Novel *AHDC1* Gene Mutation in a Brazilian Individual: Implications of Xia-Gibbs Syndrome

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Established Facts

- Pathogenic variants in the *AHDC1* gene are related to Xia-Gibbs syndrome, a neurological disorder characterized by global developmental delay, hypotonia, intellectual disability, seizures, and sleep apnea.
- Only a few cases have been described worldwide. A possible genotype-phenotype relationship has been suggested between the location of the mutations in *AHDC1* and the severity of clinical symptoms.

Novel Insights

- We described a new causative variant in *AHDC1* in a Brazilian patient. This variant is the closest one to the N-terminal region reported so far.

Keywords

Exome sequencing · Intellectual disability · Neurodevelopmental disorders · Novel mutation · Sanger sequencing

Abstract

Xia-Gibbs syndrome (XGS) is a rare neurological disorder characterized by global developmental delay, hypotonia, intellectual disability, seizures, and sleep apnea. XGS is defined by monoallelic pathogenic variants in *AHDC1*. In this study,

we identified a Brazilian patient carrying a likely de novo *AHDC1* nonsense mutation (c.451C>T; p.Arg151*) which was absent in both parents. All disease-causative variants already associated with XGS have been reviewed and the mutation described here corresponds to the closest one to the N-terminal region. Our findings were discussed based on the suggested genotype-phenotype correlation of the disease.

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Fig. 1. a–c Patient at 15 years of age, showing minimum dysmorphic features, including a broad forehead and thin upper lip (**a**). Brain MRI showing mild diffuse brain atrophy on coronal (**b**) and axial (**c**) T1-weighted inversion recovery.

In 2014, Xia et al. described 4 unrelated patients who presented with language delay, hypotonia, sleep apnea, and mild dysmorphic facial features. All of them were carriers of de novo monoallelic mutations in *AHDC1* (AT-hook DNA-binding motif-containing 1; RefSeq accession number NM_001029882.2). At that time, it was suggested that the patients presented a new genetic syndrome defined by mutations in *AHDC1*, which now is currently known as Xia-Gibbs syndrome (XGS; OMIM 615829). In addition to the main clinical characteristics primarily reported, patients with XGS may also have behavioral disturbances, seizures, and other features [Jiang et al., 2018; Ritter et al., 2018].

The prevalence of XGS is unknown, but since the first reports, approximately 100 cases have been described in the literature [Xia et al., 2014; Quintero-Rivera et al., 2015; Yang et al., 2015; Bosch et al., 2016; García-Acero and Acosta, 2017; Miller et al., 2017; Park et al., 2017; Popp et al., 2017; Jiang et al., 2018; Ritter et al., 2018; Díaz-Ordóñez et al., 2019; Murdock et al., 2019]. New cases were identified mainly through whole-exome sequencing (WES), since XGS clinical presentation is heterogeneous and nonspecific [Jiang et al., 2018].

Here, we describe a novel nonsense variant in the *AHDC1* gene in a Brazilian case of XGS, along with a de-

tailed clinical description of the proband, contributing to the genotype-phenotype correlation of the disease.

Case Report

A Brazilian male patient (Fig. 1a), was referred to a medical geneticist at 8 years of age to investigate intellectual disability, seizures, and behavior disorder. Pregnancy history was remarkable for preterm contractions. He was born at late preterm (35 weeks) to unrelated parents, with a weight of 2,750 g (75th percentile), height 46 cm (50th percentile), and an Apgar score 9/10. He remained in observation during his first hours of life due to tachypnea but evolved to brief hospital discharge without other complications. No other medical issues in the first months of life were registered. He attained motor and speech milestones during his first 2 years. Seizures started at 21 months of age, with partial loss of motor skills, and recovered by 30 months of age. Speech was seriously affected, with loss of sentences. By school age, he presented severe learning disability. At later infancy, serious behavior disorder, including difficulties in social interaction, aggression episodes, and suicide attempt were reported.

