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CLINICAL CASE

Tatton-Brown-Rahman Syndrome: Case report and *DNMT3A* variant not previously reported associated to the syndrome

Síndrome de Tatton-Brown-Rahman: Reporte de caso de variante en el gen *DNTM3A* no descrita previamente asociada al síndrome

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What do we know about the subject matter of this study?

Tatton-Brown-Rahman syndrome is characterized by overgrowth associated with intellectual disability and facial dysmorphia. It is caused by variants in the DNMT3A gene and its clinical differentiation from other overgrowth syndromes can be difficult due to phenotypic overlap.

What does this study contribute to what is already known?

We describe the case of a Chilean schoolboy with the syndrome, carrier of a variant in the DNMT3A gene not previously described in association with the phenotype. This study contributes to broadening the genotypic spectrum of the syndrome and to its phenotypic description, still under study.

Abstract

Tatton Brown Rahman Syndrome (TBRS) is a recently described overgrowth syndrome caused by variants in the *DNMT3A* gene. The description of its phenotype and the differences with its main differential diagnoses are still under development, with very few individuals of Latin American origin described to date. **Objective:** To describe a Chilean case of TBRS in order to broaden the phenotypic and genotypic spectrum of this new syndrome. **Clinical Case:** 9-year-old boy diagnosed with TBRS through whole-exome sequencing (WES), which showed a variant in *DNMT3A*: c.2311C > T, p. (Arg771*) that has not been previously reported in the literature in individuals with the condition. He presented the main characteristics of this syndrome with overgrowth from the neonatal stage, mild intellectual disability associated with autism spectrum disorder, absence of major abnormalities in internal organs, and characteristic dysmorphism with coarse facies, horizontal eyebrows, and prominent upper central incisors. An EEG showed alterations due to frequent interictal epileptiform activity in the left temporal region, with no history of seizures, and normal brain MRI. In addition, he presented advanced bone age, a common finding in other over-

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growth syndromes but not frequently reported in TBRS. A sister showed normal genetic study and the segregation study of the variant identified in the parents could not be performed. **Conclusions:** The report of this case broadens the genotypic spectrum of the syndrome and contributes to the characterization of the phenotypic manifestations including individuals of different ethnicities, emphasizing its most common characteristics and others that hinder its differential diagnosis from other overgrowth syndromes.

Introduction

Overgrowth syndromes are characterized by pre- or postnatal overgrowth with weight, height, or head circumference (HC) 2 standard deviations (SD) above the mean for age and sex, associated with other phenotypic alterations that may overlap between syndromes, and often with an increased risk of tumor development[1,2]. They are generally caused by alterations in factors involved in the control of cell proliferation or epigenetic markers, with varied underlying molecular mechanisms, including point variants in genes, imprinting disorders, and copy number variations[3].

In 2014, Tatton-Brown-Rahman Syndrome (TBRS - OMIM #615879) was described in overgrowth individuals studied by whole exome sequencing (WES) where heterozygous variants in the *DNMT3A* gene were identified[4]. It encodes a DNA methyltransferase enzyme involved in the establishment of methylation marks during embryonic development and its action is associated with other enzymes previously involved in overgrowth disorders such as NSD1, associated with Sotos syndrome[5,6].

Overgrowth and intellectual disability (ID) are the most frequent characteristics in TBRS reported in > 80% of cases, and its diagnosis is based on the presence of these two features and a germline variant in the *DNMT3A* gene[7,8]. Other findings present in 20%-80% of individuals are a distinctive facial appearance that changes over time, becoming evident in adolescence with low, prominent, horizontal eyebrows, prominent front teeth, joint hypermobility, obesity, hypotonia, psychiatric and behavioral disturbances, kyphoscoliosis, and non-febrile seizures[8]. More than 80 individuals with the syndrome have been reported with an autosomal dominant inheritance pattern with variable expressivity. Most of the reported cases have been *de novo*, however, there are reports of familial cases and paternal mosaicism[9-11].

The description of its phenotype and differences with its main differential diagnoses are still under study, with very few Latin American cases described. We present a Chilean case with overgrowth, in whom a probably pathogenic variant in the *DNMT3A* gene not previously reported in the literature in individuals with TBRS was found through WES, to broaden the phenotypic and genotypic spectrum of this new syndrome.

