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Refinement of the critical 7p22.1 deletion region: Haploinsufficiency of *ACTB* is the cause of the 7p22.1 microdeletion-related developmental disorders

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ABSTRACT

Non-recurrent microdeletion (≤2 Mb in size) in 7p22.1 is a rarely described cytogenetic aberration, only recently reported in patients with developmental delay/intellectual disability, short stature and microcephaly. The size of the deletions ranged from 0.37 to 1.5 Mb, and reported genotype-phenotype correlations identified a minimum deleted region of 0.37 Mb involving the *FBLX18*, *ACTB*, *FSCN1*, *RNF216* and *ZNF815P* genes. The authors suggested that deletion of *ACTB,* which encodes β-actin, an essential component of the cytoskeleton, could be responsible for the clinical features observed in the patients with a 7p22.1 microdeletion. Here, we describe a 23-month-old child displaying developmental delay, short stature, microcephaly and distinctive facial features. Chromosomal microarray analysis performed using high-resolution SNP-array platform revealed a *de novo* interstitial 60 Kb microdeletion in the 7p22.1 region (from 5,509,127 bp to 5,569,096 bp, hg19) encompassing only two genes: *FBXL18* and *ACTB.* To the best of our knowledge, this is the smallest deletion at 7p22.1 to date reported in medical literature (Pubmed). Combining our data with phenotypic and genotypic data of cases from literature, we were able to narrow the minimal critical region, which contained only two genes, i.e., *FBXL18* and *ACTB.* Our finding is useful to perform a more accurate genotype-phenotype correlation and strongly strengthen the hypothesis that haploinsufficiency of *ACTB* is the main cause of the clinical phenotype observed in the patients with 7p22.1 microdeletions, facilitating genetic diagnosis and counseling.

1. Introduction

De novo microdeletions/microduplications encompassing one or few genes are an easy way to identify genes involved in developmental disorders. Interstitial microdeletions involving the 7p22.1 chromosomal region are very rare, since were recently described in only five cases with developmental delay/intellectual disability, short stature and microcephaly (Shimojima et al., 2016). From a molecular point of view, two of the five patients showed a very small deletion, that allowed the authors to identify a genomic region encompassing the *FBLX18*, *ACTB*, *FSCN1*, *RNF216* and *ZNF815P* genes as the "minimal critical region" (MCR). From a medical point of view, since the clinical relevance of the *FBLX18*, *FSCN1* and *ZNF815P* genes was unknown, the authors focused their attention on the remaining two. In particular, they proposed the haploinsufficiency of *ACTB* as responsible for the clinical manifestations of 7p22.1 microdeletions.

Here, we describe a patient with developmental delay, short stature, microcephaly and dysmorphic features carriers of the smallest interstitial *de novo* microdeletion inside the chromosomal region 7p22.1 reported to date encompassing the *FBLX18* and *ACTB* genes. We compared molecular findings as well as clinical presentation of our patient and previously reported cases with deletions involving the *ACTB* gene discussing its role in the etiology of the observed clinical phenotype.

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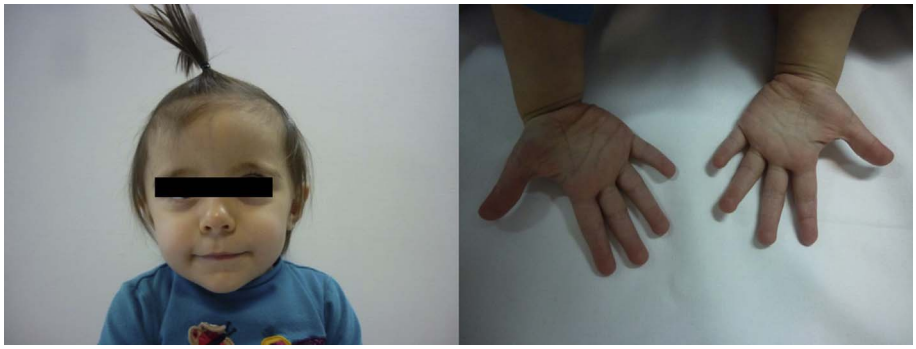

Fig. 1. The patient at 23 months. Detailed clinical description is reported in the text.

