***GATAD2B* Gene Microdeletion Causing Intellectual Disability Autosomal Dominant Type 18: Case Report and Review of the Literature**

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Keywords

Chromosomal microarray analysis · Copy number variation · *GATAD2B* · Intellectual disability · MRD18

Abstract

Pathogenic variants of the *GATAD2B* gene (1q21.3) are linked to intellectual disability autosomal dominant type 18 (MRD18; MIM 615074), characterized by dysmorphic features, psychomotor and language delay. We present an 11-year-old female patient with intellectual disability and typical clinical characteristics of MRD18. Chromosomal microarray analysis (CMA) revealed a novel CNV, approximately 200 kb in size and showed that the *INTS3* and *SLC27A3* genes are completely deleted along with the first 10 exons of the *GATAD2B* gene. *INTS3* encodes the integrator complex subunit 3 and is part of the complex that maintains genome stability; *SLC27A3* encodes a fatty acid transporter and has been associated with autism spectrum disorder. *GATAD2B* haploinsufficiency is associated with the phenotype. Furthermore, the girl had other clinical characteristics not previ-

ously described, such as emotional instability, calf hypotrophy, hypoplastic digit pads, tapered thumbs, and anterior earlobe crease. This study highlights the importance of the phenotype-genotype correlation using molecular diagnostic techniques, such as CMA, and its impact on precise diagnosis, treatment, prognosis, and genetic counseling for patients and their families.

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The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies intellectual disability (ID) as a generalized neurodevelopment disorder characterized by significant limitations in intellectual functioning (IQ <70) and adaptive behavior (including conceptual, social, and practical skills) under 18 years of age. ID, either isolated or syndromic, affects 1–8% of the worldwide population (alone 3–12.9% in the Latin American population) [Ropers, 2010; Lazcano-Ponce et al., 2013; Srivastava and Schwartz, 2014; Vissers et al., 2016].

Fig. 1. Pedigree of the family showing the proband III.2 (arrow) and her maternal aunt affected by scleroderma (II.4).

Normal brain development depends on a precise and complex sequence of events such as proliferation, migration, connection, and neuronal-glial maturation. Even in a morphologically normal brain, neuronal connectivity can be altered by glial or synaptic dysfunction, or accumulation of toxic components [Chiurazzi and Pirozzi, 2016].

ID can be caused by genetic and/or environmental factors beginning in the embryonic period until adulthood. ID has a high degree of clinical and genetic heterogeneity. Currently, some studies have estimated that up to 90% of the ID cases are caused by genetic variants and are diagnosed by modern molecular techniques such as chromosomal microarray analysis (CMA). Genetic causes account for 25% of all the patients, and in males with ID, X-linked genes are responsible for 10–12% [Ropers, 2010; Srivastava and Schwartz, 2014; Karam et al., 2015; Vissers et al., 2016].

In the Online Mendelian Inheritance in Man (OMIM; www.omim.org), ID has been classified into autosomal dominant (PS156200, 50 types), autosomal recessive (PS249500, 53 types), syndromic X-linked (PS309510, 41 types), and nonsyndromic X-linked (PS309530, 50 types). It is important to discriminate between syndromic and isolated types; however, some genetic variants may also cause syndromic *and* isolated ID. Several studies demonstrate genetic overlap between ID and other neuropsychiatric disorders [Chiurazzi and Pirozzi, 2016; Vissers et al., 2016].

The GATA zinc finger domain containing 2B gene (*GATAD2B*; MIM 614998; 1q21.3) encodes a protein transcriptional repressor p66-beta (p66β; Uniprot

Q8WXI9). *GATAD2B* belongs to the MeCP1 complex (methyl-CpG-binding domain protein 1) and its variants are related to intellectual disability autosomal dominant 18 (MRD18; MIM 615074) [de Ligt et al., 2012; Willemssen et al., 2013; Hamdan et al., 2014; Luo et al., 2017; Tim-Aroon et al., 2017; Vermeulen et al., 2017].

We report the first Peruvian female patient, and 16th worldwide, with a molecular diagnosis of MRD18 revealed by CMA.

Clinical Report

Our female patient was born at term by vaginal delivery after an uneventful pregnancy to nonconsanguineous parents born in Ancash, a suburban region of Peru. The girl's birth weight was 3,500 g (58th percentile). Apgar score head circumference, and height were not documented. Her father was 25 years old and her mother was 32 when the child was born. Medical history reported pneumonia at 6 months and strabismus at 2 years of age; her maternal aunt has scleroderma (Fig. 1). Regarding her developmental milestones, she was able to hold her head independently at 4 months, sit without support at 7 months, walk independently at 18 months, and she spoke her first word at 14 months. She was referred to our institute for genetic evaluation due to speech delay and ID. Currently, she is in third grade at primary school with poor performance.

