CLINICAL REPORT

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# Clinical Characterization of a Male Patient with the Recently Described 8q21.11 Microdeletion Syndrome

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**The 8q21.11 microdeletion syndrome (OMIM # 614230) has been recently described and is primarily characterized by intellectual disability and facial dysmorphism. We describe here a male patient of 9 years 9 months of age with moderate intellectual disability and dysmorphic facial features. A high resolution copy number variation analysis, performed with the Affymetrix Cytogenetics Whole-Genome 2.7 M SNP array, allowed the identification of a heterozygous 7.069 Mb microdeletion at chromosome 8q21.11–q21.13. Clinical comparison of our patient with literature shows many similarities. However, the whole facial appearance of our patient, especially the elongated rather than rounded face and the absence of a wide nasal bridge and epicanthal folds, confers him a phenotype similar only to a subset, but not to the majority, of the hitherto described patients.**



**Key words:** 8q21.11 microdeletion syndrome; 8q21.11–q21.13 microdeletion; SNP array; intellectual disability; dysmorphism

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## INTRODUCTION

In 2010, The International Standards for Cytogenomic Arrays Consortium recommended the use of Single Nucleotide Polymorphism (SNP) and Comparative Genomic Hybridization (CGH) arrays as a first genetic test in patients with phenotypes such as intellectual disability (ID), developmental delay (DD), autism spectrum disorders (ASDs) and multiple congenital anomalies (MCA) [Miller et al., 2010]. Thereby, the identification of submicroscopic chromosomal abnormalities, some of which were associated with neurodevelopmental phenotypes, has been facilitated. The 8q21.11 microdeletion syndrome is a genomic disorder recently described by Palomares et al. [2011], who studied the clinical characteristics of eight patients with ID and overlapping deletions at 8q21.11, ranging in size from 0.66 to 13.55 Mb. According to these authors, despite the differences in the copy number variation (CNV) sizes, the phenotype was substantially similar and characterized by facial dysmorphism (round face with full cheeks, high forehead, ptosis, corneal opacities, underdeveloped alae, short philtrum, Cupid's bow of the upper lip, down-rotated corners of the mouth, micrognathia, and low-set and prominent ears) and mild defects in fingers and toes. Additional features often shared by these patients were ID, hypotonia, balance problems, sensorineural hearing loss and behavioral problems, including a patient diagnosed with autism [Palomares et al., 2011]. Additionally, Hoffman et al. [2011] described a patient with a diagnosis of distal arthrogryposis type 2B (DA2B) and a phenotype characterized by normal

Conflict of interest: none.

Abbreviations: SNP, Single Nucleotide Polymorphism; CGH, Comparative Genomic Hybridization; ID, Intellectual Disability; DD, Developmental Delay; ASD, Autism Spectrum Disorders; MCA, Multiple Congenital Anomalies; CNV, Copy Number Variation; DA2B, Distal Arthrogryposis type 2B; MRI, Magnetic Resonance Imaging.

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cognitive development, club feet, camptodactyly, ulnar deviation and mild dysmorphic facial features including a high forehead, small mouth, broad nasal bridge, epicanthus, high palate, brachycephaly, short neck and dysplastic ears. In this report, a 7 Mb deletion, located at chromosome 8q21.11–q21.23 and affecting 23 *RefSeq* genes, was detected [Hofmann et al., 2011]. Recently, Vulto-van Silfhout et al. [2013] evaluated the clinical significance of de novo and inherited CNVs in 5,531 patients with ID and MCA and found 1,663 rare CNVs in a total of 1,388 patients, one of them with DD, macrocephaly, ventriculomegaly, hypermetropia, recurrent infections and dysmorphism (high forehead, downslanting palpebral fissures, ptosis, and prominent low-set ears) and an 8q21.11 microdeletion [Vulto-van Silfhout et al., 2013].

