants in *DNMT3A*, Heyn-Sproul-Jackson syndrome is caused by gain-of-function pathogenic variants clustering at the C-terminal end of the PWWP domain of *DNMT3A* [Heyn et al 2019].

Sporadic tumors (including adult acute myeloid leukemia and myelodysplastic syndrome) occurring as single tumors in the absence of any other findings of Tatton-Brown-Rahman syndrome frequently harbor a somatic pathogenic variant in *DNMT3A* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. Somatic variants in *DNMT3A* are an established driver of clonal hematopoiesis [Jaiswal et al 2014] and hematologic malignancies, particularly acute myeloid leukemia [Ley et al 2010]. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Table 3. Disorders with Overgrowth and Intellectual Disability in the Differential Diagnosis of Tatton-Brown-Rahman Syndrome

Gene(s)	Disorder	MOI	Clinical Characteristics
BRWD3	*BRWD3*-related OGID (OMIM 300659)	XL	• Macrocephaly • Obesity • Mild-to-moderate ID • Tall chin, prognathism, broad forehead, prominent supraorbital ridge
CHD8	*CHD8*-related OGID (See *CHD8*-Related Neurodevelopmental Disorder with Overgrowth.)	AD	• Frontal bossing, downslanted palpebral fissures, high hairline • Tall stature • Macrocephaly • Variable ID • Hypotonia
EED	Cohen-Gibson syndrome (See *EED*-Related Overgrowth.)	AD	• Hypertelorism, round face, "stuck-on" chin • Tall stature • Macrocephaly • Scoliosis • Ligamentous laxity • Hypotonia at birth

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics
EZH2	*EZH2*-related Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD	• Broad forehead, widely spaced eyes, almond-shaped palpebral fissures • Tall stature • Macrocephaly • Variable ID (some w/normal intellect) • Umbilical hernia • Camptodactyly, boutonniere deformity, talipes equinovarus • Advanced bone age
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	• Macrocephaly • ID • Prominent jaw & forehead
GPC3 *GPC4*	Simpson-Golabi-Behmel syndrome	XL	• Macrocephaly • Coarse facial features • Macrostomia, macroglossia, palatal abnormalities • Polydactyly • Supernumerary nipples • Diastasis recti • Pectus excavatum
NFIX	Malan syndrome (OMIM 614753)	AD	• Sotos syndrome-like condition • Tall stature • Variable ID • Ophthalmologic abnormalities are common. • Growth frequently normalizes in teenagers & young adults.
NSD1	Sotos syndrome	AD	• Broad/prominent forehead, dolichocephaly, bitemporal narrowing w/sparse frontotemporal hair, downslanted palpebral fissures, malar flushing (in children), long prominent chin • Pre- & postnatal overgrowth • Variable ID • Advanced bone age • Scoliosis • Joint hypermobility
SUZ12	*SUZ12*-related OGID (OMIM 618786)	AD	• Tall stature • Macrocephaly • Scoliosis • Joint hypermobility • Hypotonia

AD = autosomal dominant; ID = intellectual disability; MOI = mode of inheritance; OGID = overgrowth with intellectual disability; XL = X-linked

Management

No clinical practice guidelines for Tatton-Brown-Rahman syndrome (TBRS) have been published.

Since the majority of individuals with TBRS are in good general health, the authors recommend a pragmatic approach to management, consisting of a series of initial assessments at diagnosis, patient/family education about potential complications, and regular symptom review with treatment as required [Tatton-Brown et al 2018].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with TBRS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Tatton-Brown-Rahman Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for macrosomia
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Neurologic	Neurologic eval	• Consider brain MRI if indicated by clinical symptoms. • Consider EEG if seizures are a concern.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Joint hypermobility &/or kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Cardiovascular	Baseline echocardiogram	To assess for structural heart defects & aortic dilatation
Respiratory	Polysomnography	To assess for sleep apnea if suggested by clinical symptoms
Genitourinary	Exam for cryptorchidism in males	Consider assessment for vesicoureteral reflux [1] in those w/history of recurrent urinary tract infections.
Hematologic/ Lymphatic	Consider CBC w/differential	• Inform patients/families of potential risk of hematologic malignancy, w/emphasis on symptom awareness. • There is no evidence-based screening regimen, but low threshold should be adopted for investigation for malignancy in case of symptoms.
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of TBRS to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; CBC = complete blood count; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; TBRS = Tatton-Brown-Rahman syndrome

