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## Expanding the Genetic and Clinical Spectrum of Tatton-Brown-Rahman Syndrome in a Series of 24 French Patients

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## 1 **ABSTRACT**

2

3 Background: Tatton-Brown-Rahman syndrome (TBRS; OMIM 615879), also known  
4 as *DNMT3A*-overgrowth syndrome (DOS), was first described by Tatton-Brown in  
5 2014. This syndrome is characterized by overgrowth, intellectual disability, and  
6 distinctive facial features and is the consequence of germline loss-of-function variants  
7 in *DNMT3A*, which encodes a DNA methyltransferase involved in epigenetic  
8 regulation. Somatic variants of *DNMT3A* are frequently observed in hematological  
9 malignancies, including acute myeloid leukemia (AML). To date, one hundred TBRS  
10 individuals with *de novo* germline variants have been described. We aimed to further  
11 characterize this disorder clinically and at the molecular level in a nationwide series  
12 of 24 French patients and to investigate the correlation between the severity of  
13 intellectual disability and the type of variant. Methods: We collected genetic and  
14 medical information from 24 individuals with TBRS using a questionnaire released  
15 through the French National AnDDI-Rares Network. Results: Here, we describe the  
16 first nationwide French cohort of 24 individuals with germline likely  
17 pathogenic/pathogenic variants in *DNMT3A*, including 17 novel variants. We  
18 confirmed that the main phenotypic features were intellectual disability (100% of  
19 individuals), distinctive facial features (96%), and overgrowth (87%). We highlighted  
20 novel clinical features, such as hypertrichosis, and further described the neurological  
21 features and EEG results. Conclusion: This study of a nationwide cohort of  
22 individuals with TBRS not only confirms previously published data but also provides  
23 additional information and clarifies clinical features to facilitate diagnosis and improve  
24 care. This study adds value to the growing body of knowledge on TBRS and  
25 broadens its clinical and molecular spectrum.

1

2 **Keywords:** *DNMT3A*, Tatton-Brown-Rahman syndrome, overgrowth, intellectual  
3 disability

4

5 **Key messages**

6

7 **What is already known on this topic**

8 ⇒ Tatton-Brown-Rahman syndrome is a recently described overgrowth/intellectual  
9 disability syndrome caused by loss-of-function variants in *DNMT3A*.

10 ⇒ Few large studies have delineated the phenotype–genotype spectrum of Tatton-  
11 Brown-Rahman syndrome.

12

13 **What this study adds**

14 ⇒ Our study describes 24 additional affected individuals and 17 previously  
15 unreported *DNMT3A* genetic variants.

16

17 **How this study might affect research, practice or policy**

18 ⇒ This study adds to the aggregate knowledge of Tatton-Brown-Rahman syndrome  
19 and expands its clinical and molecular spectrum to facilitate the identification of  
20 affected individuals and improve care.

## 1 INTRODUCTION

2

3 Tatton-Brown-Rahman syndrome (TBRS, OMIM #615879) was first described in  
4 2014 by Katrina Tatton-Brown and Nazneen Rahman [1]. In a second publication, 55  
5 individuals were clinically evaluated, including 13 previously reported individuals [2].  
6 Numerous subsequent reports have confirmed the original findings [3–26]. TBRS is  
7 characterized mainly by overgrowth (defined as height and/or head circumference at  
8 least 2 standard deviations above the population mean); intellectual disability ranging  
9 from mild to severe; and distinctive facial features, including coarse features, narrow  
10 palpebral fissures, and heavy and horizontal eyebrows. In addition to these three  
11 main characteristics, other features, such as hypotonia, behavioral disorders,  
12 seizures, joint hypermobility, scoliosis, dental abnormalities, and predisposition to  
13 malignant hemopathies, are more inconsistently described. The vast majority of  
14 reported individuals are children. Most cases are sporadic and occur in individuals  
15 with *de novo* heterozygous germline variants in *DNMT3A*. However, parent-to-child  
16 transmission in some families has demonstrated autosomal dominant inheritance  
17 with variable expressivity, and inheritance from unaffected mosaic parents has been  
18 reported [5, 6, 16, 22]. An increasing number of case reports converge toward  
19 phenotypic variability and multisystem involvement in this syndrome.