One of the individuals described by Palomares et al. [2011] belongs to a four-generation family, previously described in the literature, in which five members were affected by a consistently unusual facial phenotype and learning difficulties [Belligni and Hennekam, 2010]. The remaining reported patients with 8q21.11 deletions were all sporadic [Hofmann et al., 2011; Palomares et al., 2011; Vulto-van Silfhout et al., 2013].

Here, genome-wide CNV analysis using a high-resolution SNP microarray allowed the identification of a heterozygous 7.069 Mb deletion at 8q21.11–q21.13 in a male patient with moderate ID and dysmorphic facial features.

## MATERIALS AND METHODS

DNA samples from both the patient and his mother were obtained from peripheral blood and genotyped using the Cytogenetics Whole-Genome 2.7 M SNP array and the CytoScan High-Density SNP array (Affymetrix, Santa Clara, CA), respectively. The father's sample was not available for genetic analysis. Microarray-based copy number analysis was performed using the Chromosome Analysis Suite software version 1.2.2 (Affymetrix) and the results were presented on the human genome assembly hg19.

## RESULTS

### Clinical Report

The patient was a 9 year-9 month-old male, born after 32 weeks of a twin pregnancy and delivered by cesarean due to fetal distress. His birth weight was 1,220 g and Apgar scores were 8, 10, and 10 after 1, 5 and 10 min, respectively. No significant problems were detected during the neonatal period and only a left ventricular dilatation with intraventricular and choroid plexus cysts, demonstrated by cerebral ultrasound, and the presence of an ostium secundum atrial septal defect, detected by cardiac ultrasound, were reported. His parents are healthy (with no history of learning difficulties or intellectual disability), nonconsanguineous and of European descent. His family clinical history is unremarkable and his twin brother is healthy.

At the age of 5 months, he was evaluated for the first time due to his dysmorphic facial features, as well as a significant delay in psychomotor milestones and mild generalized hypertonia. At the time of this report, physical examination showed craniofacial asymmetry with relative macrocephaly and dolichocephaly and revealed a bifrontal narrowing, prominent and wide forehead, large fontanelle, short and mild upslanting palpebral fissures, ptosis, malar hypoplasia, Cupid's bow-like mouth, short philtrum, thin lips, high palate, anteverted and hypoplastic nasal alae, micrognathia and anteverted, and low-set ears (Fig. 1). General examination showed a bilateral cryptorchidism, long and thin fingers, camptodactyly of the 2nd finger in the right hand and bilateral clinodactyly of 3–5 toes. An initial ophthalmologic exam, hearing evaluation (tested by auditory evoked potentials), abdominal ultrasound and karyotype showed normal results. A complete bone scan showed long and fine bones. Brain MRI made evident a slight increase in the frontal subarachnoid space and confirmed a slight ventricular asymmetry with a larger left ventricle, with resolution of the cysts detected on postnatal brain ultrasound. In follow-up examinations, a beta thalassemia minor and a hypothyroidism were detected. Ophthalmological evaluation revealed myopia and astigmatism and his weight and height parameters were below the 3rd centile. At the age of 2 years and 10 months, the patient underwent a bilateral orchidopexy.

Motor milestones were reported as follows: he reached cephalic control at the age of 5.5 months and unsupported sitting at 11 months, did not crawl and started walking independently at the age of 3. The patient always presented motor clumsiness, with difficulties to climb stairs and run, tending to tilt his hands and torso

