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Highly penetrant AUTS2 syndrome phenotype in a boy with *AUTS2* C-terminal intragenic deletion

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Abstract

Background: In the last decades, it has been possible to identify thousands of genes or gene loci implicated in the etiology of syndromic autism spectrum disorders. Those genes play an important role in neuronal migration, extension, branching of the neurites, synaptic function, transcriptional regulation and construction of neuronal network. *AUTS2* gene, also named as the "activator of transcription and developmental regulator", has been associated with a syndromic autism disorder named "AUTS2 syndrome" characterised by intelectual disability, autistic features, and mild dysmorphic characteristics. Since the first description of AUTS2 syndrome, there have been reported more than 60 cases, most of them from western countries. Our aim is to present the first case of a Mexican boy with AUTS2 syndrome and a novel pathogenic mutation of *AUTS2* gene.

Methods: The proband is a 7-year 2-month-old Mexican boy, with growth and global developmental delay, dysmorphic features, such as, high broad forehead, highly arched and broad eyebrows, telecanthus, epicanthic fold, anteverted nares, upturned and short philtrum, high arch palate, small mouth, abnormal teeth, mild micro-retrognathia, low-set and cupped left ear, and camptodactily of the fifth rigth finger.

Results: A cytogenetic analysis revealed a normal male karyotype of 46,XY. In order to detect copy number aberrations, a Microarray-based comparative genomic hybridization analysis was conducted. A pathogenic heterozygous CNV was identified in 7q11.2 involving exons 7–17 at the C-terminal of *AUTS2* gene. The assesment of autism was permormed applying the specific tests ADI-R and ADOS-G concluding that the patient meets criteria for ASD.

Conclusions: The phenotype of the present case corresponds to a severe syndrome according to the AUTS2 syndrome severity score, which correlates to genotype characterized by an intragenic deletion between exons 7 and 17 which affects the short AUTS2 isoform. Therefore, in this case it is confirmed the genotype-phenotype correlation described in most cases with large intragenic deletion of the c-terminal region of the *AUTS2* gene. The early recognition of syndromic autism spectrum disorders by healthcare professionals allows, in addition to accurate genetic counseling, better multidisciplinary therapeutic management and consequently great benefits for patients and their families

Keywords: *AUTS2*, AUTS2 syndrome, autism spectrum disorder, copy number variation, global developmental delay, syndromic autism

Introduction

Syndromic autism spectrum disorders represent a group of childhood neurological conditions, that has been distinguished from nonsyndromic or idiopathic autism based on the presence

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or absence of other additional morphological signs or clinical symptoms [1]. Syndromic autism is typically associated with chromosomal abnormalities or mutations in a single gene.

According to a recent review, 180 autism syndromes have been described in the literature [1]. Most of them are associated to single gene disorders (63%), whereas 32.7% are associated to unique loci as well as chromosome duplications or deletions, and finally 3.3% correspond to chromosomal aneuploidies.

Some of the well known syndromic autism conditions are Fragile X, Rett syndrome, Angelman syndrome, tuberous sclerosis complex, CHARGE syndrome and Down syndrome [2]. However, in the last decades, thanks to the improvment of the molecular techniques such as array comparative genomic hybridization (CGH) and whole-exome sequencing, it has been posible to identify thousands of genes or gene loci implicated in the etiology of autism syndromes [3-5].

Those genes play an important role in neuronal migration, extension, branching of the neurites, synaptic function, transcriptional regulation and construction of neuronal network [6].

The Autism susceptibility candidate 2 gene (*AUTS2*), (MIM*607270), also named as the "activator of transcription and developmental regulator" [HUGO Gene Nomenclature Committee (HGNC), #14262)] was identified in 2002. AUTS2 is involved in proliferation and differentiation of neural progenitor cells; neurite outgrowth and branch formation in neurons, and controls neuronal migration [7,8].