Clinical Case

A 9-year-old schoolboy, second child of non-consanguineous parents, father height 167 cm and mother height 160 cm (within the average for the Chilean population), and she had a history of pulmonary sarcoidosis. His older sister, aged 11 years old, presented an advanced bone age (13 years) at 10 years with 7 months of chronological age, without associated height alteration. In addition, she was diagnosed with attention deficit hyperactivity disorder (ADHD) and overweight, without cognitive alterations or associated dysmorphias.

The pregnancy was controlled, without associated pathologies and he was born at 37 weeks of gestational age by cesarean section weighing 3,960 kg (2.25 SD) classified as large for gestational age, length 51 cm (1.04 SD), HC 37.5 cm (3.62 SD) according to the curves of Alarcón and Pittaluga[12], and APGAR score 9-9.

During the neonatal stage, he presented hypotonic syndrome managed with motor rehabilitation with good progress. Regarding his psychomotor development, he walked at 15 months of age and presented a delayed onset of language acquisition. At 7 years of age, he was diagnosed with verbal apraxia, and at 9 years of age, he started learning to read and write in a special education school.

Since infancy, he was above normal in the growth curves for height, weight, and HC. At 9 years of age, he weighed 57.7 kg (2.67 SD), height 150 cm (2.42 SD), BMI 25.6 (2.48 SD) according to WHO anthropometric curves[13], HC 57.5 (2 SD) according to Nellhaus curves[14], and arm span 160 cm, with proportional body segments. Also, at the same age, his pubertal development was Tanner I, according to his age. He had no eating disorders throughout his life.

His hormonal and biochemical tests including thyroid hormones, IGF-1, gonadotrophins, testosterone, calcium-phosphorus, glycemia, and glycosylated hemoglobin were within normal ranges. He presented an altered lipid profile at 9 years of age with total choles-

terol of 196 mg/dL and triglycerides of 162 mg/dL. At 8 years and 10 months of age, the carpal radiography showed an advanced bone age (13 years).

Regarding neurological aspects, he was diagnosed with mild ID, high functioning autism spectrum disorder (ASD), ADHD, and was on treatment with methylphenidate 10 mg/day. The main neurocognitive manifestations were expressive language difficulties with dyslalia, fine motor impairment, and sensory modulation, in addition to sleep maintenance insomnia.

Throughout his life, he maintained comprehensive treatment with speech therapy, occupational therapy, and psycho-pedagogy, showing positive advances in all areas and without diagnoses of behavioral or conduct disorders. The electroencephalogram showed alterations with very frequent left temporal interictal epileptiform activity, with no history of seizures, and a brain MRI was performed at 9 years of age with normal results.

In the cardiovascular evaluation, there were no cardiac abnormalities, blood pressure was normal, electrocardiogram without alterations, normal rhythm monitoring (Holter), and normal echocardiogram evaluation.

Among the other studies performed, there was mild neutropenia (absolute neutrophil count 1.470/uL), with study of the JAK-2 V617F variant for myeloproliferative syndrome negative. Impedance audiometry without alterations, and normal abdominal echotomography. He underwent adenoidectomy at the age of 3 years and 6 months.

Regarding genetic aspects, karyogram study revealed 46, XY karyotype, and Fragile X syndrome was ruled out by molecular study with triplet primed PCR (TP-PCR) due to his language delay.

At the age of 9 years, he was evaluated by a specialist in clinical genetics and the physical examination revealed coarse facial features, light hair, prominent forehead, bitemporal narrowing, prominent and horizontal eyebrows, low-set ear and pinna abnormalities, increased palpebral volume, wide and flat nasal bridge, long eyelashes, down slanting palpebral fissures, deep-set and green eyes, bilateral infraorbital fold, full cheeks, anteverted nostrils, cupid's bow upper lip and full lower lip, and prominent upper front teeth (figure 1). There were no other dysmorphic features on the complete physical examination of the patient.