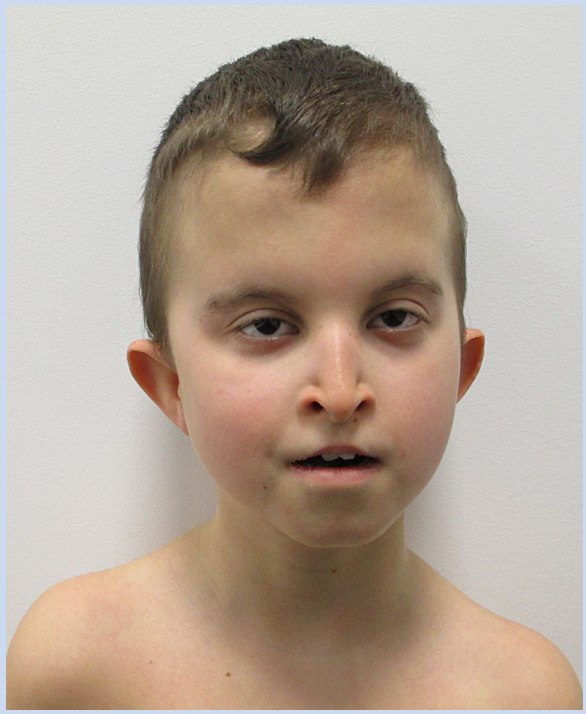

**FIG. 1. Craniofacial appearance of the patient. Note the bifrontal narrowing, a prominent and wide forehead, short and mild upslanting palpebral fissures, ptosis, malar hypoplasia, Cupid's bow-like mouth, short philtrum, thin lips, anteverted and hypoplastic nasal alae, micrognathia and anteverted, and low-set ears.**

forward. He never achieved to balance on one foot. His hand movements were uncoordinated and generally showed a mild tremor. In the language domain, his first words were at 3 years of age and his first simple 2–3 word sentences at the age of 5. His comprehensive ability is currently adequate but his expressive skills are very deficient; his speech is poorly organized and with limited lexical resources, using circumlocutions frequently; he constructs simple sentences, without nexus, uses verbs in the infinitive form, does not dominate pronouns properly and his use of articles is sparse. He is sociable and seeks contact with his peers but prefers to interact with younger children or those who have special educational needs. He is currently in the 3rd year of primary school and receives specific intervention from teachers specialized in Therapeutic Pedagogy and Hearing and Language. No signs of behavior problems have been detected and he accepts and complies well to rules.

The assessment of his intelligence quotient by the Wechsler Intelligence Scale for Children-IV, performed at the age of 7 years and 4 months, showed results concordant with a moderate ID: total intelligence quotient of 51, verbal comprehension index of 56, perceptual reasoning index of 55, working memory index of 75 and processing speed index of 57.

## Molecular Analysis

Microarray-based copy number analysis of our patient allowed the identification of a heterozygous deletion of 7.069 Mb at 8q21.11–q21.13 (chromosome 8:74,834,763-81,904,679 bp; hg19) encompassing 23 genes (*TCEB1*, *TMEM70*, *LY96*, *JPH1*, *GDAP1*, *FLJ39080*, *MIR2052*, *PI15*, *CRISPLD1*, *HNF4G*, *LOC100192378*, *ZFHX4*, *PEX2*, *PKIA*, *FAM164A*, *IL7*, *STMN2*, *HEY1*, *MRPS28*, *TPD52*, *ZBTB10*, *ZNF704*, and *PAG1*) (Fig. 2). This CNV was detected with 5,261 markers with a median intermarker distance of 1.34 kb. The genetic analysis of the patient's mother verified that she does not carry the deletion (data not shown).