At physical examination (11 years), anthropometric measurements were: weight 29.7 kg (10th percentile), height 139 cm (16th percentile), and head circumference 53.5 cm (30th percentile). The phenotype showed dysmorphic features characterized by a long face, thin brown hair, a broad forehead, hypoplastic superciliary arches, eyebrows laterally not extended, long tubular nose with bulbous nasal tip, upslanting palpebral fissures, malar hypoplasia, full cheeks, short philtrum, thin lip vermillion, prognathism, and anterior earlobe crease. Musculoskeletal abnormalities included

Fig. 2. Clinical characteristics. **a, b** Long face, thin brown hair, a broad forehead, hypoplastic superciliary arches, eyebrows laterally not extended, long tubular nose with bulbous nasal tip, upslanting palpebral fissures, malar hypoplasia, prominent cheeks, short philtrum, thin lip vermillion, and prognathism. **c** Scoliosis. **d, e, k, l** Underdeveloped distal interphalangeal crease of the fourth finger, and tapered digits. **f** Hypoplastic digit pads. **g, h** Anterior earlobe crease. **i, j** Calf hypotrophy. **m** Café-au-lait spot in the lumbar region.

an elongated chest, scoliosis, hypoplastic digit pads, underdeveloped distal interphalangeal crease of the fourth finger, tapered thumbs, flat feet, and calf hypotrophy. Furthermore, she showed a café-au-lait spot with an irregular border in the lumbar region and inappropriate laughter (Fig. 2).

Our patient had an IQ of 39 (moderate ID), chromosome analysis showed a normal karyotype (46,XX), X-rays detected dorsal and lumbar rotoscoliosis, EEG revealed frontoparietal intermittent alpha activity, and thin layer chromatography of amino acids from urine were normal.

Methods

CMA from total DNA (250 ng) was performed according to international recommendations [Miller et al., 2010], amplified, labeled, and hybridized using GeneChip CytoScan 750K Array protocols (Affymetrix, Santa Clara, CA, USA) according to the manufacturer's instructions. The array specifications included 550,000 non-polymorphic markers and 200,436 SNP markers. CEL files obtained by scanning the arrays were analyzed using the Chromosome Analysis Suite (ChAS) software (Affymetrix). Gains and losses that affected a minimum of 25/50 markers, respectively, and loss-of-heterozygosity regions that expanded over 5 Mbp were initially considered.

The patient's CNVs were compared with genomic variants in public databases, including DECIPHER [Firth et al., 2009] and UCSC (University of California, Santa Cruz) Genome Browser.

Results

CMA revealed a heterozygous deletion approximately 200 kb in size (arr[hg19] 1:153667997_153867908) in the long arm of chromosome 1 (1q21.3), which was classified as pathogenic CNV. This deletion encompassed 3 genes and involves the total loss of *INTS3* and *SLC27A3*, which are not described in OMIM. In addition, CMA detected a partial deletion (first 10 exons) of the *GATAD2B* gene, which is known to be related to MRD18 (Fig. 3). She did not show other pathogenic or likely pathogenic variants. Loss of heterozygosity showed 1.26%. CMA was not performed for the parents.

Discussion

We described a female patient with moderate ID, language delay, and dysmorphic features. More than 1,000 variants were found in clinical databases (Face2Gene®, Phenomizer®, and OMIM) according to this phenotype; hence, the clinical diagnosis was impossible. However, using massive molecular technologies such as CMA, a partial deletion of the *GATAD2B* gene was revealed,

Fig. 3. a Location of the genes involved in the proband. CNV is located in 1q31.2 showing a complete deletion (gray) of the *INTS3* (HI 24.77%) and *SLC27A3* (HI 62.33%) genes. Additionally, we found a partial deletion (red) of the *GATAD2B* gene with an HI of 10.42%, indicating a haploinsufficiency. HI, haploinsufficiency index. **b** Plot of CNV with log R ratio and B-allele frequency. **c** Relative position of variants in the *GATAD2B* protein.

which was reported previously as pathogenic CNV related to MRD18 [Willemsen et al., 2013].