AUTS2 mutations have been associated with a wide range of neurodevelopmental and psychological disorders including intelectual disability (ID), epilepsy, schizophrenia, drug addiction, and alcohol consumption [9-16].

The association of *AUTS2* with autism spectrum disorder (ASD) was initially reported in a case of two monozygotic twins diagnosed with ASD and de novo balanced translocation with disruption of *AUTS2* gene locus [17,18]. More recently the AUTS2 syndrome (OMIM #615834) was delineated [19].

The clinical presentation of the syndrome is highly variable and is mainly characterised by ID, autistic features, feeding difficulties, non-progressive microcephaly, mild dysmorphic characteristics (including ptosis, highly arched eyebrows, narrow mouth and microretrognathia, camptodactyly and faint extension creases) [19,20].

To date, more than 60 cases of AUTS2 syndrome have been reported. Here we present a new case of a 7 year old boy with global developmental delay, autism, dysmorphic features and skeletal anomalies, with a novel pathogenic heterozygous copy number variation (CNV) at the C-terminal of *AUTS2* gene.

Case Presentation

The proband is a 7-year 2-month-old Mexican boy, who was born at 40 weeks of gestation to a 29-year- old healthy mother and 43 year-old unrelated father. The pregnancy was complicated by threatened abortion and preterm labor during third trimester. The delivery was unevenfull. His birth weight was 3,060 g (3th-25th centile) and birth length was 49 cm (50th centile).

At 4 months of age, growth failure, generalized hypotonia, dysmorphic features, right cryptorchidism and hypothyroidism were diagnosed. He started treatment with levothyroxine. The patient was referred to the genetic service, where the clinical survey at 17 months of age showed weight of 7.9 kg (<3th centile), stature of 72 cm (<3th centile) and head circumference of 42 cm (<3th centile). It was noticed global developmental delay; social smile and head sustenance were accomplished at 12 months of age, he was not able to walk without support. There were observed dysmorphic features, such as high broad forehead, highly arched and broad eyebrows, telecanthus, epicanthic fold, anteverted nares, upturned and short philtrum, high arch palate, small mouth, abnormal teeth, mild microretrognathia, low-set and cupped left ear. Skeletal abnormalities were also observed, such as camptodactily of the fifth right finger (**Figure 1**).

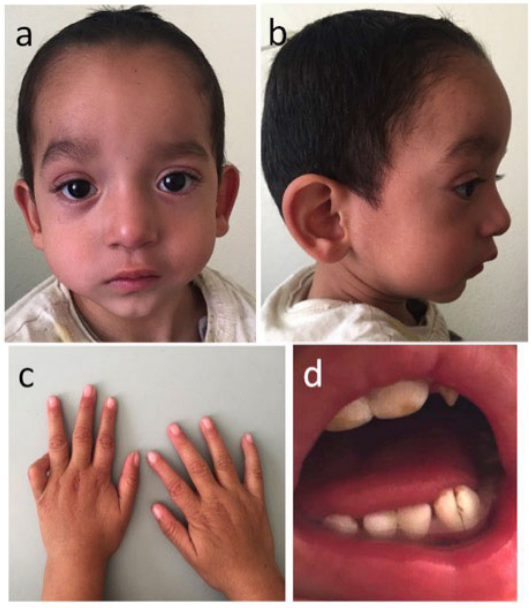

Figure 1. Patient at the age of 2 years 8 months, observe dysmorphic features and skeletal abnormalities.
(**a**) High broad forehead, highly arched and broad eyebrows, telecanthus, epicanthic fold, anteverted nares, upturned and short philtrum, small mouth.
(**b**) Mild microretrognathia.
(**c**) Camptodactily of the fifth rigth finger.
(**d**) Abnormal teeth.

A cytogenetic analysis of peripheral blood was performed and revealed a normal male karyotype of 46,XY.