## DISCUSSION

The patient described here presents moderate ID and facial dysmorphism and a heterozygous 8q21.11–q21.13 deletion of 7.069 Mb detected with a genome-wide high-density SNP microarray. Recently, Palomares et al. [2011] performed the phenotypic description and the molecular characterization of eight individuals with ID and submicroscopic deletions located at chromosome 8q21.11 and ranging in size from 0.66 to 13.55 Mb. According to these authors, the clinical manifestations of these patients were substantially similar despite the difference in size and breakpoints of these chromosomal aberrations. Thereby, they defined a phenotype with a characteristic facial dysmorphism and camptodactyly, syndactyly and broadening of the first rays. Additional clinical features shared by these patients included ID (8/8), hypotonia (5/8), sensorineural hearing loss (4/8), behavioral problems (4/8), and balance problems (2/8) [Palomares et al., 2011]. Hofmann et al. [2011] also reported a patient with a 7 Mb deletion in the 8q21.11–q21.13 region and a diagnosis of DA2B [Hofmann et al., 2011]. As previous descriptions [Palomares et al., 2011], this patient had facial dysmorphism (high forehead, small mouth, broad nasal bridge, epicanthus, high palate, brachycephaly, short neck, and dysplastic ears) and feet abnormalities (club feet, ulnar deviation and camptodactyly); however, his cognitive development at the age of 7 years and 11 months, was normal [Hofmann et al., 2011]. Very recently, Vulto-van Silfhout et al. [2013] identified a new patient with an 8q21.11 deletion and a typical facial appearance characterized by a high forehead, downslanting palpebral fissures, ptosis and prominent low-set ears [Vulto-van Silfhout et al., 2013], features all shared by previously reported patients [Hofmann et al., 2011; Palomares et al., 2011].

Clinical comparison of our patient with those previously reported [Hofmann et al., 2011; Palomares et al., 2011; Vulto-van Silfhout et al., 2013] shows similar features including the following: a high forehead, short palpebral fissures, ptosis, underdeveloped alae, Cupid's bow-like mouth, downturned corners of the mouth, highly palate, micrognathia, and low-set ears as well as anomalies in fingers and toes (camptodactyly of fingers, clinodactyly of toes, and transverse crease). In fact, the craniofacial features of our patient are very similar to at least two of the eight individuals detailed in the original description of this disorder [Palomares et al., 2011]. Moreover, he shares with previously reported patients a growth failure, a decreased balance [Palomares et al., 2011] and ophthalmological anomalies [Palomares et al., 2011; Vulto-van Silfhout et al., 2013] and, although the patient with DA2B presented a normal cognitive function [Hofmann et al., 2011], our patient, as all the patients described by Palomares et al. [2011] and Vulto-van Silfhout et al. [2013] [Palomares et al., 2011; Silfhout et al., 2013], has ID. Despite that, and different to those usually described [Hofmann et al., 2011; Palomares et al., 2011; Vulto-van Silfhout et al., 2013], our patient has as distinctive dysmorphic features a more elongated than round face, his ears (although low-set) were prominent but not posteriorly rotated and he has neither wide nasal bridge nor epicanthal folds.

Although earlier publications had reported patients with 8q alterations and phenotypes similar to that presented here and in the most recent literature [Hofmann et al., 2011; Palomares et al., 2011; Vulto-van Silfhout et al., 2013], they carried larger chromosomal aberrations identified with conventional cytogenetic techniques [Fryburg et al., 1993; Donahue et al., 1995; Dallapiccola et al., 1977; Taysi et al., 1979], making difficult the use of their clinical features and genetic findings for more accurate phenotype–genotype correlations.

A total of 23 genes are located in the interval deleted in our patient, including *TMEM70* (Transmembrane Protein 70; OMIM # 612418), related to mitochondrial complex V (ATP synthase) deficiency, nuclear type 2 (OMIM # 614052) [Cizkova et al., 2008], *GDAP1* (Ganglioside-Induced Differentiation-Associated Protein 1; OMIM # 606598) that encodes a protein expressed in the central and peripheral nervous system, primarily in Schwann cells and has been implicated in several forms of the Charcot-Marie-Tooth disease (OMIM # 607831, 607706, 608340, and 214400) [Niemann et al., 2005], *ZFHX4* (Zinc Finger Homeobox 4; OMIM # 606940), proposed as a candidate gene for congenital bilateral isolated ptosis (OMIM # 178300) [McMullan et al., 2002] and *PEX2* (Peroxisome Biogenesis Factor 2; OMIM # 170993) [Biermanns and Gartner, 2000], associated with peroxisomal

