A New 12q21 Deletion Syndrome: A Case Report and Literature Review

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Abstract

Diagnosis in children with physical and intellectual anomalies is very challenging because of the wide spectrum of causes. Array-based comparative genomic hybridization (CGH) has acquired an important role in pediatric diagnostic work up. Interstitial deletion of the long arm of chromosome 12 are rare. To date, deletions including the 12q21 region were reported in only 13 patients. The main features are development delay, eyes and central nervous system anomalies, and heart and kidney defects. We describe a 3-year-old boy with a de novo 15 Mb deletion at 12q21.1q21.32, never reported in the last cases. By screening the critical region and reviewing the literature, we identified SYT1, PPP1R12A, and CEP290 such as pathogenetic genes.

Keywords
► 12q21 deletion
► pediatrics
► genetic

Introduction

Diagnosis in children with physical and cognitive impairment is very challenging because of the wide number of etiological events. Array-based comparative genomic hybridization (CGH) has acquired an important role in diagnostic work up allowing a better definition of the diagnosis. Deletions in the 12q21 region has been rarely reported and so far only 13 cases with this anomaly have been published. We report a 3,1/2 years-old boy with development delay, craniofacial dysmorphism, strabismus, muscle mass hypotrophy, pectoral muscle asymmetry, scoliosis, and dysmorphic corpus callosum at the brain MRI. The CGH microarray disclosed a novel 15 MB deletion in the 12q21.1q21.32. Genetic analysis in the parents were normal.

Case Presentation

The proband, a 3.5-year-old boy, is the second child of unrelated parents. The family history is unremarkable. He was born at term by caesarean section for breech presentation, with a weight of 2,700 g. He did not have jaundice or asphyxiation. No teratogenic drug exposures were reported with normal neonatal period. Parents reported a failure to thrive with a regular progression in weight...
and height, always under 3rd centile. Developmentally, he achieved head support at the age of 5 months, he was able to sit unsupported at the age of 9 months, and walked unsupported at 30 months. His examination reveals prominent forehead, hypertelorism, strabismus, triangular face, low set ears, hypoplastic nostrils, and micro- and retrognathia (►Fig. 1). We noted poor muscle weight, asymmetry of the pectoral muscle (left > right), and scoliosis. Control of the sphincters not yet acquired. He is socially responsive, with delayed speech and motor impediment to fine and coarse motor skills. Brain magnetic resonance imaging (MRI) revealed a dysmorphic corpus callosum (►Fig. 2). Array-based comparative genomic hybridization (CGH) of DNA extracted from

Fig. 1 The main clinical features reported in 12q21 deletion children. The imagine was made taking inspiration from our patient and others affected by similar deletion, whose photos are published in the literature.1,3,8,11,12

Fig. 2 MRI of a 3.5 years-old boy with 12q21 deletion and dysmorphism of the corpus callosum (A–B–C–D). Sagittal T1-weighted MR image (A), Sagittal T2-weighted MR image (B), Sagittal 3D (C) and coronal 3D MPRAGE (D) images shows dysmorphism of the corpus callosum with appreciable thinning of the middle third and posterior third of the body in relation to the age of the patient (white arrows and white line); Axial T1 (E) and T2 (F) weighted MR image shows cavum velum interpositum cyst (white arrows).
peripheral blood revealed an interstitial deletion of 12q21.1q21.32. The anomaly was 15 Mb. The analysis on his parents was negative.

Discussion

The first to describe an interstitial deletion of the long arm of chromosome 12 was Meinecke's in the 1987, describing a syndrome with multiple malformations including cleft lip and palate and cardiac abnormalities in 12q13.3q21.1 deletion.\(^1\) Two years later, Watson et al described a 12q15q21.2 deletion in a child with physical abnormalities and development delay.\(^2\) Thirty-two years have passed since these first report; the reports on this topic increased after the introduction of array-based CGH examination which allowed researchers to extend the phenotype of this disorder. Several molecular mutations have been reported in other patients.\(^1\)–\(^12\) Common features included development delay, clinical dysmorphism, heart defects, and anomalies in the central nervous system. Most of the 12q21 deletion syndrome cases reported in the literature involve the SYT1, PPP1R12A, and CEP290 genes.

We compared the phenotype with the data available in the publica database DECIPHER (\(\text{Fig. 3}\)). The main characteristic in common with our child were developmental delay, musculoskeletal abnormalities, and corpus callosum anomalies. A previous study, published in 2020 by Niclass et al described two candidate genes as critical component

Fig 3 Image modified from Decipher with the genes involved in the mutation of the proband.

Fig. 4 Modified from SFARI genes where genes involved with high confidence.
### Table 1  Comparing the deletions and phenotypic features of our patient with 15 reported cases with deletion in the region of 12q21