1. Which may include renal ultrasound and/or voiding cystourethrogram (VCUG)

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Tatton-Brown-Rahman Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Obesity	Referral to dietician & accompanying lifestyle advice recommended	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Behavioral/ psychiatric diagnoses	Standard treatment per psychologist/psychiatrist	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for TBRS. • Education of parents/caregivers [1]
Joint hypermobility	Standard treatment incl PT &/or OT	
Kyphoscoliosis	Standard treatment per orthopedist	
Congenital heart defects / Aortic dilatation	Standard treatment per cardiologist	
Sleep apnea	Standard treatment per otolaryngologist &/or sleep medicine specialist	
Cryptorchidism	Standard treatment per urologist	
Acute leukemia	Standard treatment per hematologist/oncologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 6. Recommended Surveillance for Individuals with Tatton-Brown-Rahman Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters incl head circumference in infancy & childhood	At each visit
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavior assessment for anxiety, attention, & aggressive or self-injurious behavior	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures & changes in tone.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility & self-help skills	
Respiratory	Assess for signs & symptoms of sleep apnea.	
Hematologic/ Lymphatic	Assess for signs & symptoms of hematologic malignancy, w/low threshold for CBC w/differential & further investigations if clinically indicated.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	
Cardiovascular	Echocardiogram to assess aortic root indices	Ongoing surveillance to be determined by size of aortic root, advice of cardiologist, health care framework, & data from longitudinal studies

CBC = complete blood count; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Tatton-Brown-Rahman syndrome (TBRS) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Nearly all probands reported to date with TBRS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo DNMT3A* pathogenic variant.
- Rarely, individuals diagnosed with TBRS have the disorder as the result of a *DNMT3A* pathogenic variant inherited from a parent. Reports describing parental transmission of a pathogenic variant include inheritance from an unaffected mosaic parent [Xin et al 2017, Balci et al 2020] and from an affected parent [Lemire et al 2017].
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. * Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for a *DNMT3A* pathogenic variant may be mildly/minimally affected.

Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the *DNMT3A* pathogenic variant identified in the proband, the risk to sibs of inheriting the variant is 50%.
- If the *DNMT3A* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be slightly greater than that of the general population because of the possibility of parental germline mosaicism [Xin et al 2017].

Offspring of a proband. Each child of an individual with TBRS has a 50% chance of inheriting the *DNMT3A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *DNMT3A* pathogenic variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DNMT3A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  DNMT3A overgrowth syndrome
- **TBRS Community**
  www.tbrsyndrome.org
- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: nfo@childgrowthfoundation.org
  www.childgrowthfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Tatton-Brown-Rahman Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
DNMT3A	2p23.3	DNA (cytosine-5)-methyltransferase 3A	DNMT3A	DNMT3A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Tatton-Brown-Rahman Syndrome (View All in OMIM)

602769	DNA METHYLTRANSFERASE 3A; DNMT3A
615879	TATTON-BROWN-RAHMAN SYNDROME; TBRS

Molecular Pathogenesis

DNMT3A encodes one of a family of DNA methyltransferases that catalyze the methylation of cytosine residues to 5-methylcytosine. The DMNT3A enzyme plays a role in establishment of parent-of-origin methylation during gametogenesis [Kaneda et al 2004] and reestablishment of methylation during embryogenesis [Okano et al 1999].

Methylation studies in mouse models and humans have demonstrated that *TBRS* pathogenic variants (including pathogenic missense variants, truncating variants, and whole-gene deletion) are associated with a characteristic

hypomethylation pattern, indicating that these pathogenic variants cause loss of methyltransferase activity [Smith et al 2021]. This is likely to have widespread effects on gene expression.

