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Cytogenomic Delineation and Clinical Follow-up of Two Siblings with an 8.5 Mb 6q24.2-q25.2 Deletion Inherited From a Paternal Insertion[†]

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Abstract

The chromosomal segment 6q24-q25 comprises a contiguous gene microdeletion syndrome characterized by intrauterine growth retardation, growth delay, intellectual disability, cardiac anomalies, and a dysmorphic facial phenotype. We describe here a 10-year follow-up with detailed clinical, neuropsychological, and cytogenomic data of two siblings, male and female, who presented with developmental delay, microcephaly, short stature, characteristic facial dysmorphisms, multiple organ anomalies, and intellectual disability. Microarray analysis showed an 8.5 Mb 6q24.2-q25.2 interstitial deletion. Fluorescence in situ hybridization analyses confirmed the deletions and identified an insertion of 6q into 8q13 in their father, resulting in a high recurrence risk. This is the first report in sibs with distinct neuropsychological involvement, one of them with stenosis of the descending branch of the aorta.

Keywords

interstitial deletion; chromosome 6; array; cytogenomics; congenital heart disease; aortic coarctation; clinical follow-up

[†]This article was published online on 4 June 2014. Errors were subsequently identified in Fig. 2. The corrected figure is shown here.

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INTRODUCTION

Reports of interstitial deletions of the long arm of chromosome 6 are rare. There are 10 reports in literature describing 15 patients with 6q24-q25 interstitial deletions [McLeod et al., 1990; Narahara et al., 1991; Pirola et al., 1998; Sukumar et al., 1999; Bisgaard et al., 2006; Tanteles et al., 2007; Caselli et al., 2007; Nowaczyk et al., 2008; Nagamani et al., 2009; Thienpont et al., 2010]. Sukumar et al. [1999] published the first report of chromosome 6q24.2q25.1 interstitial deletion, which included three patients with deletions of different sizes, studied by karyotyping and FISH. Nowaczyk et al. [2008] reported three patients with an apparently de novo paternal 6q24.3 deletion and proposed a contiguous gene syndrome with dysmorphic features and growth failure (OMIM #612863). To date, the patients described present a large spectrum of clinical features, depending on the size of the deleted segment, making the genotype–phenotype correlation difficult, in part because there are few papers with precise molecular breakpoint determinations.

Most patients present intrauterine growth retardation (IUGR), growth delay (GD), intellectual disability (ID), cardiac defects, and a dysmorphic facial phenotype [Kumar et al., 1997; Caselli et al., 2007; Nowaczyk et al., 2008]. We report on the 10-year clinical follow-up, neuropsychological, and cytomolecular data of two siblings with an 8.5 Mb interstitial deletion of segment 6q24.2-q24.2, inherited from their father who presented an insertion of the 6q segment into chromosome 8q13.

PATIENTS

We describe two siblings (Fig. 1) born to a healthy young, nonconsanguineous couple, who already had a normal older daughter and one spontaneous abortion. Their parents and older sister had normal stature and head circumference (data not shown). The patients' father has four brothers and three sisters, one of them presented three miscarriages, but we were not able to perform karyotyping.

Patient 1

Male, born at term by vaginal delivery, with a weight of 3,000 g (50th centile), length of 49 cm (50th centile), and unknown OFC. In addition to a neonatal hospitalization, three more were necessary until the age of 5 years, due to bronchopneumonia episodes. Developmentally, he walked independently and had single words at 36 months. At the age of 6 years and 7 months, his measurements were: height 97 cm (<5th centile), weight 15 kg (<3rd centile), OFC 48 cm (<3rd centile), and he presented the following main dysmorphic features: proportionate short stature, downslanted palpebral fissures, bilateral palpebral ptosis, bilateral epicanthus, long and thick eyelashes, abnormal tooth implantation, low-set and posteriorly rotated ears, joints and skin hyperextensibility of both hands, *pes planus*, and thoracolumbar scoliosis; hypotonia, moderate neuromotor development delay and high-pitched voice. The patient had seizures during infancy treated with carbamazepine until the age of 10 years. At 11 years of age, polysomnography showed mild obstructive sleep apnea, and electroencephalography (EEG) showed abnormal epileptic waves, but no medication was needed. At the age of 12, bilateral inguinal hernia and retractile testis were surgically corrected. When he was 14-year-old, his voice changed from a high-pitch to a hoarse and

deep tone. The echo-cardiogram showed thickening of the mitral valve with prolapse detected at the age of 18.

Patient 2

Female, born at term by vaginal delivery after a normal gestation, weighing 2,000 g (<3rd centile) and unknown length and OFC. Bronchopneumonia episodes and one urinary tract infection were diagnosed before the age of four. Developmentally, she had single words at 30 months and walked independently at 24 months. At 4 years and 3 months, her measurements were: height 87.5 cm (<5th centile), weight 11 kg (<3rd centile), OFC 46.5 cm (<3rd centile), and she presented the following main dysmorphic features: proportionate short stature, downslanted palpebral fissures, bilateral palpebral ptosis, bilateral epicanthus, long and thick eyelashes, abnormal tooth implantation, low-set and posteriorly rotated ears, joints and skin hyperextensibility of both hands, *pes planus*, and thoracolumbar scoliosis; hypotonia, moderate neuromotor development delay and a high-pitched voice. At the age of 11 years and 6 months, she started with epileptic episodes, controlled by carbamazepine. Like in her brother, her voice changed to a hoarse and deep tone. At 15 years of age, a cardiac MRI showed a stenosis of the descending branch at the thoraco-abdominal transition of the aorta and an atrial septal defect.