In order to detect copy number aberrations, a Microarray-based comparative genomic hybridization (aCGH) analysis was conducted, after written consent was obtained, on the aCGX- HD platform (4x180K). DNA was extracted from the

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whole blood using the Puregene DNA Blood. Kit (Gentra, Minneapolis, MN, USA), according to the manufacturer's instructions. The entire genome was covered with resolution of 100 kb (average resolution of 20kb) including subtelomeric and pericentromeric regions. This array is designed to cover interest regions in more tan 245 known syndromes, and 980 functional genes with pathologic association (including 200 loci associated with autism spectrum disorders). Results were analyzed by aCGH analysis software (Genoglyphix™; Signature Genomic Laboratories, Spokane, WA).

A pathogenic heterozygous CNV in 7q11.2 of 0.034 Mb was identified, involving exons 7–17 at the C-terminal of *AUTS2* gene [arr 7q11.22(70,217,747-70,251,859) x1]. No other CNVs with clinical significance were found in the patient.

Neurological examination at that time demonstrated axial hypotonia, no paresis, no extrapyramidal movement disorder, no ataxia, normal to high deep tendon reflexes, and a normal sensitivity. Computer Tomography of the brain showed global cortico subcortical atrophy with left temporal predominance.

Echocardiogram revealed the presence of interatrial communication ostium secundum of 5.4 mm with no hemodynamic repercussion. No cardiac murmurs were adverted during physical examination.

At 30 months old, patient was able to walk without support. At the age of 5 years, 3 months, his weight was 13.9 kg (<3th centile), his height was 97.5 cm (<3th centile), and his OFC was 48.5 cm (<3th centile). Physical Medicine survey at this time concluded deficits in visuomotor coordination of upper limbs, abnormal gait pattern due to forefoot abduction, and fluctuation in postural tone with tendency to distal hypertonia.

Autistic features were evaluated by psycology using Autism Diagnostic Interview Revised (ADI-R) (**Table 1**), and Autism Diagnostic Observation Schedule-Genetic (ADOS-G) (**Table 2**). According to the results of the ADOS and taking into consideration the diagnostic guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), it is concluded that the patient meets sufficient criteria to be diagnosed with ASD.

Cognitive function was assesed at 7 years ussing Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) (**Table 3**). The main final measurements of the patient were verbal comprehension 46, and intelligence quotient 41, which are considered extremely low.

In order to evaluate cognitive development, the Spanish version of the Batelle Developmental Inventory (BDI) was administered at the age of 6 years 9 months. The skills assessed by the BDI scale are adaptive, personal-social communication, motor, and cognitive. The total developmental quotient obtained was 51, which corresponds to a significant developmental delay (**Table 4**).

Table 1. Autism Diagnostic Interview Revised (ADI-R) of the patient at the age of 82 months.

Domain	Score
Qualitative abnormalities in reciprocal social interaction	
Failure to use nonverbal communication to regulate social interaction (a1)	1
Failure to develop peer relationships (a2)	4
Lack of shared enjoyment (a3)	1
Lack of socio-emotional reciprocity (a4)	1
Subtotal (cut-off 10)	7
Qualitative impairments in communication and language (non verbal)	
Lack of, or delay in, spoken language and failure to compensate through gesture (b1)	3
Lack of carried spontaneous make-believe or social imitative play (b4)	5
Subtotal (cut-off 8)	8
Restricted, repetitive and stereotyped behaviors and interests.	--
Encompassing preoccupations or circumscribed pattern of interest (c1)	0
Apparently compulsive adherence to nonfunctional routines or rituals (c2)	0
Stereotyped and repetitive motor mannerism (c3)	1
Preoccupation with part of objects or nonfunctional elements of material (c4)	1
Subtotal (cut-off 03)	2
Abnormality of development evident at or before 36 months (cut-off 1)	1
Total (cut-off)	**18**

Discussion/Conclusion

AUTS2 gene is located on chromosome 7q11.22, spans 1.2 Mb, and contains 19 exons encoding two AUTS2 isoforms which are expressed in the developing human brain but with different patterns of expression [**18**,**21**]. The long AUTS2 isoform is expressed in undifferentiated cells, and is replaced by the short isoform during neuronal differentiation [**21**]. N-terminal region of AUTS2 is specific to the long isoform, while C terminus corresponds to the short isoform (exons 7–19), which is expressed in human brain and starts in exon 9 [**19**,**21**].