A WES study was performed (CENTOGENE Lab) through the Illumina sequencing platform, finding a heterozygous variant in the *DNMT3A* gene, NM_022552.4:c.2311C > T, p.(Arg771*), located on chromosome 2, position 25463182 (Reference position rs779626155) according to the GRCh37/hg19 version of the human genome. The detected variant is in a region of adequate coverage and depth by sequencing reads (≥ 20x) and was confirmed by Sanger sequencing. The variant generates a premature termination codon and, according to the American College of Medical Genetics and Genomics (ACMG) criteria, was classified as probably pathogenic. This variant has not been previously identified in individuals with TBRS, however, it has been described to be associated with colorectal adenocarcinoma[15].

Given the sister's history of advanced bone age, overweight, and ADHD, she was also studied by WES, ruling out the presence of the *DNMT3A* gene variant identified in the proband, and no pathogenic variants associated with the described phenotype were identified. It was not possible to perform the segregation study of the identified variant in the parents, however, neither of them presented alterations in the clinical history or dysmorphias on physical examination suggestive of disease, both having a history of normal intellectual, anthropometric, and pubertal development.

Discussion

In recent decades, overgrowth syndromes have been steadily increasing and WES has demonstrated high diagnostic performance in identifying the molecular cause in up to 50% of cases, with at least 14 genes involved[3]. A significant number of cases are caused by pathogenic variants in epigenetic regulatory genes (*NSD1*, *EZH2*, *DNMT3A*, *CHD8*, and *EED*)[2] with the most frequently found in *NSD1* (34%), *EZH2* (4.8%), and *DNMT3A* (2.5%). The first two genes are associated with Sotos and Weaver Syndrome, respectively[3].

Our patient presented a phenotype compatible with TBRS with overgrowth from the neonatal stage along with neurodevelopmental disorders (table 1). ID in individuals with TBRS varies from borderline to severe ID, frequently accompanied by ASD, whose severity usually decreases with age[7,16].

The main differential diagnoses of this new overgrowth syndrome are Sotos syndrome (OMIM #117550), Weaver syndrome (OMIM #277590), and Malan syndrome (OMIM #614753)[1]. These share in their presentation postnatal overgrowth associated with neurodevelopmental disturbances and differ primarily in facial dysmorphias. The advanced bone age of our patient is a common feature in Sotos syndrome and Weaver syndrome but has not been reported frequently in TBRS[16]. The advanced bone age in the proband's sister, who does not carry the variant identified in the *DNMT3A* gene, raises the possibility that there are other familial factors associated with this manifestation.

The facial dysmorphia of the patient is compatible with those of other patients with TBRS, with coarse

Figure 1. Facial phenotype at 9 years-old. Note coarse facial features, light hair, prominent forehead, bitemporal narrowing, prominent and horizontal eyebrows, low-set ear and pinna abnormalities, full cheeks, anteverted nostrils, cupid's bow upper lip and full lower lip, and prominent upper front teeth.

features with the presence of horizontal eyebrows and prominent upper front teeth as the most frequent[1,8]. The facies typically described in Sotos syndrome is elongated, with a prominent forehead, long and prominent chin, sparse frontotemporal hair, and down slanting palpebral fissures[17]. On the other hand, Weaver syndrome presents large and thick pinna, broad forehead, ocular hypertelorism, and micro- and retrognathia[18]. In addition, among the manifestations in other systems, for Sotos syndrome stands out hypotonia, cardiac, renal, and cerebral anomalies, and skeletal conditions such as scoliosis and flat feet; while in Weaver syndrome, skin laxity, camptodactyly, and umbilical hernia are frequent[17,18]. Many of these characteristics can also be present in TBRS with different frequencies (table 1).

There are currently no specific follow-up or treatment guidelines for the syndrome, however, it is recommended an echocardiogram at diagnosis, to evaluate the degree of hypotonia and joint hypermobility in order to determine the need for targeted exercises, and that clinicians be alert to complications such as behavioral/psychiatric disturbances, kyphoscoliosis, and seizures[8]. The finding of neutropenia requires follow-up despite there are no defined tumor monitoring protocols, and clinical surveillance for possible symptoms associated with hematologic cancer is recommended[8].

