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Short clinical report

Molecular cytogenetic characterization of 2p23.2p23.3 deletion in a child with developmental delay, hypotonia and cryptorchism

Maria Santa Rocca*, Flavio Faletra, Raffaella Devescovi, Paolo Gasparini, Vanna Pecile

Institute for Maternal and Child Health-IRCCS "Burlo Garofolo", Via dell'Istria 65/1, 34137 Trieste, Italy

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ABSTRACT

Deletions of the short arm of chromosome 2 are exceedingly rare and only nine cases involving regions from 2p23 to 2pter have been reported to date. Most of these deletions had only been analysed by GTG banding. Here, we report an interstitial de novo deletion resulting in a microdeletion of 3.9 Mb involving 2p23.2-p23.3 segment, detected by SNP-array analysis, in a 5 year-old boy showing hypotonia, overweight, dysmorphic facial features and cryptorchidism. We compared the clinical features of the present case to previously described patients with deletions within this chromosomal region. Our case adds new information to the deletion of the distal part of chromosome 2p improving the knowledge on this rearrangement.

1. Introduction

Pure interstitial deletions of the distal short arm of chromosome 2 are rare, with only nine reported cases of such deletions involving regions from 2p23 to 2pter. Most of these observations are based on cytogenetic investigations [1,2,3,4,5], while four patients with deletion of 2p23-pter have been studied by molecular methods [6,7,8,11]. The variable phenotype could be due to the amount of genetic material lost. We report a 5-year-old boy with an interstitial de novo deletion of 3.9 Mb in 2p23.2-p23.3 detected by SNP-array analysis. The phenotype of this patient includes hypotonia, he is overweight, he has dysmorphic facial features and cryptorchidism.

2. Clinical report

The patient was referred at the age of 15 months because of developmental delay and hypotonia. He is the first child of non-consanguineous parents. There was no family history of congenital abnormalities or mental delay. Ultrasound examination during the pregnancy revealed bilateral choroid plexus cysts and a single umbilical artery. Prenatal karyotype showed a normal 46,XY karyotype. He was born at term after an uneventful pregnancy by normal delivery [birth weight 3600 g (70–90th centile); length 52 cm (90th centile); APGAR 7/8]. During the neonatal period a diffuse hypotonia and bilateral cryptorchidism were diagnosed. A delay in motor development was noted from the first month of life with head control achieved at 7 months and sitting position at 14 months of age.

The growth parameters at the age of 15 months were: weight 11,5 kg (75th centile), height 81 cm (90th centile) and OFC 47 cm (50th centile).

He spoke his first words when he was 2 years old. A developmental assessment was performed at the age of 2.4 years by means of the Brunet–Lezine Scale, which revealed a severe mental delay (DQ:48), corresponding to the equivalent score of a 14 months old child, with lower scores in visual-motor coordination (DQ:48) and posture (DQ:39) and best performances in language (DQ:53) and social skills (DQ:58) respectively.

On consecutive neurological examination the child showed a marked developmental and mental delay, axial and segmental hypotonia and joint hyperflexibility. There were no pyramidal signs even though a mild hyperreflexia in the legs was present.

On behavioural observation he exhibited stereotyped movements like swinging of the head.

Several sleep EEG recordings did not show an adequate organisation for his age and unstable focal abnormalities such as biphasic spikes. The child has never experienced seizures.

A brain MRI scan revealed a mild corpus callosum hypoplasia and mega cisterna magna.

Echocardiography and abdominal ultrasounds did not find any abnormalities.

He had red-brown hair, high forehead, telecanthus, rare eyebrows, broad nasal bridge, short bulbous nose, long philtrum and thick lips (Fig. 1).

* Corresponding author. Tel.: +39 040 3785226; fax: +39 040 3785540.
E-mail address: roccams1@gmail.com (M.S. Rocca).