Truncating variants, splice site variants, and whole-gene deletions are assumed to cause disease as a result of haploinsufficiency. The pathogenic missense variants reported to date are clustered within the three functional domains of DNMT3A (proline-tryptophan-tryptophan-proline [PWWP] domain, ATRX-DNMT3A-DNMT3L-type zinc finger [ADD] domain, and DNA methyltransferase domain), suggesting that they are likely to cause disease by affecting the function of these domains [Tatton-Brown et al 2018, Tenorio et al 2020]. This mechanism is supported by the observation that pathogenic missense variants are associated with a similar pattern of hypomethylation compared to loss-of-function pathogenic variants [Smith et al 2021]. There is evidence that, in addition to reducing activity of the mutated DNMT3A enzyme, heterozygous variants at Arg882 exert a dominant-negative effect by inactivating wild type DNMT3A [Russler-Germain et al 2014]. Variants affecting Arg882 have been shown to cause more significant hypomethylation than other variants, which may explain why they are more frequently observed in individuals with sporadic malignancy [Smith et al 2021].

For individuals with TBRS who have psychiatric issues, it has been suggested that abnormal catalytic function of the methyltransferase domain could affect metabolic pathways in the brain [Tenorio et al 2020], but further work, including longitudinal observation of individuals with TBRS progressing into adulthood, is required to confirm whether this is a robust genotype-phenotype association.

Mechanism of disease causation. The mechanism of disease is loss of function. The common pathogenic variants at Arg882 (R882), which are associated with both TBRS and sporadic acute myeloid leukemia, may exert an additional dominant-negative effect.

***DNMT3A*-specific laboratory technical considerations.** Somatic variants in *DNMT3A* are associated with clonal hematopoiesis and sporadic hematologic malignancies [Ley et al 2010, Jaiswal et al 2014], suggesting that they may be enriched in population databases derived from peripheral blood samples. This has significant implications for variant interpretation, and caution is advised when assessing population frequencies. In particular, the presence of a variant in population databases does not necessarily provide evidence against pathogenicity, as its occurrence in the general population may represent somatic rather than germline variation.

Table 7. Notable *DNMT3A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_175629.2 NP_783328.1	c.2645G>A	p.Arg882His	Most common somatic variant in sporadic AML [Ley et al 2010]; has also been reported as a germline variant in TBRS [Tatton-Brown et al 2018, Balci et al 2020]
	c.2644C>T	p.Arg882Cys	Common somatic variant in sporadic AML [Ley et al 2010]; has also been reported as a germline variant in TBRS [Tlemsani et al 2016, Tatton-Brown et al 2018]
	c.2246G>A	p.Arg749His	Arginine residue in methyltransferase domain w/multiple pathogenic germline variants reported [Tatton-Brown et al 2018]
	c.2245C>T	p.Arg749Cys	Arginine residue in methyltransferase domain w/multiple pathogenic germline variants reported [Tatton-Brown et al 2018]
	c.2207G>A	p.Arg736His	Arginine residue in methyltransferase domain w/multiple pathogenic germline variants reported [Tatton-Brown et al 2018, Tenorio et al 2020]
	c.2711C>T	p.Pro904Leu	C-terminal proline residue w/multiple pathogenic germline variants reported [Tatton-Brown et al 2018, Balci et al 2020]

AML = acute myeloid leukemia; TBRS = Tatton-Brown-Rahman syndrome
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

DNMT3A is a known driver of clonal hematopoiesis [Jaiswal et al 2014] and hematologic malignancy in the general population, with somatic pathogenic variants present in more than 20% of individuals with sporadic acute myeloid leukemia (AML) [Ley et al 2010]. The Arg882 (R882) residue is affected in more than 50% of these cases [Ley et al 2010]. *DNMT3A* variants are an independent predictor of poor prognosis in AML [Ley et al 2010, Papaemmanuil et al 2016]. There is evidence that mutation of *DNMT3A* is an early event in clonal hematopoiesis, which predisposes to malignancy but is not in itself sufficient to lead to malignancy [Papaemmanuil et al 2016].

