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Case Report

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Unlikely Evolution: A Rare Case of Jarid2 Haploinsufficiency Not Associated with Intelectual Disability

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Abstract

Global developmental delay consists of an inability to meet expected neurodevelopment milestones in various areas of functioning in children younger than five years-old. About 1/3 of these children will develop intellectual disability, which is a neurodevelopmental disorder consisting of limitations in both intelligence and adaptive skills, affecting at least one of the three adaptive domains. Genetic abnormalities represent one of the most frequent etiologies and may justify the wide spectrum of clinical manifestations of intellectual disability.

Mutations in chromosome 6p22.3 may lead to JARID2 (jumonji, AT rich interactive domain 2) gene haploinsufficiency and explain a neurodevelopmental syndrome characterized by some dysmorphic features, cardiovascular and renal malformations, intelectual disability, among others. However, the presence of the mutation not always predicts the patient's phenotype thus it is essential to advise parents of the multiple possible outcomes.

Keywords: global developmental delay; intellectual disability; JARID2; haploinsufficiency; genetic mutation; chromosome 6p22.3

Introduction

Global developmental delay (GDD) is defined as the inability to meet expected neurodevelopment milestones in various areas of functioning (intellectual and adaptative) in children younger than five years-old [1-3]. Its prevalence is 1-3% in the general population and about 1/3 of the children with GDD will develop intellectual disability (ID), which is a neurodevelopmental disorder consisting of limitations in both intelligence and adaptive skills, affecting at least one of the three adaptive domains (conceptual, social, and practical). There is a wide spectrum regarding the severity of the ID, and, as far as etiology is concerned, there is a panoply of possible causes and conditions that may explain the occurrence of ID, with genetic abnormalities being one of the most predominant causes [1-4].

The authors present a case of a mutation in chromosome 6p22.3, encompassing the JARID2 (jumonji, AT rich interactive domain 2) gene, which encodes an important transcriptional repressor protein, that regulates the activity of various histone methyltransferase complexes [5,6]. JARID2 has an important role in epigenetic regulation of development, differentiation and maintenance of embryonic cells (including in the cardiovascular system, liver, hematopoiesis and neural tube fusion) [5-8].

Partial or total deletions of JARID2 gene or even single-nucleotide arrangements lead to its haploinsufficiency, thus explaining a clinically distinct neurodevelopmental syndrome [5-6,8].

Case Description

A 19 month-old girl was referred to the Pediatric consultation with suspected neurodevelopmental delay. Pre and perinatal history were irrelevant. Physical examination showed a frontal hemangioma (already under treatment with propranolol, with good response), prominent forehead, strabismus, hypertelorism, pectus excavatum and slightly hypotonic lower limbs, without other alterations. She also presented, as suspected, a GDD, more accentuated in terms of global motricity.

First-tier etiological investigation included array-CGH, which revealed a "de novo" 36kb deletion on the short arm of chromosome 6 at p22.3 level, encompassing the JARID2 gene, critical in cardiovascular development and also associated with autism spectrum disorder, ID and some dysmorphic characteristics. Genetic testing revealed that this deletion was not inherited from the parents. The child started early multidisciplinary therapeutic intervention including speech therapy and occupational therapy, with a good clinical evolution in the subsequent years. She maintains regular follow-up and currently, at 11 years-old, she is attending school (5th grade) with good school performance, without needing special education services.

Discussion/ Conclusion

There have been only very few cases of JARID2 haploinsufficiency described in literature and regarding clinical presentation, ID (mild to severe) seems to be transversal to the majority of the patients with JARID2 haploinsufficiency. Patients may also present some dysmorphic characteristics such as eye abnormalities, craniofacial malformations (prominent forehead, hypo or hypertelorism, strabismus, full lips, among others), abnormalities involving hands or feet (pes planus, clinodactyly, single palmar crease), kidney and heart defects, and other nneurological abnormalities, such as epilepsysy, lack of coordination and/or muscular hypotonia [5-8].

In fact, a study [5] analysed five patients with JARID2 haploinsufficiency and their clinical presentation: all of the patients presented ID, ranging from borderline to severe, several dysmorphic characteristics and most of them had gait

Disturbance. Two of the patients also had hypotonia and other two had seizures [5].

In another cohort of 16 patients, 11 patients presented ID, three presented borderline functioning and one patient had learning difficulties. All of them had a history of neurodevelopment delay and all presented a wide combination of dysmorphic characteristics. Half of them presented features of autism spectrum disorder, 44% exhibit behaviour abnormalities such as aggressive demeanour and trouble socialisation, and one subject presented two psychotic episodes [6].

With similar results to the ones described, in another study [8] with 11 patients, most of them had ID and all of them had a history of GDD. Three of the patients had gait disturbance and three had hypotonia. Most of them also presented dysmorphic characteristics [8].

In contrast, in our case, the child presented mild GDD with no evolution to ID. In fact, she is enrolled in the 5th grade and has been having good grades with no adaptive or inclusive measures. She also has some dysmorphic characteristics that became more evident with growth, such as forehead hemangioma, prominent forehead, strabismus, hypertelorism and pectus excavatum. She exhibits a phenotype concordant with those described in literature, but milder.

Many authors have been proposing that different breakpoints and sizes of the deletion may explain the wide spectrum of phenotypical characteristics [5-6,8]. In the presented case, the size of the deletion was 36Kb.

Our case highlights the fact that a genetic diagnosis does not define the patient's prognosis: a rare mutation that has been described in literature to be associated with a neurodevelopment syndrome with ID, exhibited a different neurocognitive pattern in our patient, with a favourable outcome.

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