At the time of his first evaluation (8 years of age), the seizures and behavior disorder were partially controlled with valproic acid and haloperidol. At physical examination, he presented normal growth and head circumference, with minor dysmorphic features, including widow's peak, broad forehead, synophrys, and a melanocytic nevus on left thigh. Karyotyping, genetic testing for Fragile X syndrome, and neuroimaging had normal results, and the clini-

Fig. 2. The upper chromatogram represents the result of the son affected by Xia-Gibbs syndrome, showing the presence of the c.451C> T mutation in *AHDC1*. The other chromatograms represent those of both parents, emphasizing only the presence of the wild allele.

cal features were assigned to multifactorial etiology. The patient then returned at 13 years of age, after worsening of epilepsy and behavior disorder. He also presented with dysphagia, scoliosis, movement disorder (bradykinesia, myoclonic tremor, and cerebellar signs), and sleep apnea. He was on psychiatric follow-up, with schizophrenia diagnosis. Neuroimaging detected mild cerebral atrophy (Fig. 1b, c). The patient was receiving 3 antiepileptic and 3 antipsychotic drugs, with poorly controlled aggressive behavior. During 1 month of psychiatric internment at 17 years of age, he was submitted to a pharmacological washout with improvement of the psychiatric symptoms.

Molecular Analysis

Patient blood sample was sent to CENTOGENE for WES as diagnostic workup. Singleton-based (index case) WES was performed as described previously [Trujillano et al., 2017a]. In short, the Nextera Rapid Capture Exome Kit (Illumina, San Diego, CA, USA) or the SureSelect Human All Exon Kit (Agilent, Santa Clara, CA, USA) were used for enrichment, and a HiSeq4000 (Illumina) instrument for the actual sequencing (average coverage was targeted to 100×). Variants calling, annotation, and prioritization were based on a set of publicly available and in-house tools [Trujillano et al., 2017a].

Selection of the variants for reporting was done taking into account the compatibility with the suspected phenotype and suspected disease mechanism. All provided clinical data, family history, disease onset/course, available test results, and clinical suspicion were considered. All modes of inheritance and all relevant variant information were evaluated: zygosity, nature of the variant, and the frequency in public databases (gnomAD, ExAc, and disease-centered databases – HGMD [Stenson et al., 2003] and CentoMD®

[Trujillano et al., 2017b]). Variant nomenclature followed standard recommendations [den Dunnen et al., 2016].

The best candidate variant was detected in *AHDC1*, heterozygous NM_001029882.3:c.451C>T; p.(Arg151*). The variant leads to a premature protein termination, similar to other reported variants in XGS, and it is not reported in any database, including CentoMD. Sanger sequencing confirmed the presence of the variant in the proband and its absence in both maternal and paternal DNA (Fig. 2), in line with a de novo origin. The variant was classified as pathogenic according to the ACMG guidelines [Richards et al., 2015]. The *AHDC1* variant has been deposited in the LOVD 3.0 database (<https://www.lovd.nl/>) under the accession number #0000478183.

Discussion and Conclusion

Since the first report of XGS in 2014, approximately a hundred cases have been identified around the world, with only 2 in Latin America, in 2 Colombian girls [García-Acero and Acosta, 2017; Díaz-Ordoñez et al., 2019]. This is the first case reported in Brazil. The index case is also one of the oldest patients in the literature, with the majority of the cases being children under 10 years of age.

The classical findings of XGS were found in the proband, such as neuropsychomotor developmental delay, seizures, and mild dysmorphic facial features [Jiang et al., 2018]. The patient also showed less common clinical features such as aggressive behavior, scoliosis, and movement disorders. Psychiatric disturbances, which seemed

Table 1. Molecular and clinical features of patients with Xia-Gibbs syndrome reported so far