Endocrinologic studies were performed to assess the proportionate short stature and were normal in both patients (data not shown). They both successfully underwent blepharoplasty for ptosis, Patient 1 at the age of 16 and Patient 2 at the age of 14.

The patients underwent an assessment of intellectual, neuropsychological, and literacy skills. Intellectual performance was investigated by means of the Wechsler Intelligence Scale for Children (WISC-III). Neuropsychological assessment included tasks of visuoconstructive skills (Copy of the Complex Figure of Rey), episodic verbal memory (Rey auditory verbal learning test), working memory (digit span and Corsi Block test, both backwards), attention (Conners Continuous Performance test), and executive functions (phonological verbal fluency). Formal tasks of reading/ writing and arithmetic were adopted for the investigation of literacy skills. Both patients showed full intellectual quotient (IQ) in deficiency levels, but were strikingly different from each other with regard to neuropsychological functions. Patient 1 had normal scores in some of the WISC Scale subtests (Vocabulary, Digits and Picture Completion) and also in the verbal working memory tasks. He also showed literacy skills within normal ranges, but marked difficulties in arithmetic. Patient 2 presented a severe deficit (<1st centile) in all neuropsychological tests, as well as low performance in all academic domains.

Both patients were registered in the Database of Chromosomal Imbalance and Phenotype in Humans (DECIPHER), number FSP273678. Informed consent was obtained from the patients' parents according to the Research Ethics Committee of UNIFESP.

Cytogenetic and Molecular Studies

A G-banding analysis at 550-band resolution showed normal karyotypes in the lymphocyte cultures of the patients, their parents and their older sister. However, chromosomal microarray (CMA) analysis with CytoScan® 750K Array (Affymetrix Inc., Santa Clara,

CA) revealed an 8.5 Mb interstitial deletion in both patients, described as: arr[hg19] 6q24.2q25.2(144,444,361–152,966,111) × 1 (Fig. 2a). Fluorescence in situ hybridization (FISH) analysis using an RP11-632J15 probe (6q24.3 region) confirmed the deletion in both siblings (Fig. 2c) and showed an insertion of the 6q chromosome segment into chromosome 8q13 in the patients' father (Fig. 2d).

DISCUSSION

The family history of sibs from a healthy couple with a previous normal child and one miscarriage, all of them with normal G-banded karyotypes, suggested an autosomal recessive disorder, but the array and FISH approaches showed an 8.5 Mb 6q24.2-q25.2 deletion. Searching for patients with similar chromosomal imbalances in the Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resource (DECIPHER, <https://decipher.sanger.ac.uk/>) we found another 17 patients that share at least part of the deleted region, in addition to 15 other patients from literature. Table I shows a comparison of the present patients' phenotypes to those of 15 published patients with deletions encompassing the 6q24.2-q25.2 segment, characterized at least by high-resolution banding methodology. Most of the patients had intrauterine growth retardation (IUGR) and/or growth delay. Some interesting facial features observed in the present patients such as unilateral palpebral ptosis in the male patient and bilateral ptosis in the female patient have not been described before. Other dysmorphic facial features found in the patients, such as widely spaced eyes, long philtrum, thin upper lip and low-set ears, were highly similar to other patients described in literature, especially to the patient reported by Caselli et al. [2007] who had a ~2.6 Mb deletion and Patient 1 of Bisgaard et al. [2006] who had an ~7 Mb deletion. Patient 2 reported by Nowaczyk et al. [2008], who had a ~9.2 Mb deletion, also shared a deleted region with these patients, but her facial features were not similar to the patients reported here. Patient 3 of Nagamani et al. [2009] who had a ~10.3 Mb deletion, had a more severe phenotype than the patients reported here, including agenesis of the corpus callosum, but she had no cardiac anomaly. Except for Patients 1 and 3 reported by Nowaczyk et al. [2008], all patients shared an ~300 kb region of chromosome 6 that encompasses the genes *KATNA1*, *LAST1*, *NUP43*, and *PCMT1* (Fig. 2b) suggesting that this region could be critical for the syndrome under study. Another region shared by all patients except for Patient 3 of Nagamani et al. [2009] and Patients 1 and 3 of Nowaczyk et al. [2008], is a 93 kb segment that encompasses the gene *TAB2* (Fig. 2b).