GATAD2B encodes a p66 β /GATAD2B protein, as a part of the MeCP1 molecular complex (Fig. 4a). This complex is composed of 10 polypeptides including MBD2

(methyl-CpG-binding domain), 7 NuRD (nucleosome remodeling and histone deacetylation) system components, and 2 polypeptides of 66 kDa (p66 α /GATAD2a) and 68 kDa (p66 β /GATAD2B). NuRD is a macromolecular multiprotein complex composed of 1 CHD3 or CHD4

Fig. 4. a MeCP1 multiprotein complex structure and p66 β functions. The figure is composed of 10 polypeptides including MBD2, 7 NuRD system components, and p66 α /p66 β proteins. The CR1/CR2 domains of p66 β (GATAD2B) are indicated; both are required for the correct association of MeCP1 complex and unmodified histone tail binding, respectively. **b** MeCP1 complex functions. It is a transcriptional regulator complex, during chromatin compacting and decompacting (chromatin remodeling), due to ATPase/deacetylase enzymatic activity. It recognizes and binds to Me-CpG DNA regions facilitated by the MBD2 protein.

protein (chromodomain, helicase, DNA-binding domain), 1 HDAC1 or HDAC2 protein (histone deacetylase core), 3 MTA1/2/3 proteins (metastasis associated), 1 MBD3 protein, 6 RbAp46/48 proteins (retinoblastoma-associated protein), and 2 DOC-1 proteins (deleted in oral cancer). All of the abovementioned function as a transcriptional regulator complex by compacting and decompacting chromatin (chromatin remodeling) due to ATPase/deacetylase enzymatic activity [Torchy et al., 2015].

The MBD2 protein is necessary for the assembly of the MeCP1 complex (Fig. 4b) because it recruits NuRD components and directs them towards methylated DNA re-

gions to form the MeCP1 complex. This complex, through preferential binding, remodeling, and deacetylating methylated nucleosomes in the presence of ATP, represses transcription by inhibition of transcriptional factors adhesion to the promoter and delays the RNA polymerase transcription process, hence leading to repression or silencing of methylated genes sequences [Feng and Zhang, 2001].

MBD2 acts as a scaffolding protein to drive p66 α and p66 β towards chromatin histone tails. The p66 proteins are transcriptional repressors due to histone deacetylase activity that contains 2 conserved regions (CR1/2). The CR1 region folds into the α -helix and binds directly to

Table 1. Clinical and molecular description of patients with variants in *GATAD2B* described in the literature

	Single variant			CNV			Vermeulen et al., 2017	Present case	Total
	De Ligt et al., 2012	Willmsen et al., 2013	Hamdan et al., 2014	Luo et al., 2017	patient 1	patient 2			
Age, years	2	12	5	11	12	12	11	11	–
Intellectual disability	Severe	Severe	Severe	Moderate	Moderate	Moderate	Moderate–severe	Moderate	16/16
Language delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	16/16
Psychomotor delay	Yes	Yes	Yes	Yes	No	Yes	Yes	No	7/9
Broad forehead	NA	Yes	NA	NA	NA	NA	NA	Yes	4/4
Short philtrum	NA	Yes	NA	NA	NA	NA	NA	Yes	3/3
Strabismus	Yes	Yes	NA	NA	NA	NA	NA	Yes	6/6
Hypermetropia	NA	Yes	NA	NA	NA	NA	NA	NA	2/2
Eyelid fissure	Narrow	Narrow	NA	NA	Narrow	Narrow	NA	Narrow	6/6
Hypertheliorism	NA	NA	NA	Yes	Yes	NA	NA	Yes	4/4
Tubular nose	Yes	NA	NA	NA	NA	NA	NA	Yes	3/3
Nasal bridge	Broad	Broad	NA	Short	Flat, short	NA	NA	Broad	5/7
Wide mouth	Yes	Yes	NA	NA	NA	NA	NA	No	3/3
Thin hair	Yes	Yes	NA/NA	NA	NA	Yes	NA	Yes	6/6
Other features	Grimaces, long fingers, feet with wide distal phalanges	Hypoplasia of optic nerve, high pain threshold, grimaces, thin upper lip, long and slender fingers	Epilepsy, epicanthus, prognathism, diastema	Upslanting palpebral fissure	Misaligned teeth, hyperactivity	Hypotonia, frustration, intolerance, square nasal tip	GERD, hearing loss, telecanthus, thin lips, blunt nasal tip, dysplastic low-set ears, bilateral clinodactyly	Growth retardation, pectus carinatum, scoliosis, microcephaly, severe spastic quadriplegia, laxity in both hands, periventricular leukomalacia, pontocerebellar hypoplasia	Emotionally unstable, grimaces, scoliosis, calf hypoplasia, digit pads, tapered thumbs, anterior earlobe crease
Variant	p.N195Kfs*30	p.Q470*	c.1217–2A>G	p.L28Mfs*18	p.K184Nfs*2	Chr1:153893110_154132780	Chr1:153460453_154523588	Chr1:153514121_156171335	Chr1:153667997_153867908
Compromised genes in haploinsufficiency, HI <10%	GATAD2B	GATAD2B	GATAD2B	GATAD2B	GATAD2B	CRCT2, GATAD2B, TPM3	ARNT, PSMID4, CHTOP, ILF2, GATAD2B, CRT2, UBAP2L, SHC1, CKSBI, LMNA, 68	NA	GATAD2B
No. of deleted genes	–	–	–	–	–	10	35	NA	3
Effect	Frameshift	Nonsense	Canonical splice site	Frameshift	Frameshift	Haploinsufficiency 240 kb	Haploinsufficiency 1.06 Mb	Haploinsufficiency 2.6 Mb	Haploinsufficiency 200 kb
Size	1 bp	1 bp	1 bp	1 bp	1 bp	240 kb	1.06 Mb	2.6 Mb	200 kb