Reference	Age	Gender	Variant	Effect	Developmental delay	Intellectual disability	Speech	Hypotonia	Dysmorphic	Ataxia	Sleep disturbance
This case	17 ys	M	c.451C>T	p.Arg151*	Delayed	Yes	Delayed	Yes	Yes	Yes	Yes
Jiang et al., 2018	6 ys	F	c.784C>T	p.Gln262*	Walking at 3 ys	NA	Full sentence	Yes	Yes	No	No
Murdoch et al., 2019	52 ys	M	c.979C>T	p.Gln327*	Yes	Yes	Delayed	No	Yes	Yes	No
Yang et al., 2015	4 ys	F	c.1122dupC	p.Gly375Argfs*3	Walking at 20 mo	Yes	Single words	Yes	No	Yes	NA
Bosch et al., 2016	12 ys	F	c.1402dupT	p.Cys468Leufs*49	Yes	NA	First words at 4 yrs	NA	Yes	NA	Yes
Yang et al., 2015	16 ys	F	c.1480 A>T	p.Lys494*	NA	Yes	No verbal speech	No	Yes	No	NA
Díaz-Ordoñez et al., 2019	13 ys	F	c.1529delG	p.Gly510Alafs*12	No walking difficulties	NA	Delayed, first monosyllables at 18 mo	Yes	Yes	No	Yes
Ritter et al., 2018	24 ys	M	c.1759C>T	p.Arg587*	Motor delay, walking at 19 mo	Yes	Delayed	Yes	Yes	NA	NA
Yang et al., 2015	5 ys	M	c.1881delG	p.Gln627Hisfs*105	NA	Yes	NA	Yes	Yes	Yes	NA
Yang et al., 2015	2 ys	M	c.1945delG	p.Ala649Profs*83	No independent walking	NA	No verbal speech	Yes	Yes	No	Yes
García-Acero and Acosta, 2017	8 ys	F	c.2030_2030del	p.Gly677Alafs*55	Sitting at 12 mo, walking at 28 mo	Yes	Single words	Yes	Yes	NA	Yes
Jiang et al., 2018	20 ys	F	c.2062C>T	p.Arg688*	Walking at 22 mo	NA	No sentence, but more than 50 words	No	Yes	Yes	No
Jiang et al., 2018	13 ys	M	c.2229delG	p.Ser744Profs*188	Walking at 3 ys	NA	No words	Yes	Yes	No	Yes
Xia et al., 2014	18 mo	F	c.2373_2374delTG	p.Cys791Trpfs*57	No sitting	NA	No words	Yes	Yes	NA	Yes
Xia et al., 2014	8 ys	M	c.2373_2374delTG	p.Cys791Trpfs*57	Sitting at 9 mo, walking at 18 mo	Yes	First words after 1 yr, persistent speech therapy	Yes	Yes	NA	Yes
Yang et al., 2015	5 ys	M	c.2373_2374delTG	p.Cys791Trpfs*57	Walking at 2 ys	Yes	2 word sentences	Yes	Yes	Yes	NA
Jiang et al., 2018	21 ys	M	c.2373_2374delTG	p.Cys791Trpfs*57	No independent walking	NA	No sentence, but more than 50 words	Yes	Yes	Yes	Yes
Jiang et al., 2018	6 ys	F	c.2415delG	p.Leu806Trpfs*126	Walking at 2 ys	NA	Full sentence	Yes	Yes	Yes	No
Ritter et al., 2018	14 ys	F	c.2473C>T	p.Gln825*	Motor delay, walking at 3 ys	Yes	Delayed	Yes	Yes	NA	Yes
Jiang et al., 2018	9 ys	M	c.2520delIT	p.Arg841Alafs*91	No independent walking	NA	No words	Yes	Yes	Yes	No
Yang et al., 2015	7 ys	F	c.2529_2545del17	p.Asp845Argfs*40	Walking at 3 ys, 10 mo	Yes	2 to 3-word sentences	Yes	Yes	Yes	Yes
Xia et al., 2014	11 ys	M	c.2547delC	p.Ser850Profs*82	Sitting at 15 mo, no independent ambulation	Yes	No words	Yes	Yes	NA	Yes
Jiang et al., 2018	10 ys	M	c.2644C>T	p.Gln882*	Walking at 3 ys	NA	No words	Yes	Yes	No	No
Jiang et al., 2018	4 ys	F	c.2691delA	p.Val898Trpfs*34	Walking at 2.5 ys	NA	Less than 50 words	Yes	NA	Yes	No
Jiang et al., 2018	6 ys	F	c.2773C>T	p.Arg925*	Walking at 2 ys 4 mo	NA	Less than 50 words	Yes	Yes	Yes	No
Jiang et al., 2018	3 ys	M	c.2773C>T	p.Arg925*	No independent walking	NA	No words	Yes	Yes	No	Yes
Ritter et al., 2018	12 ys	M	c.2885dupC	p.Pro963fs	Motor delay, walking at 5.5 ys	Yes	Delayed	Yes	Yes	NA	NA
Xia et al., 2014	4 ys	F	c.2898delC	p.Tyr967Thrfs*175	Sitting at 19 mo, walking at 24 mo	Yes	2 words	Yes	Yes	NA	Yes
Jiang et al., 2018	6 ys	F	c.2908C>T	p.Gln970*	Walking at 2.5 ys	NA	Full sentence	Yes	Yes	Yes	No
Jiang et al., 2018	11 ys	F	c.2908C>T	p.Gln970*	Walking at 2 ys	NA	Full sentence	Yes	NA	Yes	No
Jiang et al., 2018	2 ys	M	c.3773C>G	p.Ser1258*	No independent walking	NA	No words	No	NA	No	Yes
Yang et al., 2015	9 ys	M	c.3809delA	p.Gln1270Argfs*75	Walking at 4 ys, 9 mo	Yes	No verbal speech	Yes	Yes	Yes	NA
Popp et al., 2017	NA	NA	c.3814C>T	p.Arg1272*	NA	Yes	NA	NA	Yes	NA	NA
Jiang et al., 2018	17 ys	M	c.3989C>A	p.Ser1330*	Walking at 19 mo	NA	No words	Yes	NA	No	No
Ritter et al., 2018	29 ys	M	c.4494dupG	p.Cys1499Valfs*9	Motor delay, walking at 3 ys	Yes	Delayed	Yes	Yes	NA	NA
Park et al., 2017	1 ys	M	hg18 del 1p36.1p35.3 (27,750,155–28,754,771)	NA	Yes	NA	Delayed	Yes	NA	NA	NA
Ritter et al., 2018	8 mo	F	hg19 arr 1p36.1p35.3 (27,916,308–28,273,494)×1	NA	Motor delay	NA	Delayed	Hypertonia	Yes	NA	NA