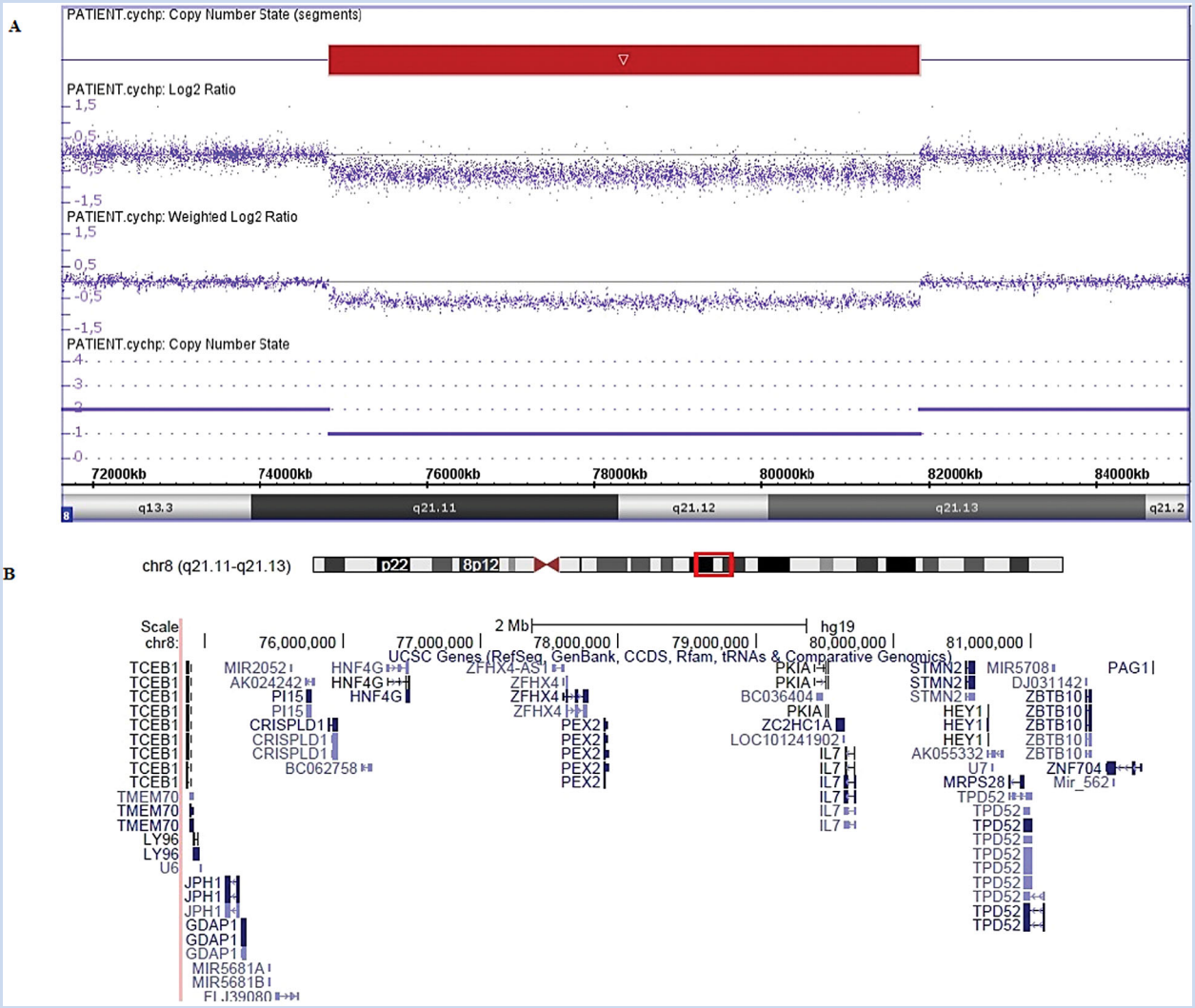


**FIG. 2. Microarray-based copy number analysis performed with the Affymetrix Cytogenetics Whole-Genome 2.7 M SNP array and visualized using the Affymetrix Chromosome Analysis Suite version 1.2.2. A) Image of the 8q21.11–q21.13 microdeletion (chromosome 8:74,834,763-81,904,679 bp; hg19) identified in our patient. B) UCSC genes included in the 8q21.11–q21.13 microdeletion, as plotted in the UCSC Genome Browser (hg19).**