20 DNA methyltransferase 3 alpha (DNMT3A) is one of three active human  
21 methyltransferases, with the others being DNMT3B and DNMT1. DNMT3A is  
22 involved in *de novo* DNA methylation during development. This enzyme also plays a  
23 role in the maintenance and remodeling of DNA methylation patterns, especially at  
24 CpG sites and in histone proteins. In addition to this central role in epigenetic  
25 regulation and chromatin configuration, a role in gene regulatory functions such as

1 transcriptional silencing and activation has been reported [27, 28]. DNMT3A is also  
2 essential for parental imprinting [29] and XIST repression, which is involved in X  
3 chromosome inactivation [30].

4 DNMT3A contains three functional domains: i) a proline-tryptophan-tryptophan-  
5 proline (PWWP) domain present in transcription factors involved in the regulation of  
6 developmental processes, ii) an ATRX-DNMT3-DNMT3L (ADD) domain implicated in  
7 protein–protein and protein–DNA binding interactions, and iii) a methyltransferase  
8 (MTase) domain essential for methyltransferase activity.

9 In individuals with TBRS, *DNMT3A* germline variants lead to protein loss of function.  
10 Germline gain-of-function variants in the *DNMT3A* PWWP domain have been  
11 implicated in Heyn-Sproul-Jackson syndrome (HESJAS, OMIM #618724), which is  
12 characterized by a mirrored phenotype to TBRS, i.e., microcephalic dwarfism.

13 In addition to *DNMT3A* constitutional variants, somatic mutations have been reported  
14 in acute myeloid leukemia (AML, OMIM #601626) and other hematopoietic  
15 malignancies. More than half of *DNMT3A* somatic variants occur at amino acid  
16 p.Arg882, which is located in the MTase domain [31, 32]. However, the spectrum of  
17 germline variants overlaps with that observed in hematological malignancies [15].

18 Furthermore, TBRS is associated with perturbed hematopoiesis and the development  
19 of hematopoietic malignancy in children and young adults [2, 10, 11, 13, 33].

20 Approximately one hundred individuals have been reported in the literature to date;  
21 however, with the increasing availability of next-generation sequencing, the number  
22 of individuals diagnosed with germline mutations in *DNMT3A* is growing, making it  
23 necessary to improve our knowledge of the disease, its evolution and its individual  
24 management.



1 In this nationwide study, we report 24 novel individuals exhibiting TBRS associated  
2 with 17 novel disease-causing variants in *DNMT3A*.

3

#### 4 **SUBJECTS AND METHODS**

5

6 **Individual recruitment.** A national collaboration through the French National AnDDI-  
7 Rares (*Developmental Abnormalities with or without Intellectual Deficiency of Rare*  
8 *Causes*) health network made it possible to collect 24 individuals with TBRS between  
9 January 2021 and January 2023. The inclusion criteria were as follows: 1) the  
10 presence of a germline likely pathogenic or pathogenic variant in *DNMT3A* and 2)  
11 available molecular and clinical data. A *DNMT3A*-specific clinical proforma was sent  
12 to genetic specialists (including clinical elements present in overgrowth and  
13 intellectual disability syndromes and clinical symptoms already reported in the  
14 literature in individuals with TBRS). When available, we collected photographs,  
15 growth curves, and imaging data. Brain imaging was reinterpreted by a local  
16 specialist for seven individuals with available radiological data. *DNMT3A* variants  
17 were detected via gene panel, exome, or genome sequencing. The reference  
18 transcript used for variant designation was NM\_022552.5. Variants were interpreted  
19 according to the American College of Medical Genetics and Genomics (ACMG)  
20 guidelines [34]. All individuals or legal guardians provided written informed consent  
21 for genetic analyses. As required by French law, we informed all participants of their  
22 right to oppose the use of their data. Individuals or legal guardians have given their  
23 consent for the use of their photographs in the publication. This study was approved  
24 by the ethics committee of Nancy University Hospital (referral n°429) and was  
25 conducted in accordance with the Declaration of Helsinki.

1

2 **Literature review.** We performed a comprehensive PubMed search with the search  
3 terms “DNMT3A” and “Tatton-Brown-Rahman syndrome” and manually assessed the  
4 articles to identify those reporting TBRS cases. A total of 107 individuals with  
5 germline likely pathogenic/pathogenic variants in *DNMT3A* and available clinical data  
6 were collected.