It has been proposed that the loss-of function mutations in different parts of a gene can explain the large phenotypic interindividual variability observed in patients with AUTS2 syndrome. Due to this variation, was establish an AUTS2 syndrome severity score (ASSS) [**20**]. The ASSS is based on 32 features and is composed of 4 grades expressed as the sum of all features: 0-6, 7-12, 13-18 y 19-32. However, each characteristic has the same value, and it has been suggested that the main features such as ID and autism receive additional

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Table 2. Autism Diagnostic Observation Schedule (ADOS) of the patient at the age of 82 months.

Domain	Score
Language and Communication	
Frequency of spontaneous vocalization directed to other (A2)	1
Stereotyped/Idiosyncratic use of words or phrases (A5)	0
Use of another´s body (A6)	0
Pointing (A7)	1
Gestures (A8)	1
Subtotal (AUT 4, AS 2)	**3**
Reciprocal Social Interaction	--
Unusual eye contact (B1)	0
Facial expression directed to others (B3)	0
Share enjoyment in interaction (B5)	0
Showing (B9)	2
Spontaneous initiation of joint attention (B10)	1
Response to joint attention (B11)	2
Quality of social overtures (B12)	1
Subtotal (AUT 7, AS 4)	**6**
Total of SA and SC (AUT 12, AS 7)	**9**
Play	--
Functional play with objects (C1)	0
Imagination/Creativity (C2)	2
Subtotal	**2**

Table 3. Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) of the patient at the age of 7 years.

Test	Composite score	
Verbal IQ (VIQ)	46	--
Performance IQ (PIQ)	47	--
Global Language (GL)	59	--
IQ	41	--
Subtest	**Part Of:**	**Scaled Score**
Information	VIQ	1
Vocabulary	VIQ	1
Word reasoning	VIQ	1
Block design	PIQ	1
Matrix reasoning	PIQ	2
Picture concepts	PIQ	1
Object assembly	PIQ	1
Receptive vocabulary	GL	4
Picture naming	GL	2

points to better establish the severity of the phenotype [22].

The present case has a score of 19/32, according to de ASSS corresponds to a severe syndrome (Table 5). It has been observed a genotype-phenotype correlation, patients with 3′ deletions present more pronounced dysmorphic features, whereas, patients with 5 in-frame deletions have a mild phenotype. Our patient presents an intragenic deletion between exons 7 and 17 which affects the short AUTS2 isoform, therefore in this case it is confirmed the genotype-phenotype

Table 4. Battelle Developmental Inventory BDI-2 (at 6 years 9 months).

Domains	DQ Score	Subdomains	Age equivalent Years	Age equivalent Months	Scaled score	Percentiles	DQ Score
Adaptive	55	Personal responsability	2	11	1	<1	SDD
Personal-social	SDD						
	60	Self-concept and social role					
	SDD						
	55	Receptive language	4	6	2		
	SDD	Expressive language					
Communication	55	Perceptual motor	3	0	1	9	
	SDD	Reasoning and academicskills	2	8	6		
Motor	55						
	SDD	Perceptión and concepts	3	1			
Cognitive			3	1	1	<1	
			1	11			
Devolopmental Quotient (DQ): 51 SDD							

SDD significant developmental delay.

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Table 5. AUTS2 syndrome severity score of the patient at the age of 7 years.

