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Structural Genome Variations Associated with Autism Spectrum Disorders (ASD), A Case Report

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Abstract: ***The advent of methodologies and technologies to scan the human genome will bring new strategies for the identification of risk mutations, with the aim of providing genetic/familial counseling, timely diagnosis, prognosis, appropriate clinical approach and targeted treatment in different pathologies and mainly neurodevelopmental pathologies, such as Autism Spectrum Disorder (ASD). We present the case of a patient with double structural alteration of the genome related to ASD, with the aim of highlighting the importance of genetic/molecular study to facilitate cataloging, characterization, and clinical interpretation, as well as genetic counseling. Describe ASD in terms of the underlying structural features of each patient's genome.***

Keywords: Autism Spectrum Disorder (ASD); X-linked; Genes; Genome; Intellectual Disability

1.Introduction

Autism Spectrum Disorder (ASD) is a common clinical and genetically heterogeneous neurodevelopmental disorder characterized by alterations or delays in the development of functions related to the maturation of the central nervous system, which begin in childhood and follow a stable evolutionary course [1]. ASD is observed in all populations with an incidence of 16.8 cases per 1000 children [2, 3]. The estimated prevalence of ASD in siblings is 5% to 10% [2, 4, 5].

ASD encompasses a wide variability of clinical manifestations and developmental trajectories, characterized by compromised social interaction and communication in various contexts, associated with restricted interests and stereotyped, repetitive and inflexible behaviors [6, 7].

ASD presents variable expression and according to the support needs of the person who suffers from it; it is classified according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-5, in three levels of severity, depending on the need for help as follows: a) With need for help, b) notable need and c) very notable [6, 8].

In addition, individuals with ASD also frequently have one or more comorbidities, which may include intellectual disability, epilepsy, motor and sensory abnormalities; and/or attention deficit/hyperactivity disorder [6, 9].

We report the case of a patient classified as ASD with several problems in his social interaction, associated with: special phenotype, short stature, behavioral disorders and significant neurodevelopmental delay, who was found to have clinically important mutations in his genome.

2.Case Report

Case report of a 4-years-old male patient, product of a G1/P1/A0 mother, uncontrolled and unplanned pregnancy of 32 weeks of gestation. Birth weight: 1810 g (-0.6 Standard Deviations (SD)); birth length: 43 cm (0 SD). Important antecedents: Neonatal Intensive Care Unit, requiring non-invasive supplemental oxygen for 3 days; multidisciplinary follow-up since 2-years-old in the Infantil Napoleón Franco Pareja Children's Hospital, for recurrent infection syndrome with predominantly non-severe respiratory focus, severe short stature and delayed neurodevelopmental milestones with: head support at 3 months, sitting at 8 months, walking at 16 months and language with first words at 2 years and without sphincter control. Schooling: attended by Instituto Colombiano de Bienestar Familiar (ICBF), observing deficiencies in reciprocal social interactions, communication problems and a restricted range of behaviors and interests. Family history: Maternal height, 150 cm with a history of Diabetes Mellitus; Paternal height, 161 cm, whom has undergone studies for suspected primary immunodeficiency. Physical examination: Height 84 cm (-4.7 SD); Arms pan equal to her height; Upper/lower segment ratio 1.4; Weight 10 kgs (-5.1 SD); BMI-1.5 SD; Head Circumference (HC) 51 cm (height/age HC: + 2.2 SD); Severe short stature, macro-crania, broad and prominent forehead, low ears implantation, broad and flattened nasal bridge, ogival palate arch. Diagnostic studies by specialties in Table 1.

Table 1: Studies performed in the patient with ASD.