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Deletion type</th>
<th>Dysmorphic features</th>
<th>Development</th>
<th>SNC anomalies</th>
<th>Cardiac</th>
<th>Renal</th>
<th>Musculo skeletal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al (1989)</td>
<td>12q15q21.2</td>
<td>Present</td>
<td>Delayed</td>
<td>No reported</td>
<td>No reported</td>
<td>No reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brady et al (1999)</td>
<td>12q21.2q23.32</td>
<td>Present</td>
<td>Delayed</td>
<td>No reported</td>
<td>No reported</td>
<td>No reported</td>
<td>Short stature</td>
<td>GH deficit</td>
</tr>
<tr>
<td>Rauen et al (2002)</td>
<td>12q21.2q22</td>
<td>Present</td>
<td>Delayed</td>
<td>Hydrocephalus</td>
<td>Septal defect</td>
<td>No reported</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Klein et al (2005)</td>
<td>12q21.2q22</td>
<td>Present</td>
<td>Delayed</td>
<td>Mild ventriculomegaly</td>
<td>PDA and PFO</td>
<td>right moderate hydronephrosis and duplication of right collecting system</td>
<td>Scoliosis 2/3 toe syndactyly</td>
<td>Atopic dermatitis, hyperopia, bilateral conductive hearing loss, gastrostomy, bitemporal alopecia, bilateral hydroceles</td>
</tr>
<tr>
<td>James et al (2005)</td>
<td>12q21.2q22</td>
<td>Present</td>
<td>Delayed</td>
<td>No reported</td>
<td>No reported</td>
<td>No reported</td>
<td>Normal</td>
<td>Skin hyperkeratotic, papular eruption</td>
</tr>
<tr>
<td>Matsumoto et al (2014)</td>
<td>12q21.2-q21.33</td>
<td>Present</td>
<td>Delayed</td>
<td>Mild ventriculomegaly and hypoplasia of the CC</td>
<td>No reported</td>
<td>No reported</td>
<td>Mild spastic diplegia</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Oliveira et al (2015)</td>
<td>12q21.2q22</td>
<td>Present</td>
<td>Delayed</td>
<td>Anomalous subcortical white matter hyperechogenicity ventriculomegaly and hypoplasia of CC</td>
<td>No reported</td>
<td>right vesicoureteral reflux and left renal pelvis dilatation</td>
<td>2/3 toe syndactyly 4th/5th clinodactyly</td>
<td>Axial hypotonia hyperkeratosis pilaris and ulerythema ophryogenes</td>
</tr>
<tr>
<td>McKenna et al (2019)</td>
<td>12q21.1q21.33</td>
<td>Present</td>
<td>Delayed</td>
<td>Slight ventriculomegaly</td>
<td>PFO</td>
<td>No reported</td>
<td>Small left-side hydrocele</td>
<td></td>
</tr>
<tr>
<td>Niclass et al (2020)</td>
<td>12q21.1q21.3</td>
<td>Present</td>
<td>Delayed</td>
<td>Ventriculomegaly dysmorphic CC and developmental abnormality of the frontal vein</td>
<td>No reported</td>
<td>Horseshoe kidneys</td>
<td>Muscle weakness</td>
<td></td>
</tr>
<tr>
<td>Niclass et al (2020)</td>
<td>12q21.2q21.31</td>
<td>Present</td>
<td>Delayed</td>
<td>No reported</td>
<td>No reported</td>
<td>No reported</td>
<td>Pectus excavatum</td>
<td>Autism spectrum disorder</td>
</tr>
</tbody>
</table>

Abbreviation: CC, corpus callosum; GH, growth hormone; PDA, patent ductus arteriosus; PFO, patent forame ovale; SNC, central nervous system.
Table 2 Clinical features of previous patients and our case

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Previous case</th>
<th>Our patient</th>
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<tbody>
<tr>
<td>Hypertelorism</td>
<td>10/13</td>
<td>+</td>
</tr>
<tr>
<td>Hypothelorism</td>
<td>2/13</td>
<td>–</td>
</tr>
<tr>
<td>Low set ears</td>
<td>11/13</td>
<td>+</td>
</tr>
<tr>
<td>Short neck/webbed neck</td>
<td>3/13</td>
<td>–</td>
</tr>
<tr>
<td>Retrognathia</td>
<td>7/13</td>
<td>+</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>9/13</td>
<td>+</td>
</tr>
<tr>
<td>Prominent forehead</td>
<td>10/13</td>
<td>+</td>
</tr>
<tr>
<td>Bulbous nasal, short nose</td>
<td>8/13</td>
<td>+</td>
</tr>
</tbody>
</table>

of the deletion: SYT1 and PPP1R12A. SYT1 encodes an integral membrane protein of postsynaptic vesicles thought to serve as Ca\(^{2+}\) sensors in the process of vesicular trafficking and exocytosis. Mutations in the SYT1 cause neurodevelopmental disorder described in a rare syndrome, Baker–Gordon syndrome. They reported 11 individuals affected by infantile hypotonia, congenital ophthalmic abnormalities, childhood-onset hyperkinetic movements disorder, motor stereotypies, and developmental delay. In addition, SYT1 is included as a syndromic gene for the autism spectrum disease in the SFARI database. Although the patient herein reported carries a very large deletion, the phenotype is consistent with that described by Niclass et al. It underlines that a small region, including the candidate-genes SYT1 and PPP1R12A, can be considered critical and sufficient for the clinical manifestations of 12q21 microdeletion syndrome.

PPP1R12A encodes a regulatory subunit of myosin phosphatase. This enzyme is recently associated in the cellular processes such as cell cycle, gene expression regulation, neurotransmitter release, and even embryonic development.

We suppose also CEP290 as one of the main genes for our child. In the literature, there are suggestive evidence in autism reports. Although the molecular function is playing a role in ciliary transport processes, defects in this gene are associated with several neurologic diseases, for example Joubert’s syndrome, Leber’s congenital amaurosis, or Meckel’s syndrome.

Ethical Approval
This study was conformed to the ethical guidelines of Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Authors’ Contributions
Each author committed a substantial contribution to the conception or design of the work and to revise it critically for important intellectual content. In addition, each author approved the final version to be published. Conversely, each author agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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None.

Conflict of Interest
None declared.

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References