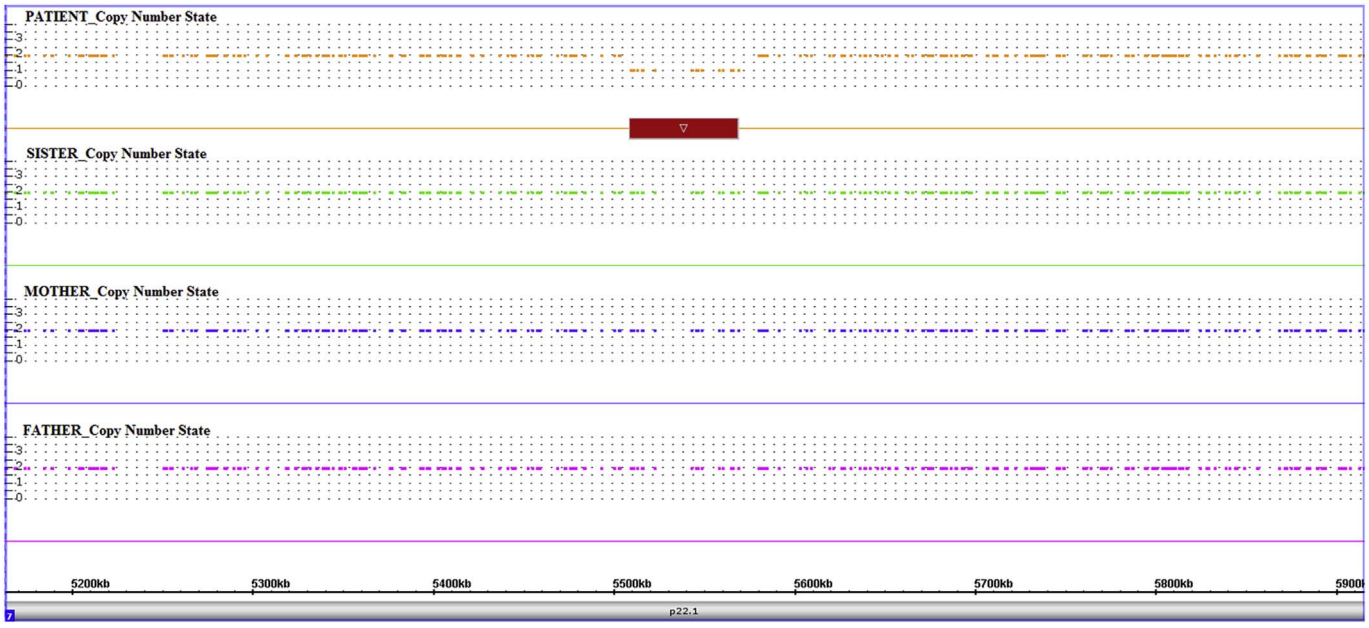

Fig. 2. Results of chromosomal microarray analysis in the patient, her parents and her sister. Copy number state of each probe is drawn along chromosome 7 from 5200 to 5900 kb. The red box indicate the *de novo* interstitial microdeletion identified in the genomic profile of the patient. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2. Clinical report

The patient, a female, is a bigeminy twin of a bicorial-biamniotic pregnancy achieved by intra cytoplasmic sperm injection (ICSI). Family history was unremarkable for any genetic disorders and parents were not consanguineous. She was born preterm at 33 weeks of gestation by elective cesarean section because maternal cholestatis. Birth weight was 1400 g (10th centile), length was 39 cm (3rd-10th centile) and occipitofrontal circumference (OFC) was 28.2 cm (< 3rd centile). Apgar scores were 5 and 7 at 1 and 5 min, respectively. She was admitted for prematurity to Neonatal Intensive Care Unit for four weeks and required ventilation because respiratory distress. Clinical geneticist evaluated the patient at 23 months of age (corrected age 21 months). Motor developmental milestones were slight delayed, expressive language was limited to few words. Her medical history was positive for failure to thrive, celiac disease was excluded, hematochemical and thyroid function exams were in normal range. Her growth parameters were all < 3rd centile: length was 72.3 cm, weight was 6950 kg and OFC was 44 cm. Physical examination revealed distinctive dysmorphic features with frontal bossing, bitemporal narrowing, prominence of metopic suture, large anterior fontanelle, high anterior hairline, lateral sparse eyebrows, long eyelashes, long philtrum, thin lips and pointed chin. In addition, moderate hypotonia, mild joint laxity and bilateral clinodactyly of the 5th finger (Fig. 1) were noted. Electroencephalogram (EEG) did not show any abnormalities, and echocardiogram was normal. Addominal ultrasound showed mild unilateral pyelectasis. Ophthalmological evaluation detected hypermetropia and exotropia. Audiological assessments were in normal range. Cerebral magnetic resonace imaging (MRI) did not demonstrate structural anomalies.

In the same occasion was evaluated also her twin. Length was 78.5 cm (3rd-10th centile), weight was 8500 kg (< 3rd centile), occipitofrontal circumference was 44.7 cm (3rd-10th centile). No dysmorphic features like her sister were noted. Her neuromotor development was according to age.

3. Materials and methods

SNP array based Copy Number Variations (CNVs) analysis was performed on genomic DNA extracted from peripheral blood lymphocytes of the patient, her sister and her parents, after obtaining written informed consent, using the CytoScan HD Array (Affymetrix, Santa Clara, CA, USA) as previously described (Palumbo et al., 2014). Data analysis was performed using the Chromosome Analysis Suite software version 3.1 (Affymetrix, Santa Clara, CA, USA). A CNV was validated if at least 25 contiguous probes showed an abnormal $\log_2$ ratio. The clinical significance of each CNV detected was assessed by comparison with an internal database of 3500 patients studied in our laboratory by SNP array since 2010 with a diagnosis of syndromic/non-syndromic neurodevelopmental disorders.