7

8 **Statistical analyses.** We determined whether there was an association between the  
9 severity of intellectual disability and the type of variant using a chi-square test in the  
10 83 individuals with available data merged from our cohort and the literature.

11

12 **RESULTS** (Table 1, Supplementary Table 1)

13

14 We collected clinical and molecular data from 24 individuals (10 males and 14  
15 females) from 23 families (Tables 1 and Supplementary Table 1). The mean age was  
16 15.6 years (we excluded Patient 7’s mother from the calculation). Patient 5 has  
17 already been reported in the literature [14]. All individuals benefited from molecular  
18 diagnosis that identified pathogenic or likely pathogenic variants in *DNMT3A* with  
19 predicted loss of function.

20

21 **Molecular characteristics** (Figure 1)

22 We identified 13 different missense variants (in 15 individuals), 5 different nonsense  
23 variants, a frameshift variant, a splice-site variant, a deletion of several exons and an  
24 in-frame duplication. The pathogenicity of this in-frame duplication relies on the high  
25 interspecies conservation level of the 6 duplicated amino acids, proximity to the

1 PWWP domain and DNA methylation profile showing a concordant TBRS  
2 epesignature. The results of a methylation study performed for this individual using  
3 the Illumina Infinium EPIC array v1.0 have previously been reported [35]. Among the  
4 variants, 17 have never been reported before (9 missense variants, 4 nonsense  
5 variants, 1 frameshift variant, 1 splice-site variant, 1 multiexon deletion, and 1 in-  
6 frame duplication). The remaining 5 variants (found in 6 individuals: 3, 5, 11, 15, 22  
7 and 24) have previously been reported in individuals with TBRS [2, 5, 11, 14, 15, 18].  
8 Nineteen individuals carried a *de novo* variant, and 2 individuals inherited the variant  
9 from an affected parent; for the remaining 3 individuals, parental DNA was  
10 unavailable. Only one of the two affected parents was included in this study due to  
11 the lack of clinical information.

12

### 13 **Pregnancy and the perinatal period**

14 No toxic exposure or assisted reproductive technology was reported. The average  
15 age at delivery was 28 years for the mothers and 35 years for the fathers.  
16 Pregnancies were marked by various nonspecific complications in 33% (8/24) of the  
17 patients, including increased nuchal translucency (n = 1), macrosomia without  
18 gestational diabetes (n = 1), intrauterine growth retardation and further normalization  
19 (n = 1), intrauterine growth restriction with preterm delivery and neonatal hypoxia (n =  
20 1), and fetal distress (n = 1). In 17% (4/24) of the patients, various nonspecific  
21 neonatal abnormalities, including hypoglycemia, hypotonia, sleeping disorders,  
22 feeding difficulties, and bronchopulmonary dysplasia, were reported.

23

### 24 **Growth and endocrinology**

1 Most individuals had generalized overgrowth since birth. At birth, 48% (10/21) had a  
2 length above the 90<sup>th</sup> centile, 64% (14/22) had a weight above the 90<sup>th</sup> centile, and  
3 53% (10/19) had a head circumference above the 90<sup>th</sup> centile. At the time of the last  
4 clinical examination (mean age: 13 years, standard deviation: 8 years), overgrowth  
5 (defined as height and/or head circumference at least 2 standard deviations above  
6 the population mean) was observed in 87% (20/23) of the individuals, 65% (15/23)  
7 had a tall stature, 46% (10/22) were overweight according to BMI, 76% (16/21) were  
8 overweight according to weight, and 68% (15/22) had macrocephaly. The available  
9 weight and height curves (for 4 male and 5 female individuals) showed that the  
10 measurements remained approximately stable within the same range (data not  
11 shown).

12 Thirty percent (3/10) of male patients had cryptorchidism. Twenty-nine percent (4/14)  
13 of female patients had early onset of puberty. Hypertrichosis was observed in 46%  
14 (11/24) of patients. Hair extended into the frontal regions associated with thick  
15 eyebrows, and hypertrichosis sometimes involved the face, back, and arms (Figure  
16 2C).