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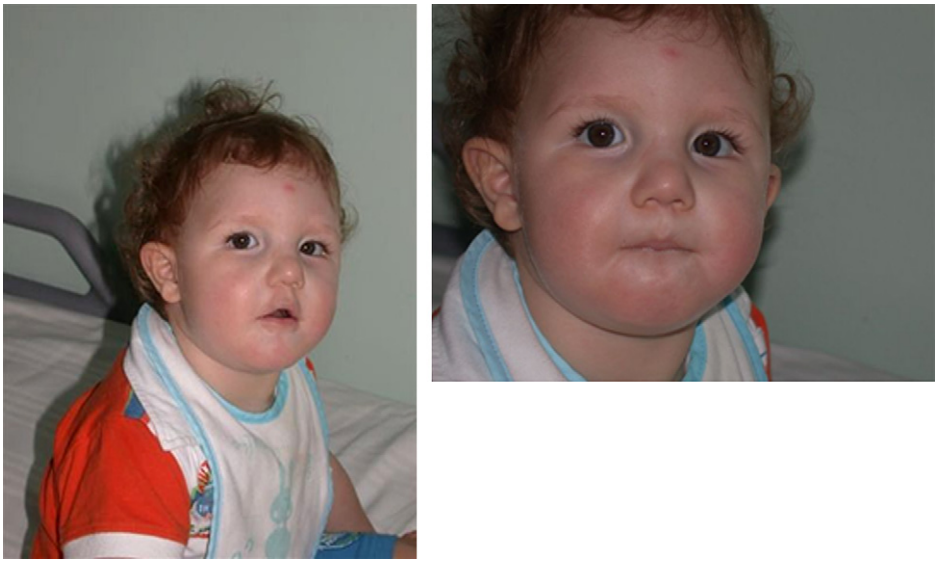

Fig. 1. Facial image of the proband.

He walked without support at 3 years and 6 months old with marked instability due to pronation and complete external rotation of his feet.

3. Material and methods

SNP array analysis, from DNA isolated from peripheral blood lymphocytes, was carried out using the Illumina HumanCNV370-Quad genotyping microarray according to the protocol. Data analysis was performed using the Illumina GenomeStudio v.2010 software program and then we utilized the data with the program including Illumina cnvPartition (ver 2.3.4). To obtain authentic CNVs in this study, we performed a family-based CNV validation and family-based boundary mapping using the PennCNV algorithm. Parent-specific copy number variant (CNV) regions and copy number variants overlapping with reported CNVs in Database of Genomic Variants (DGV) identified in this study were not considered. Furthermore, we excluded all CNVs that had $\leq$20 contributing SNPs.

4. Results

SNPs-Array analysis revealed an interstitial deletion of 3.9 Mb in the 2p23.3-p23.2 from chr2:23,902,957 to chr2:27,876,624 (GRCh37/hg19). The deleted region contains over 70 genes most of them with a known function.

In order to study the parental origin of the deletion, parental chromosomes of our patient were studied. SNP-array analysis in this family demonstrated that the unbalance was not present in parents and arose on the paternal chromosome.

5. Discussion

We describe a patient with dysmorphic features, hypotonia and cryptorchism carrying a de novo cryptic deletion of chromosome 2p23.2-p23.3 detected by SNP-array analysis.

Pure monosomies of 2p are very rare and are usually observed as part of more complex aberrations involving other chromosomes [7]. Due to the diagnostic difficulties in the identification and exact localization of 2p deleted segments in pre-array era, the phenotype–karyotype correlations are restricted by the fact that the precise positions and sizes of these deletions are uncertain.

For this reason we have compared the clinical features of the proband with those patients whose deletions of 2p23.3 have been studied by molecular methods (Table 1).

Shoukier et al. have described a boy whose deletion overlaps with that of our case from position 23,9 to 26,08 Mb (Fig. 2). Hypotonia and cryptorchidism were the only clinical features in common with our patient.

They have indicated *DTNB* (dystrobrevin-beta, OMIM *602415) and *FKBP1B* (calstabin, OMIM *600620) as candidate genes responsible for the clinical findings of their case.

In particular, they assume that the deletion of *FKBP1B* may contribute to the dilated cardiomyopathy (DCM) observed in their patient, because the expression levels of this gene have been reported to be increased or decreased in animal models exhibiting contractile heart dysfunctions and cardiomyopathies. Our boy and two patients reported in the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER), ID 255430 and ID 252051, present a deleted *FKBP1B* gene, but do not show any dilated cardiomyopathy and for this reason we can't support the hypothesis of a key role of this gene in heart dysfunctions suggested by Shoukier at al.

DTNB is a component of the dystrophin–protein complex (DPC) and it is abundantly expressed in the brain and other tissues but not in the muscles. Blake et al. [9] have suggested that β-dystrobrevin may be relevant to the cognitive disabilities affecting many patients with Duchenne muscular dystrophy and Becker muscular dystrophy.

DTNB is deleted in our patient who shows a severe mental delay that confirms the hypothesis of a role of this gene in cognitive dysfunctions.

Among the deleted genes in our proband there is *POMC* (OMIM *176830) that encodes melanocortin peptides that are released by tissue-specific proteolytic processing. Loss-of-function mutations of the *POMC* gene typically result in adrenal insufficiency, obesity and red hair.

Krude et al. [10] have described heterozygous *POMC* mutation carriers with a body weight shifted to higher than normal or even mildly obese levels, suggesting a dosage effect of the *POMC* gene product on weight regulation. Furthermore the DECIPHER database