Chapter Notes

Author Notes

Professor Kate Tatton-Brown is a medical geneticist. She runs a research study to investigate the genetic causes and clinical presentations of conditions associated with increased growth and learning disability. The research study is funded by the Baily Thomas Charitable fund and the St George's Charity.

Dr Philip Ostrowski is a clinical genetics registrar at St George's Hospital and Great Ormond Street Hospital in London. He has a special interest in cardiovascular genetics, and has published case series describing the overgrowth phenotypes associated with pathogenic variants in *CHD8* and *BRWD3*, jointly with Professor Tatton-Brown.

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References

Literature Cited

Balci TB, Strong A, Kalish JM, Zackai E, Maris JM, Reilly A, Surrey LF, Wertheim GB, Marcadier JL, Graham GE, Carter MT. Tatton-Brown-Rahman syndrome: six individuals with novel features. Am J Med Genet A. 2020;182:673–80. PubMed PMID: 31961069.

Cecchi AC, Haidar A, Marin I, Kwartler CS, Prakash SK, Milewicz DM. Aortic root dilatation and dilated cardiomyopathy in an adult with Tatton-Brown-Rahman syndrome. Am J Med Genet A. 2022;188:628–34. PubMed PMID: 34644003.

Ferris MA, Smith AM, Heath SE, Duncavage EJ, Oberley M, Freyer D, Wynn R, Douzgou S, Maris JM, Reilly AF, Wu MD, Choo F, Fiets RB, Koene S, Spencer DH, Miller CA, Shinawi M, Ley TJ. DNMT3A overgrowth syndrome is associated with the development of hematopoietic malignancies in children and young adults. Blood. 2022;139:461–4. PubMed PMID: 34788385.

Hage C, Sabini E, Alsharhan H, Fahrner JA, Beckers A, Daly A, Salvatori R. Acromegaly in the setting of Tatton-Brown-Rahman Syndrome. Pituitary. 2020;23:167–70. PubMed PMID: 31858400.

Heyn P, Logan CV, Fluteau A, Challis RC, Auchynnikava T, Martin CA, Marsh JA, Taglini F, Kilanowski F, Parry DA, Cormier-Daire V, Fong CT, Gibson K, Hwa V, Ibáñez L, Robertson SP, Sebastiani G, Rappsilber J, Allshire RC, Reijns MAM, Dauber A, Sproul D, Jackson AP. Gain-of-function DNMT3A mutations cause microcephalic dwarfism and hypermethylation of Polycomb-regulated regions. Nat Genet. 2019;51:96–105. PubMed PMID: 30478443.

Hollink IHIM, van den Ouweland AMW, Beverloo HB, Arentsen-Peters STCJM, Zwaan CM, Wagner A. Acute myeloid leukaemia in a case with Tatton-Brown-Rahman syndrome: the peculiar DNMT3A R882 mutation. J Med Genet. 2017;54:805–8. PubMed PMID: 28432085.

Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Mermel CH, Burtt N, Chavez A, Higgins JM, Moltchanov V, Kuo FC, Kluk MJ, Henderson B, Kinnunen L, Koistinen HA, Ladenvall C, Getz G, Correa A, Banahan BF, Gabriel S, Kathiresan S, Stringham HM, McCarthy MI, Boehnke M, Tuomilehto J, Haiman C, Groop L, Atzmon G, Wilson JG, Neuberg D, Altshuler D, Ebert BL. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488–98. PubMed PMID: 25426837.

Kaneda M, Okano M, Hata K, Sado T, Tsujimoto N, Li E, Sasaki H. Essential role for de novo DNA methyltransferase Dnmt3a in paternal and maternal imprinting. Nature. 2004;429:900–3. PubMed PMID: 15215868.

Kosaki R, Terashima H, Kubota M, Kosaki K. Acute myeloid leukemia-associated DNMT3A p.Arg882His mutation in a patient with Tatton-Brown-Rahman overgrowth syndrome as a constitutional mutation. Am J Med Genet A. 2017;173:250–3. PubMed PMID: 27991732.