Different types of pathogenic variants have been described in the *DNMT3A* gene causing TBRS, including missense variants, nonsense variants, frameshift variants, and complete deletions of the gene. The missense variants affecting the main functional domains of the protein are the most frequent[7,11,19].

Somatic variants in the *DNMT3A* gene are common in malignancies, being found in about one-third of patients with acute myeloid leukemia (AML) and other hematologic malignancies[20]. Two cases of patients with TBRS with AML and one case with medulloblastoma have been reported. It is still undetermined whether there is an increased risk of malignancy associated with this syndrome[20-23]. The spectrum of variants between those somatic variants identified in malignancies and germline variants in individuals with TBRS is different, but there are cases of TBRS caused by some of the most common variants in AML[20]. In the case reported, the variant had previously been described as a somatic variant in colorectal adenocarcinoma[15].

On the other hand, somatic variants in the *DNMT3A* gene are commonly observed in healthy individuals associated with age-related clonal hematopoiesis and may be present in control population databases, which should be considered when analyzing their pathogenicity[7,22].

The nonsense variant found in the proband was

Table 1. Frequency of the main clinical features in Tatton Brown Rahman Syndrome according to previous reports[7,8,13] and manifestations in the patient of this report

	Previous reports	Current report
Neurodevelopmental abnormalities		
Intellectual disability	94%	Present
Behavioral and psychiatric disorders	51%	Present
ADHD	7%	Present
ASD	36% - 44%	Present
Seizures	20%	Absent
Global developmental delay	8%	Present
Delayed language development	6%	Present
Growth abnormalities		
Height > 2DE	71%	Present
Weight > 2DE	59%	Present
Head circumference > 2DE	41%	Present
Birth weight > 2DE	28%	Present
Birth length > 2DE	18%	Absent
Facial dysmorphic features		
Horizontal eyebrows	24%	Present
Thick eyebrows	20%	Absent
Broad forehead	16%	Present
Long oval face	12%	Absent
Marked philtrum	11%	Absent
High palate	9%	Absent
Down-slanting palpebral fissures	8%	Present
Thin upper lip / vermillion	7%	Present
Broad nasal base	2%	Present
Other features		
Joint hypermobility	55%	Absent
Hypotonia	51%	Present
Kyphoscoliosis	29%	Absent
Pes planus	7%	Absent

ADHD: Attention-deficit/hyperactivity disorder. ASD: Autism Spectrum Disorder.

initially classified as probably pathogenic by the performing lab. According to ACMG criteria, its current classification is a pathogenic variant because it is a truncating variant in a gene whose function loss and haploinsufficiency is a known mechanism of disease, due to its absence in large control population databases (gnomAD genomes); and pathogenicity predictions by *in silico* computational tools (Mutationtaster) which predict that it truncates the protein or produces

nonsense-mediated mRNA decay (NMD)[16,24,25]. There are still no functional studies reported that demonstrate its pathogenicity *in vitro*

Conclusion

WES study allowed the identification of a pathogenic variant in the *DNMT3A* gene that has not been previously reported in the literature in patients with TBRS, in a Latin American individual. The diagnosis of the underlying cause of the overgrowth made it possible to conclude the performance of tests in search of an etiology and to focus the evaluations on the early detection of potential complications through an initial cardiological evaluation, neurological and hemato-oncological follow-up aimed at the monitoring of hematological malignancies. In addition, the diagnosis underscores

the need for ongoing multidisciplinary management with emphasis on treatment and surveillance of neuropsychiatric manifestations associated with TBRS and allowed for genetic counseling of parents according to the reported inheritance of the syndrome. A limitation of this report is that the presence or absence of the variant in the parents was not confirmed, so it cannot be affirmed that it is a presumably *de novo* variant.

On the other hand, the report of new cases of different ethnicities will allow us to generate better genotype-phenotype correlations in this syndrome, of unknown prevalence, and possibly underdiagnosed, in order to delimit its natural history and develop follow-up guidelines. The broadening of the spectrum of variants will allow a better understanding of the underlying molecular mechanism, the relationship between somatic and germline variants in this gene, and determine whether this is related to an increased risk of neoplasms.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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