The cases were sorted according to cDNA location of the variant. mo, months; NA, not available; ys, years.

ing of other proteins to AT-rich sequences in DNA and facilitate DNA structure changes [Aravind and Landsman, 1998; Xia et al., 2014]. *AHDC1* also contains another evolutionarily conserved AT-hook domain, which contains no known functional property. Other known domains are similar to KIAA2022, a target for truncated mutations that cause intellectual alteration, and REV3L, a protein involved in DNA repair and genomic stability [Gan et al., 2008; Jiang et al., 2018]. We hypothesize that a good way to elucidate these mechanisms is through the study of *AHDC1* interaction partners, which must be implicated in human neurogenesis and neurodevelopment.

In conclusion, our results expand the spectrum of *AHDC1* pathogenic variants associated with XGS, a possibly underdiagnosed genetic syndrome. As for the phenotype, in agreement with previous reports, our case shows that XGS is much more a nonspecific developmental disorder rather than a recognizable syndrome. The disease should be considered as a differential diagnosis of moderate to severe intellectual disability and childhood-onset behavior disorder in any age range, particularly when associated with mild dysmorphic features, sleep apnea, scoliosis, or ataxia.

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Statement of Ethics

Written consent for this case report was obtained from the patient's guardian. The study was approved by the Hospital de Clinicas de Porto Alegre.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization: A.C.C.d.S., T.O.S., F.d.O.P., T.W.K., J.A.M.S., L.S.F. Writing and original draft preparation: A.C.C.d.S., A.A.B., T.O.S., L.S.F. Critical review: F.d.O.P., A.S.F., A.A.B., T.W.K., J.A.M.S., L.S.F. All authors analyzed and interpreted the data and approved the manuscript in its final form.