General	
Sex	**Male**
De novo occurrence	?
Growth and feeding	
Low birth weight	-
Short stature	+
Microcephaly	+
Feeding difficulties	-
Neurodevelopmental disorders	
Intellectual disability/development delay	+
Autism/autistic behavior	+
Sound sensitivity	+
Hyperactivity/ADHD	+
Neurological disorders	
Generalized hypotonia	+
Structural brain anomaly	+
High muscle tone/spasticity	+
Dysmorphic features	
Highly arched eyebrows	+
Hypertelorism	+
Proptosis	-
Short palpebral fissures	-
Upslanting palpebral fissures	-
Ptosis	-
Epicanthic fold	+
Strabismus	-
Prominent nasal tip	-
Anteverted nares	+
Deep nasal bridge	-
Short/upturned philtrum	+
Micro/retrognathia	+
Low-set ears	+
Ear pit	-
Narrow mouth	+
Skeletal abnormalities	
Kyphosis/scoliosis	-
Arthrogryposis/shallow palmar creases	+
Tight heel cords	+
Congenital malformations	
Hernia umbilicalis/inguinalis	-
Patent foramen ovale/atrial septum defect	+
AUTS2 syndrome severity score	**19/32**

correlation described in most cases. Although the *AUTS2* gene was cloned in 1997 and named *KIAA0442* [23], the name AUTS2 was propose because of its association with autism present in the case of twin sisters [18]. In subsequent case reports in which mutations in the *AUTS2* gene were documented, autism has been reported in only 60% of cases [24]. The present case was evaluated by a child neuropsychologist applying the specific tests for the diagnosis of autism, ADI-R and ADOS-G. From the symptomatology present in the patient and taking into consideration the DSM-5 criteria, it was inferred that the patient presents an ASD with noticeable deficits in social communication, restricted and repetitive behaviors with accompanying intelectual and language impairment, as well as unintelligible speech.

The prevalence of AUTS2 syndrome is variable between the different populations analized. Among children with ID and developmental delay (DD) in western countries, the occurece rate has been calculated in 1/2000, while in chinese population is 3.75/1000 [25,26]. In Latin America the prevalence is unknown. To our knowledge, this is the second case of AUTS2 syndrome documented, after the first report in monocigotic twins of latin american origin with mental retardation and autism.

Some syndromic autism spectrum disorders as AUTS2 syndrome, due to their recent description, are not easily recognised and are therefore underdiagnosed. We consider that a better knowledge and understanding of this spectrum is relevant in order for health professionals to be able to recognise the patterns of somatic morbidity that can be observed from early stages, even at birth, before neurodevelopmental disturbances become apparent.

The early recognition of syndromic autism spectrum disorders allows, in addition to accurate genetic counseling, better multidisciplinary therapeutic management and consequently great benefits for patients and their families.

List of abreviations

ASD: Autism Spectrum Disorder
ADI-R: Autism Diagnostic Interview Revised
ADOS-G: Autism Diagnostic Observation Schedule-Genetic
AUTS2: Autism Susceptibility Candidate 2 gene
ASSS: AUTS2 Syndrome Severity Score
BDI: Batelle Developmental Inventory
CGH: Array Comparative Genomic Hybridization
CNV: Copy Number Variation
DQ: Devolopmental Quotient
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition
GL: Global Language
ID: Intelectual Disability
IQ: Intelligence Quotient
HUGO: Human Genome Organization
HGNC: Hugo Gene Nomenclature Committee
PIQ: Performance IQ
SDD: significant developmental delay
VIQ: Verbal IQ
WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, third edition

Competing interests
The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	BL	CJAG	RMG	VVL	MR
Research concept and design	√	--	--	--	--
Collection and/or assembly of data	--	√	√	√	√
Data analysis and interpretation	√	√	--	--	--
Writing the article	√	--	√	--	--
Critical revision of the article	--	--	--	√	--
Final approval of article	√	√	√	√	√
Statistical analysis	--	--	--	--	--

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