17

### 18 **Facial features**

19 Distinct facial features were observed in 96% of the individuals (23/24). Fifty percent  
20 (12/24) had coarse features, and 38% (9/24) had a round face. Forty-six percent  
21 (11/24) had narrow palpebral fissures, and 21% (5/24) had enophthalmia. Twenty-  
22 nine percent (7/24) had a high palate. Seventy percent (17/24) had atypical eyebrows  
23 (thick, horizontal or synophrys). Facial features were more apparent in early  
24 adolescence and less specific in early childhood and adulthood. Sixty-seven percent  
25 (16/24) had dental abnormalities: large upper incisors (n = 13), widely spaced upper

1 incisors (n = 6), abnormal dental implantation (n = 10), multiple caries lesions (n = 2),  
2 and late (n = 1) or early loss (n = 1) of the milk teeth (Figure 2A).

3

#### 4 **Neurodevelopment and behavior**

5 One hundred percent (24/24) of individuals had intellectual disability with varying  
6 degrees of severity. Of the 14 individuals for whom impairment severity was  
7 specified, 29% (4/14) had mild intellectual disability (ID), 57% (8/14) had moderate  
8 ID, and 14% (2/14) had severe ID. For 21% (5/24) of the individuals, a regression in  
9 psychomotor acquisitions was observed. Eight percent (2/24) of individuals had  
10 stuttering disorders. Twenty-nine percent (7/24) had autism spectrum disorders  
11 (ASDs). Sixty-three percent (15/24) had behavioral disorders, including attention-  
12 deficit/hyperactivity disorder (ADHD) (n = 3), obsessive-compulsive disorder (n = 3),  
13 aggressive behavior (n = 4), and anxiety disorders (n = 4). Twenty-five percent (6/24)  
14 of the individuals had eating disorders, namely, compulsions (n = 2) and hyperphagia  
15 (n = 4); all six were overweight.

16

#### 17 **Neurology**

18 Forty-two percent (10/24) of individuals had at least one episode of clinical seizures.  
19 6 individuals had isolated febrile or cluster of febrile seizures; and the remaining 4  
20 individuals had non-febrile epilepsy (with or without previous febrile seizures): febrile  
21 seizures and generalized epilepsy (n = 1); febrile seizures, focal seizures and later  
22 continuous spikes and waves during sleep (CSWS) (n = 1); febrile seizures, focal  
23 seizures and absence seizures (n = 1); and focal seizures and absence seizures (n =  
24 1). Patient with generalized epilepsy was successfully treated with valproate. Patient  
25 with CSWS was treated with clobazam, levetiracetam, ethosuximide and

1 corticosteroids. Patients with focal and absence seizures were successfully treated  
2 by lacosamide and levetiracetam for one or lamotrigine and zonisamide for the other.  
3 The two individuals with severe ID had at least one episode of clinical seizures.  
4 Electroencephalography (EEG) information was available for 50% (12/24) of the  
5 individuals, including 6 individuals with clinical seizures; focal abnormalities were  
6 observed in 3 individuals, and generalized abnormalities were observed in one  
7 individual. Among individuals without clinical seizures (n = 6), only one presented  
8 with EEG abnormalities, i.e., focal left centrotemporal spikes.

9

10 Other neurological manifestations were observed in 58% (14/24) of the individuals,  
11 including cerebellar syndrome (n = 7), hypotonia (n = 6), a decrease in fine motor  
12 coordination (n = 5), symptomatology of peripheral neuropathy (n = 3), tremor (n = 3),  
13 pyramidal syndrome (n = 2) and right upper limb monoparesis (n = 1).

14

15 Brain magnetic resonance imaging (MRI) was performed for 75% (18/24) of the  
16 individuals, and 72% (13/18) of these patients had abnormalities (Figure 2E). The  
17 most frequent abnormality was a thin or dysplastic corpus callosum in 44% of the  
18 individuals (n = 8). Other abnormalities were nonspecific: thick cranial vault bones (n  
19 = 3), brain atrophy (n = 2), white matter hyperintensities (n = 2), pineal cysts (n = 2),  
20 arachnoid cysts (n = 1), choroidal fissure cysts (n = 1), ventriculomegaly (n = 1), a  
21 narrow posterior fossa (n = 1) and olfactory bulb hypoplasia (n = 1). None of the  
22 individuals had Chiari malformations, as previously described for TBRS individuals;  
23 however, protrusion of the cerebellar amygdala was observed in one individual, and  
24 basilar impressions were observed in another individual.