Lane C, Tatton-Brown K, Freeth M. Tatton-Brown-Rahman syndrome: cognitive and behavioural phenotypes. Dev Med Child Neurol. 2020;62:993–8. PubMed PMID: 31845314.

Lemire G, Gauthier J, Soucy JF, Delrue MA. A case of familial transmission of the newly described DNMT3A-overgrowth syndrome. Am J Med Genet A. 2017;173:1887–90. PubMed PMID: 28449304.

Ley TJ, Ding L, Walter MJ, McLellan MD, Lamprecht T, Larson DE, Kandoth C, Payton JE, Baty J, Welch J, Harris CC, Lichti CF, Townsend RR, Fulton RS, Dooling DJ, Koboldt DC, Schmidt H, Zhang Q, Osborne JR, Lin L, O'Laughlin M, McMichael JF, Delehaunty KD, McGrath SD, Fulton LA, Magrini VJ, Vickery TL, Hundal J, Cook LL, Conyers JJ, Swift GW, Reed JP, Alldredge PA, Wylie T, Walker J, Kalicki J, Watson MA, Heath S, Shannon WD, Varghese N, Nagarajan R, Westervelt P, Tomasson MH, Link DC, Graubert TA, DiPersio JF, Mardis ER, Wilson RK. DNMT3A mutations in acute myeloid leukemia. N Engl J Med. 2010;363:2424–33. PubMed PMID: 21067377.

Okamoto N, Toribe Y, Shimojima K, Yamamoto T. Tatton-Brown-Rahman syndrome due to 2p23 microdeletion. Am J Med Genet A. 2016;170A:1339–42. PubMed PMID: 26866722.

Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell. 1999;99:247–57. PubMed PMID: 10555141.

Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, Potter NE, Heuser M, Thol F, Bolli N, Gundem G, Van Loo P, Martincorena I, Ganly P, Mudie L, McLaren S, O'Meara S, Raine K, Jones DR, Teague JW, Butler AP, Greaves MF, Ganser A, Döhner K, Schlenk RF, Döhner H, Campbell PJ. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374:2209–21. PubMed PMID: 27276561.

Paz-Alegría MC, Gómez-Forero D, Osorio-Patiño J, Jaramillo-Echeverry A. Behavioral and dental management of a patient with Tatton-Brown-Rahman syndrome: case report. Spec Care Dentist. 2020;40:597–604. PubMed PMID: 32815590.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Russler-Germain DA, Spencer DH, Young MA, Lamprecht TL, Miller CA, Fulton R, Meyer MR, Erdmann-Gilmore P, Townsend RR, Wilson RK, Ley TJ. The R882H DNMT3A mutation associated with AML dominantly inhibits wild-type DNMT3A by blocking its ability to form active tetramers. Cancer Cell. 2014;25:442–54. PubMed PMID: 24656771.

Shen W, Heeley JM, Carlston CM, Acuna-Hidalgo R, Nillesen WM, Dent KM, Douglas GV, Levine KL, Bayrak-Toydemir P, Marcelis CL, Shinawi M, Carey JC. The spectrum of DNMT3A variants in Tatton-Brown-Rahman syndrome overlaps with that in hematologic malignancies. Am J Med Genet A. 2017;173:3022–8. PubMed PMID: 28941052.

Smith AM, LaValle TA, Shinawi M, Ramakrishnan SM, Abel HJ, Hill CA, Kirkland NM, Rettig MP, Helton NM, Heath SE, Ferraro F, Chen DY, Adak S, Semenkovich CF, Christian DL, Martin JR, Gabel HW, Miller CA, Ley TJ. Functional and epigenetic phenotypes of humans and mice with DNMT3A overgrowth syndrome. Nat Commun. 2021;12:4549. PubMed PMID: 34315901.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Sweeney KJ, Mottolese C, Belot A, Szathmari A, Frappaz D, Lesca G, Putoux A, Di Rocco F. The first case report of medulloblastoma associated with Tatton-Brown-Rahman syndrome. Am J Med Genet A. 2019;179:1357–61. PubMed PMID: 31066180.