GERD, gastroesophageal reflux disease; HI, haploinsufficiency index; NA, no data available.

Fig. 5. Comparison of patients with CNVs in 1q21.3 in relation to clinical features and size of the deleted chromosome.

MBD2 C-terminal α -helix (also to MBD3, MTA2, HDAC1/2, and RBBP7/4), so p66 is required for the correct association of the MeCP1 complex. The CR2 region includes a GATA zinc finger domain involved in unmodified histone tail binding [Brackertz et al., 2002; Allen et al., 2013].

The p66 β protein (GATAD2B) is highly and widely expressed in the brain, specifically in the amygdala, cor-

pus callosum, cerebellum, caudate nucleus, hippocampus, and substantia nigra [Hirose et al., 1999].

The microdeletion found in this patient involves the *INTS3*, *SLC27A3*, and *GATAD2B* genes; however, only *GATAD2B* has been described. The *GATAD2B* gene has 11 exons, and in our patient, 10 exons are deleted. The conserved regions CR1 and CR2 are coded in exons 4 and 7–9, respectively. The haploinsufficiency index reported

in DECIPHER and ClinGen for *GATAD2B* was 10.42 and 3%, respectively; hence, if the patient has only one functioning copy of this gene, it leads to a lower protein quantity and loss of function [Firth et al., 2009; Huang et al., 2010]. Also, the low concentration of the p66 protein may result in the reduction of the activity of the MECP1 complex. Evaluating dosage sensitivity for *INTS3* and *SLC27A3* shows haploinsufficiency indexes of 24.77 and 62.33%, respectively, according to DECIPHER; however, ClinGen does not have any score yet. Nevertheless, *INTS3* is part of the core complex together with human single-stranded DNA protein 1 which participates in DNA damage response and maintains genomic stability [Zhang et al., 2013; Vidhyasagar et al., 2018]. Furthermore, the *SLC27A3* gene encodes one of the most relevant fatty acid transporter for supplying fatty acids to the fetal brain; our patient's variants were described in autism spectrum disorder (ASD) [Maekawa et al., 2015], although this case did not show clinical features of ASD.

To date, this female patient is the 16th case reported in the literature, of which 10 have CNVs and 6 single nucleotide variants (SNVs) (Fig. 4c). Patients with SNVs in *GATAD2B* have main clinical characteristics such as facial dysmorphism, grimaces, ID, development delay, poor speech, and hypotonia. Other psychopathological syndromes described are ASD, anxiety disorder, and sleep problems (Table 1). Unpublished additional clinical features related to patients with single variants in the *GATAD2B* gene were café-au-lait spots, calf hypotrophy, hypoplastic digits pads, scoliosis, anterior earlobe creases, and tapered thumbs. Comparing our clinical data with other CNV reports is more difficult because the number of compromised genes is variable (between 10 and 68) and dysmorphisms as well as the size of deletions of the 6

patients reported by Vermeulen et al. [2017] were not described. Nevertheless, the patients described in the literature have overlapping clinical features such as facial dysmorphism, ID, development delay, speech delay, hypermetropia, and thin blond hair (Fig. 5; Table 1) [Willemsen et al., 2013; Sonmez et al., 2017; Tim-Aroon et al., 2017; Vermeulen et al., 2017].

This variant has been reported as pathogenic and is consistent with the diagnosis of MRD18.

Conclusion

In this study, we emphasize the importance of applying modern molecular technologies, such as CMA, in order to delineate genotype-phenotype correlation, enabling precise diagnosis in patients with clinical features of broad genetic heterogeneity, such as ID, influencing the patient's medical treatment, prognosis, and risk recurrence and mainly when other routine tests are not sufficient for diagnosis. We describe a novel *GATAD2B* variant and expand the clinical spectrum of MRD18.

Statement of Ethics

The present study was performed following the ethical regulations of the Instituto Nacional de Salud del Niño (Lima, Peru). Written informed consent was obtained from the parents for publication.

Disclosure Statement

The authors declare no conflicts of interest.

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