25

## 1 **Additional symptoms**

2 Twenty-eight percent (9/24) of the individuals had sleep disorders, including poor  
3 sleep and nocturnal awakening (n = 6), mild obstructive sleep apnea (OSA) or  
4 snoring (n = 4), night sweats (n = 1) and nocturnal enuresis (n = 1). Thirteen percent  
5 (3/24) of patients had recurrent infections. Forty-two percent (10/24) had refractive  
6 disorders. Thirteen percent (3/24) had other ophthalmic abnormalities, such as  
7 bilateral cataracts with surgical treatment (n = 1), poor central vision (n = 1), or  
8 papillary excavation (n = 1). Twenty-five percent (6/24) had a history of  
9 cardiovascular disease, including nonobstructive ventricular septal defect (n = 1),  
10 atrial septal defect requiring surgery (n = 1), malformation of the aortic arch with the  
11 retroesophageal subclavian artery (n = 1), recurrent episodes of pericarditis (n = 1),  
12 familial Wolff–Parkinson–White syndrome (n = 1), and ventricular extrasystoles (n =  
13 1). A total of 33% (8/24) had a respiratory or pulmonary history of mild obstructive  
14 sleep apnea (OSA) or snoring (n = 4), history of repeated bronchitis and/or  
15 pneumonia (n = 2), or asthma (n = 2) with recurrent pneumothorax leading to surgical  
16 treatment in one individual. Twenty-one percent (5/24) had an umbilical hernia.

17

18 Seventy-five percent (18/24) of patients presented with abnormalities of the  
19 extremities (hands and/or feet), including long and thin fingers (n = 9), short and/or  
20 widely spaced toes (n = 10), flat feet (n = 10) and, most often, a large shoe size for  
21 their age (Figure 2B). Forty-six percent (11/24) had joint hypermobility. Forty-two  
22 percent (10/24) had scoliosis. Twenty-one percent (5/24) had other skeletal  
23 abnormalities, including major pectus excavatum (n = 1), patellar dislocation (n = 1),  
24 Scheuermann's disease (n = 1), plagiocephaly (n = 1) and dorsal gibbosity (n = 1)  
25 (Figure 2D).

1

2 Patient 5, who was previously reported [14], presented at the age of 17, with  
3 unsteady gait, headaches, rotatory vertigo, stage 1 papilledema on funduscopy  
4 examination, ataxic gait, nystagmus, and dysdiadochokinesia. MRI revealed a fourth  
5 ventricular mass causing obstructive hydrocephalus. She underwent a craniotomy,  
6 and uncomplicated gross total resection. Further investigations revealed the lesion to  
7 be a localized medulloblastoma in the standard risk category. She received adjuvant  
8 craniospinal radiotherapy under general anesthesia. Her clinical follow-up revealed  
9 no clinical or radiological evidence of disease recurrence. She continued to have a  
10 cerebellar syndrome on follow-up [14].

11

## 12 **Genotype–phenotype association**

13 We compared the ID severity between individuals with truncating variants and  
14 individuals with missense variants located in one of the three known functional  
15 domains of the DNMT3A protein in this series and in the literature. The chi-square  
16 independence test did not reveal a correlation between genotype and severity of  
17 intellectual disability, suggesting that the mechanism of pathogenicity of missense  
18 variants is a loss of function of the protein.

19

## 20 **DISCUSSION**

21

22 Katrina Tatton-Brown and Nazneen Rahman clinically evaluated a total of 55 TBRS  
23 individuals [2]. Tlemsani et al. [18] and Tenorio et al. [8] reported 7 individuals, Balci  
24 et al. [5] reported 6 individuals, and Xin et al. [6] reported 6 individuals from two  
25 families. To our knowledge, the present series of 24 French TBRS individuals is the



1 second largest series described to date. Our study confirmed the main features of the  
2 syndrome and provided further molecular and clinical data on this rare overgrowth  
3 condition. We confirmed that the phenotypic spectrum is very broad, ranging from  
4 nonsyndromic ID for one of our individuals (Patient 19) to very severe and syndromic  
5 ID for two individuals (Patients 5 and 15).