Tatton-Brown K, Loveday C, Yost S, Clarke M, Ramsay E, Zachariou A, Elliott A, Wylie H, Ardissone A, Rittinger O, Stewart F, Temple IK, Cole T, Mahamdallie S, Seal S, Ruark E, Rahman N, et al. Mutations in

epigenetic regulation genes are a major cause of overgrowth with intellectual disability. Am J Hum Genet. 2017;100:725–36. PubMed PMID: 28475857.

Tatton-Brown K, Seal S, Ruark E, Harmer J, Ramsay E, Del Vecchio Duarte S, Zachariou A, Hanks S, O'Brien E, Aksglaede L, Baralle D, Dabir T, Gener B, Goudie D, Homfray T, Kumar A, Pilz DT, Selicorni A, Temple IK, Van Maldergem L, Yachelevich N, van Montfort R, Rahman N, et al. Mutations in the DNA methyltransferase gene DNMT3A cause an overgrowth syndrome with intellectual disability. Nat Genet. 2014;46:385–8. PubMed PMID: 24614070.

Tatton-Brown K, Zachariou A, Loveday C, Renwick A, Mahamdallie S, Aksglaede L, Baralle D, Barge-Schaapveld D, Blyth M, Bouma M, Breckpot J, Crabb B, Dabir T, Cormier-Daire V, Fauth C, Fisher R, Gener B, Goudie D, Homfray T, Hunter M, Jorgensen A, Kant SG, Kirally-Borri C, Koolen D, Kumar A, Labilloy A, Lees M, Marcelis C, Mercer C, Mignot C, Miller K, Neas K, Newbury-Ecob R, Pilz DT, Posmyk R, Prada C, Ramsey K, Randolph LM, Selicorni A, Shears D, Suri M, Temple IK, Turnpenny P, Val Maldergem L, Varghese V, Veenstra-Knol HE, Yachelevich N, Yates L, Rahman N, et al. The Tatton-Brown-Rahman syndrome: a clinical study of 55 individuals with de novo constitutive DNMT3A variants. Wellcome Open Res. 2018;3:46. PubMed PMID: 29900417.

Tenorio J, Alarcón P, Arias P, Dapía I, García-Miñaur S, Palomares Bralo M, Campistol J, Climent S, Valenzuela I, Ramos S, Monseny AM, Grondona FL, Botet J, Serrano M, Solís M, Santos-Simarro F, Álvarez S, Teixidó-Tura G, Fernández Jaén A, Gordo G, Bardón Rivera MB, Nevado J, Hernández A, Cigudosa JC, Ruiz-Pérez VL, Tizzano EF, Lapunzina P, et al. Further delineation of neuropsychiatric findings in Tatton-Brown-Rahman syndrome due to disease-causing variants in DNMT3A: seven new patients. Eur J Hum Genet. 2020;28:469–79. PubMed PMID: 31685998.

Tlemsani C, Luscan A, Leulliot N, Bieth E, Afenjar A, Baujat G, Doco-Fenzy M, Goldenberg A, Lacombe D, Lambert L, Odent S, Pasche J, Sigaudy S, Buffet A, Violle-Poirsier C, Briand-Suleau A, Laurendeau I, Chin M, Saugier-Veber P, Vidaud D, Cormier-Daire V, Vidaud M, Pasmant E, Burglen L. SETD2 and DNMT3A screen in the Sotos-like syndrome French cohort. J Med Genet. 2016;53:743–51. PubMed PMID: 27317772.

Xin B, Cruz Marino T, Szekely J, Leblanc J, Cechner K, Sency V, Wensel C, Barabas M, Therriault V, Wang H. Novel DNMT3A germline mutations are associated with inherited Tatton-Brown-Rahman syndrome. Clin Genet. 2017;91:623–8. PubMed PMID: 27701732.

Yokoi T, Enomoto Y, Naruto T, Kurosawa K, Higurashi N. Tatton-Brown-Rahman syndrome with a novel DNMT3A mutation presented severe intellectual disability and autism spectrum disorder. Hum Genome Var. 2020;7:15. PubMed PMID: 32435502.

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