biogenesis disorders 5 A (OMIM # 614866) and 5B (OMIM # 614867) [Steinberg et al., 2006; Waterham and Ebberink, 2012]. Amongst these 4 genes, only *ZFHX4* is included in the deletion found by Hoffman et al. [2011] and in the shortest region of overlap described by Palomares et al. [2011] [Hofmann et al., 2011; Palomares et al., 2011]. This gene consists of 11 exons and has an approximate size of 180 kb. In humans, *ZFHX4* encodes a transcription factor expressed in adult brain, liver and skeletal muscle, while in mice *Zfhx4*, which has a 90% homology with the human gene, is expressed in developing brain and muscle during embryogenesis. Consequently, it has been suggested that *ZFHX4* and *Zfhx4* play a role in neuronal and muscle differentiation in humans and mice, respectively [Hemmi et al., 2006]. Apart from that, *ZFHX4* has been proposed as a candidate gene for congenital bilateral isolated ptosis [McMullan et al., 2002], a feature evident in almost all patients reported in the literature with 8q21.11 deletions [Belligni and Hennekam, 2010; Palomares et al., 2011] and also present in our patient. Additionally, as mentioned above, Vulto-van Silfhout et al. [2013] identified a de novo 8q21.11 deletion encompassing the last 7 exons of *ZFHX4* in a patient with DD, macrocephaly, ventriculomegaly, hypermetropia, recurrent infections and dysmorphism [Vulto-van Silfhout et al., 2013], strengthening its role as a candidate gene for the 8q21.11 microdeletion syndrome.

Another important gene deleted in our patient, *PEX2,* is also deleted in the proband with DA2B and in seven out of the eight patients with ID described by Palomares et al. [2011] [Hofmann et al., 2011; Palomares et al., 2011]. This gene has a size of approximately 17.5 kb consisting of 4 exons [Biermanns and Gartner, 2000] and has been associated with peroxisome biogenesis

disorders 5 A, also called Zellweger syndrome, (OMIM # 614866) and 5B (OMIM # 614867). The Zellweger syndrome is a severe condition leading frequently to death within the first year of life [Steinberg et al., 2006] and although mildly affected patients may have a mild phenotype characterized by DD, hypotonia, liver dysfunction, sensorineural hearing loss, retinal dystrophy and vision damage [Waterham and Ebberink, 2012], any hypothetical connection between the *PEX2* deleted gene and clinical features present in 8q21.11 deletion patients seems unlikely, insofar as, to date, (as in many other autosomal recessive conditions) heterozygous carriers are asymptomatic.

Despite the association of both *ZFHX4* [Hemmi et al., 2006; McMullan et al., 2002] and *PEX2* [Biermanns and Gartner, 2000; Steinberg et al., 2006; Waterham and Ebberink, 2012] with neurodevelopment, these genes are deleted in patients with normal cognitive function [McMullan et al., 2002; Hofmann et al., 2011] so that, additional genetic factors within and/or outside the deleted interval and epigenetic and/or environmental modifiers may favor the occurrence of ID in patients with 8q21.11 microdeletions [Palomares et al., 2011; Vulto-van Silfhout et al., 2013] such as in the patient described above.

In the last few years, the application of molecular techniques in the clinical setting has favored the emergence of new microdeletion and microduplication syndromes associated with neurodevelopmental phenotypes as the one discussed here. Specifically, the application of a genome-wide high-resolution SNP microarray in a patient with moderate ID and dysmorphic facial features allowed us to detect a heterozygous 7.069 Mb deletion located at chromosome 8q21.11–q21.13 and spanning or overlapping deletions previously described in patients with ID and/or dysmorphic features.

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