6

7 We analyzed the mutational landscape of *DNMT3A*. Seventeen pathogenic or likely  
8 pathogenic variants observed in our cohort have never been described before,  
9 including an in-frame duplication affecting six highly conserved amino acids in  
10 proximity to the PWWP domain for which the DNA methylation profile showed a  
11 concordant epismutation [35]. Furthermore, these positions have been shown to be  
12 crucial in the DNMT1-DNMT3A interaction [36]. The majority of the variants are  
13 missense variants localized in one of the three described functional domains of the  
14 DNMT3A protein. Importantly, *DNMT3A* is one of the most common genes  
15 associated with clonal hematopoiesis of indeterminate potential (CHIP) [37]. Indeed,  
16 some somatic mutations in *DNMT3A* provide a preneoplastic growth advantage that  
17 can result in the accumulation, over a period of years, of lymphocytes bearing the  
18 somatic variant. Therefore, some pathogenic germline variants are common in the  
19 general population due to age-related clonal hematopoiesis, thus limiting the utility of  
20 databases such as gnomAD in the pathogenicity stratification of *DNMT3A* germline  
21 variants [2] since the gnomAD-derived variants were largely derived from lymphocyte  
22 DNA and many gnomAD participants were middle-aged or older. GnomAD missense  
23 variants occurring in the three main DNMT3A functional domains are represented by  
24 histograms in figure 1.

25

1 As previously shown [19], we found no significant correlation between the type of  
2 variant and ID severity.

3

4 There is relatively little pregnancy and neonatal data in the literature. We collected  
5 only 10 TBRS individuals with abnormalities during the fetal period, including 4 with  
6 macrosomia (one individual in our cohort) and 4 with preeclampsia (absent in our  
7 cohort). In comparison, preeclampsia was described in 17% of individuals with Sotos  
8 syndrome, another genetic overgrowth syndrome [18]. In conclusion, pregnancy and  
9 neonatal data in patients with TBRS vary and are nonspecific.

10

11 The analysis of antenatal ultrasound data, birth parameters and their evolution favors  
12 overgrowth with constitutional macrocephaly present from birth or early childhood,  
13 with an evolution in the range of +2 SDs consistent with the literature [2, 38].

14 Physical examination revealed facial features already described in the literature,  
15 including a round face with coarse features, thick horizontal eyebrows, narrow  
16 palpebral fissures and dental abnormalities. As previously described, facial features  
17 are more apparent in early adolescence and less specific in early childhood and  
18 adulthood [2, 38]. Among dental abnormalities, malocclusion, caries and double teeth  
19 have been reported [38], and a recent work highlighted the importance of appropriate  
20 dental care for individuals with TBRS [12].

21 We observed hair abnormalities in 11 individuals with hypertrichosis in our cohort.  
22 This manifestation has not been previously noted and could aid in the clinical  
23 diagnosis of TBRS. The early onset of puberty observed in 4 female individuals in our  
24 cohort could also be a new feature of TBRS syndrome.

25

1 In our cohort, psychomotor development was delayed, with regression in 4  
2 individuals. One hundred percent of individuals had mild to severe ID, with moderate  
3 ID being most common, and 29% of individuals had ASD. These data are consistent  
4 with the literature [38, 39]. We noted compulsive eating and/or hyperphagia in 6 of  
5 our individuals, as previously reported [2, 5]. This could contribute to the obesity  
6 observed in this syndrome.

7 At least one epileptic event occurred in 42% of our individuals; most were isolated  
8 febrile seizures, with afebrile events occurring in only 4 individuals. EEG profiles have  
9 rarely been described in previous studies. We collected EEG data for 12 TBRS  
10 individuals, with focal abnormalities in 3 symptomatic individuals, generalized  
11 abnormalities in one symptomatic individual, and focal abnormalities in 1 individual  
12 without clinical seizures.

13 Fourteen individuals (58%) had neurological features, with hypotonia, cerebellar  
14 syndrome, a decrease in fine motor coordination, tremor and symptomatology of  
15 peripheral neuropathy being the most frequent findings. Neurological findings are  
16 poorly described in the literature, highlighting the need for systematic examination of  
17 TBRS individuals by an experienced neurologist to confirm and validate these  
18 findings in further studies. Recently, the description of an individual with congenital  
19 myopathy and rhabdomyolysis and another individual with axonal polyneuropathy led  
20 to the extension of the TBRS phenotype to include neuromuscular features and  
21 polyneuropathy [24, 26].