Endocrinological:	f-T4: 0.77 ng/dl; TSH: 1.36 µIU/ml; cortisol a. m: 14 µg/dl; IGF-1: 66 ng/ml; calcium: 10.1 mg/dl; magnesium 2.1 mg/dl; phosphorus 5.68 mg/dl; pituitary MRI*: normal. Karyotype: 46, XY
Genetics:	IC1 methylation studies normal and Silver-Russell negative; Comparative Genomic Hybridization: XP22.11 deletion; PTCHD1, typical of type 4 X-linked autism. Whole Exome sequencing: Heterozygous variant, 7q11.22 gene mutation; AUTS2: c.1690-4A>G, with uncertain significance in association with mental retardation with Dominant Inheritance Pattern.
Immunologicals:	Leukocytes: 8340 mm^3, Lymphocytes: 5198 mm^3. CD4 2225/42.8 cel/mm^3, CD8 845/16.2 (-2SD 300/14) cel/mm^3 Ratio 2.63. IgG 1835 mg/dl, IgM 217 mg/dl, IgA 1336 mg/dl, IgE 59.79 mg/dl.
Neurological:	Cranial CT^+: Increased cephalic diameters. Transfontanelar ultrasound: mild hydrocephalus. EEG: Paroxysm of spikes and sharp waves in lateral fronto-central regions of medium and high voltage. Brain MRI*: Increased cephalic diameters.
Others:	Echocardiogram: Normal. Alpha-thalassemia study: Negative.
*MRI: Magnetic Resonance Imaging. + CT: Computerized axial tomography.	

3.Discussion

ASD is observed in all populations, with an incidence of 16.8 cases per 1000 children; approximately four (4) times more males compared to females, probably due to genetic bases (although it is considered that there is a female under-reporting), lack of identification, variability of clinical expression, and technical difficulties of diagnosis [2, 3]. Cytogenetically detectable chromosomal abnormalities in ASD cases are found to be associated with 7.4%, ranging from 0% to 54% [3]. Estimates of familial inheritance for ASD are approximately 90% [10]. The estimated prevalence of ASD in siblings is 5% to 10% [2, 4, 5]. As molecular studies are conducted in the population with suspected ASD, it may be possible to describe it in terms of the underlying structural features of each patient's genome [11].

The presentation and severity of ASD patient characteristics vary widely among individuals, suggesting etiologic heterogeneity [12]. ASD has an important genetic burden, being considered a disorder derived from a combination of *"novo"* mutations, associated with a predisposition derived from common inherited variations, involving genes encoding synapse proteins [1, 13]. The highest occurrence of events is observed in syndromic forms of ASD, such as Fragile X syndrome and Rett syndrome, among others [14].

With the increasing use of high-resolution chromosomal microarrays in clinical practice to investigate the underlying genetic causes of neurodevelopmental disorders, more and more causative mutations are being found; and, as the use of exome and whole genome sequencing in the clinical setting increases, many more will undoubtedly be identified [11, 15]. Genes associated with ASD and intellectual disability have been identified, such as NRXN1, SHANK2, SHANK3 and PTCHD1; however, there is still very little information on the clinical presentation of individuals with these mutations [15].

In different studies already reported, patients with alteration of the PTCHD1 coding region may have significant behavioral problems associated with subtle dysmorphic features, including a long face, prominent forehead, puffy eyelids and thin upper lip, without having congenital abnormalities or growth problems [3, 15, 16]. Other findings described in patients with alterations in PTCHD1 are orofacial hypotonia and mild motor incoordination [17, 18].

Deletions in AUTS2 gene, have been associated with: mild facial dysmorphias, short stature, intellectual disability, cerebral palsy, neurodevelopmental delay; and, significant findings in the paternal family line of learning disabilities [19, 20].

Therefore, the current case reported, corresponds to a patient with mutations found in the Comparative Genomic Hybridization of: PTCHD1; and in the Whole Exome Sequencing of: AUTS2, having a peculiar phenotype as previously described, severe short stature, neurodevelopmental delay, associated with ASD. When comparing it with the previously described studies, similarities in its clinical and phenotypic expression are found with each of them [3, 15-20]. Unfortunately, so far it has not been possible to perform a parent's genetic evaluation because the patient is in the custody of a guardian, through the ICBF.

Despite the strong association between chromosomal abnormalities and ASD, due to the failure to perform complementary genetic studies on these patients, none of the causes already established will account for more than 2% of the diagnosed causes [21, 22].

4.Conclusion

ASD is considered an urgent public health problem; such a problem could benefit from population-based studies to identify ASD earlier in order to try to determine risk factors (if is possible to prevent them); and to address behavioral, educational, residential and occupational needs once the diagnosis has been made [23]. A case is reported in which important structural changes in its genome are demonstrated, related to behavioral and social problems, neurodevelopmental delay and several phenotypic alterations, similar to previously described studies. The importance of molecular studies nowadays is

that they provide better support in genetic counseling to families and health professionals: they are useful to know the penetrance, clinical expressivity; to focus on the multidisciplinary clinical management of the patient; their prognosis; and in some diseases, to know the treatment and possible outcome.

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