22 On brain imaging, we found the same various nonspecific abnormalities as previously  
23 described in other overgrowth syndromes. However, corpus callosum abnormalities  
24 were present in 8 individuals (44%). This finding is consistent with a recent study  
25 suggesting that structural neuroimaging abnormalities have been previously

1 underestimated in TBRS patients and revealing the presence of corpus callosum and  
2 brain tract alterations, likely caused by microstructural cortical defects and/or primary  
3 anomalies in connection development [23]. In contrast to the findings of previous  
4 studies, ventriculomegaly or Chiari malformation were rarely observed in our cohort.

5

6 We observed a cardiovascular phenotype in 25% of our individuals. Cardiovascular  
7 phenotypes include congenital malformations diagnosed early in life and aortic root  
8 dilatation, dilated cardiomyopathy or arrhythmia diagnosed in late childhood or  
9 adulthood; periodic surveillance with echocardiography is needed to assess aortic  
10 root size [2, 4, 6, 11, 15, 17, 18, 40]. Among respiratory abnormalities, sleep apnea is  
11 the most common manifestation, as previously described [2, 5]. Musculoskeletal  
12 pathologies are common and include joint hypermobility and scoliosis.

13

14 Although neoplasia was rarely observed in our cohort, several cases of cancer of  
15 various types have been described in the literature, including acute myeloid leukemia  
16 and other hematologic or solid tumors [10, 14, 41]. As there are no consensus  
17 guidelines regarding screening for hematologic malignancy in individuals with TBRS  
18 [33, 38, 42], we recommend that hematological malignancies such as easy bruising  
19 and petechiae, recurrent bleeding, pallor, persistent fatigue, fever and recurrent  
20 infections be assessed at each follow-up visit [2]. Furthermore, TBRS individuals and  
21 their families should be educated about the signs and symptoms that would warrant  
22 medical evaluation. Complete blood count and further investigations should be  
23 performed in the event of signs of hematologic malignancy. In addition, any other  
24 change in signs and symptoms in these patients should be investigated further to  
25 exclude the development of tumors. Natural history studies of a larger number of

1 TBRS individuals would be needed to enable surveillance guidelines for  
2 malignancies particularly hematological malignancies to be established.

3

4 In conclusion, this national collaborative study included the second largest cohort of  
5 individuals with TBRS. Our findings are consistent with known clinical features  
6 described in the literature, including ID of varying severity, overgrowth and  
7 recognizable facial features. It is essential to keep in mind the limits induced by  
8 reporting bias, which can lead to probable overestimation of the frequency and  
9 severity of neurodevelopmental disorders. However, we have highlighted the lack of  
10 specific antenatal signs of Tatton-Brown-Rahman syndrome. Constitutional  
11 overgrowth, although not typically detected in the antenatal period, seems to be  
12 present at birth or in early childhood. We broadened the phenotype by reporting  
13 localized congenital hypertrichosis and early onset of puberty in females. We  
14 highlight the neurological phenotype and specific EEG abnormalities. Although  
15 malignancies seem to be rare, monitoring blood parameters is essential. We did not  
16 identify any phenotype–genotype correlations.

17 This study may contribute to improving the care of TBRS individuals. Furthermore,  
18 given the involvement of the *DNMT3A* gene in methylation, current therapeutic  
19 advances targeting chromatin marks may benefit TBRS patients in the future.

20

#### 21 **Data availability**

22 All the data underlying the results are available as part of the article.

23

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25

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3 *Abnormalities with or without Intellectual Deficiency of Rare Causes*) health network.  
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5

6 **Competing interests** None declared

7

8 **Ethics approval**

9 This study was approved by the ethics committee of Nancy University Hospital  
10 (referral n°429) and was conducted in accordance with the Declaration of Helsinki. All  
11 individuals or legal guardians provided written informed consent for genetic analyses.  
12 As required by French law, we informed all participants of their right to oppose the  
13 use of their data. Individuals or legal guardians have given their consent for the use  
14 of their photographs in the publication.

15

16 **Contributorship**

17 CB is the guarantor.

18 LL, MR and CB conceptualized and designed the study.

19 CB collected the samples.

20 LL, MR, ER, JW, SZ, BL, DG, MW, CC, ES, SB, MV, MN, LR, EP, PE, LF, JLA, ML,  
21 CQ, SO, CM, AA, SJ, AG, ASM, SN, MD, CM and VCD clinically characterized the  
22 individuals.

23 TA, CP, ND, JMR, MW, MB, AB, VR, MM, MD, GV, AP, BG, BC, GL, NC, MT, FT,  
24 VD, MF, NC, BK, SR, EB, GB, TH, AO and CB performed the genetic studies and  
25 data analysis and interpretation.

- 1 TH, DC, FL, GN and CC generated DNA methylation data from patient 13 and
- 2 interpreted the DNMT3A epesignature.
- 3 HT collected the clinical data.
- 4 TA and CB collected the molecular data.
- 5 HT wrote the first draft of the manuscript.
- 6 TA, ER, JMR, LL and CB revised the manuscript.
- 7 CB supervised the project and edited the manuscript.
- 8 All the authors critically revised and approved the final manuscript.
- 9

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## 1 **Figure Legends**

2

3 **Figure 1. Molecular data and genomic context** (A) The DNMT3A protein structure  
4 and details of the 24 disease-causing variants described in this work. The three  
5 DNMT3A domains are shaded in blue: the proline-tryptophan-tryptophan-proline  
6 (PWWP) domain, the ATRX-DNMT3-DNMT3L (ADD) domain and the  
7 methyltransferase (MTase) domain. The missense variants and the *in-frame*  
8 duplications are represented in the upper panel. Truncating and splice variants are  
9 represented in the lower panel. Orange line: deletion of exons 7-23. GnomAD  
10 missense variants (except variants annotated in ClinVar as pathogenic, likely  
11 pathogenic or of uncertain significance; n=309) are displayed in blue as controls from  
12 the general population. (B) The blue histogram indicates GnomAD missense variants  
13 from the general population occurring in the three main DNMT3A functional domains  
14 (except for variants annotated in ClinVar as pathogenic, likely pathogenic or of  
15 uncertain significance), and the red stars indicate the positions of the disease-  
16 causing missense variants described in this work. None of the variants reported in  
17 this work are present without annotation in GnomAD. Missense variants affecting the  
18 same protein position result in a change in different amino acids.

19

20 **Figure 2. Morphological features of Tatton-Brown-Rahman syndrome.** (A) Teeth  
21 abnormalities. (B) Hands and feet. (C) Hypertrichosis in individuals 1 and 3. (D)  
22 Pectus excavatum in individual 2. Hyperlordosis and elbow hyperextension in  
23 individual 3. (E) Brain MR image of individual 11: sagittal T1-weighted image:  
24 complete but thin corpus callosum. Normal posterior fossa. There was no cerebellar  
25 tonsillar herniation.

1 **Table 1.** Clinical features of the 24 patients in the French cohort by frequency compared to those of previously published patients  
 2 [38]  
 3

<b>Features</b>	<b>French cohort (n = 24) (%)</b>	<b>Ostrowski, P. J., &amp; Tatton-Brown, K. in GeneReviews® [38] (n = 90) (%)</b>
Intellectual disability (ID)	100%	100%
Mild ID	29%	28%
Moderate ID	57%	58%
Severe ID	14%	14%
Distinctive facial features	96%	ND
Overgrowth*	87%	>80%
Tall stature (height $\geq 2$ SD above mean)	65%	$\sim 70\%$
Macrocephaly (head circumference $\geq 2$ SD above mean)	68%	$\sim 50\%$
Overweight (BMI)	46%	ND
Weight $\geq 2$ SD	76%	$\sim 65\%$
Joint hypermobility	46%	$\sim 75\%$
Hypotonia	25%	$\sim 55\%$
Behavioral/psychiatric issues	63%	$\sim 50\%$
Autistic traits	29%	44%
Kyphoscoliosis	42%	$\sim 30\%$
Seizures	42%	$\sim 20\%$
Cryptorchidism	30% of males	$\sim 20\%$ of males
Cardiovascular disease	25%	$\sim 10\%$
Corpus callosum abnormalities	44%	ND
Ventriculomegaly	4%	<10%
Chiari malformation	0%	<10%
Malignant tumors	4%	$\sim 5\%$

1  
2 \* defined as height and/or head circumference at least 2 standard deviations above the population mean  
3  
4