The *KATNA1* gene encodes Katanin p60, a heterodimeric enzyme found in the brain and neurons, essential for proper neuronal migration and mitotic cell division [Karabay et al., 2004; Toyo-Oka et al., 2005] being a strong candidate for the neurological impairment. The *Lats1* gene knockout in mice resulted in a lack of mammary gland development, infertility, and growth retardation. This plays a role in mammalian tumorigenesis and specific endocrine dysfunction [St John et al., 1999] and might be related to the growth deficiency observed in the deleted patients.

Caselli et al. [2007] suggested that another deleted gene, the *PPP1R14C*, which is expressed in the brain and heart, could be correlated with motor development delay and cardiac anomalies presented by their patient. However, the deleted segment in that patient also

encompassed the *TAB2* gene, which is expressed in human heart development as well (Fig. 2b and Table I). The deleted segment of Patient 1 reported by Bisgaard et al. [2006] also encompassed these two genes (*PPP1R14C* and *TAB2*) and the patient had a ventricular septal defect (VSD), short stature, and slightly delayed psychomotor development.

Microcephaly was found in the two patients described here and in those described by Pirola et al. [1998], Narahara et al. [1991] (Patient 3), Sukumar et al. [1999] (Patients 1 and 2), Nagamani et al. [2009] (Patient 3), and Thienpont et al. [2010] (Patient Fp). Distinctly from the two patients described here, agenesis of corpus callosum was presented in the patients described by Nagamani et al. [2009] (Patient 3) and Pirola et al. [1998]. Additionally, hypoplasia of corpus callosum was presented in two patients registered in DECIPHER (Patient 1911 and Patient 250481), even though these patients shared the same deleted region. However, other patients with the same deleted segment do not have either microcephaly or agenesis of corpus callosum (Table I and Fig. 2b), which makes it difficult to correlate this region to microcephaly.

Among the deleted genes in the shared region, *TAB2* emerges as an important gene related to congenital heart disease (CHD). Thienpont et al. [2007, 2010] demonstrated that the *TAB2* gene plays a role in several stages of human cardiac development, including vasculogenesis and valve formation, which might explain the different cardiac abnormalities observed in the patients with CHD. However, the exact mechanisms by which the *TAB2* gene causes this variability is unclear. Both of the patients described here had CHD, as did some patients reported by Thienpont et al. [2010]. Patient A from Thienpont et al. [2010] with a 6q22.2q25.1 deletion had an aortic coarctation, hypoplastic aortic arch, and a VSD; Patient Fp and his mother (Patient Fm) from Thienpont et al. [2010] had a 6q24.3q25.1 deletion that caused distinct cardiac alterations: Patient Fp had centrovalvular insufficiency of the aortic and pulmonary valves and his mother had aortic and mitral valve stenosis and sinus tachycardia episodes. Patient 1 in the present report had mitral valve thickening with prolapse in both cusps and Patient 2 had stenosis of the descending branch at the thoraco-abdominal transition of the aorta and atrial septal defect, supporting the association of *TAB2* with varied cardiac alterations.

The patients described here also had hyperelastic and redundant skin of hands and feet, as described by McLeod et al. [1990] and Tanteles et al. [2007]. Patient 2 of McLeod et al. [1990] had a 6q23q25 deletion detected by high-resolution banding karyotype and presented facial dysmorphisms similar to the patients described here. Besides the hyperelastic redundant skin on hands and feet, he also had imperforate anus, sacral agenesis, and a lipoma in sacral region. The patients did not have any sacral or anorectal anomalies. The patient described by Tanteles et al. [2007] had a 6q24.3q25.2 deletion detected by G-banding karyotype and FISH and had mild dysmorphic features, early feeding difficulties, skin laxity of the hands and feet, but normal motor and intellectual development.

This report of a 10-year clinical follow-up, with a detailed clinical description, neuropsychological evaluation, and a comparison with similar patients from the literature and DECIPHER provided additional information to the genotype-phenotype correlation. This study further confirms the array technique as a powerful tool for the identification of

cryptic deletions, and underlines the essential role of FISH in assessing the position of the chromosomal segment involved in a deletion, and in detecting balanced carriers, such as the patients' father who had a chromosomal insertion, resulting in a high recurrence risk for the disease.

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FIG. 1.

Brother and sister at 6 years 7 months and 5 years 3 months (a, d, and h). Male patient at 11 years (b, e, and g) and 18 years (f). Female patient at 9 years 6 months (c, i, and k) and at 16 years (j). Patients after surgical correction of ptosis (f and j).

FIG. 2.

Array showing the 8.5 Mb interstitial deletion with one copy in chromosome 6q24.2-q25.2 (a). Zoom in the deleted region in the patients reported here (P1 and P2) and schematic representation of overlapping deletions from published patients (P) that were studied by molecular approaches, which permitted a better breakpoint definition. The red bars represent the deleted segments with the >> and << signals representing that the deletion continues to the indicated direction. The black vertical rectangles show some genes in deleted regions shared by the patients (b). FISH-BAC using RP11-632J15 probe (6q24.3 region) confirming the deletion in the patient (c) and showing an insertion of the 6q segment into 8q in the patients' father (d).

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TABLE 1

Comparison between our Patients (1 and 2) with 15 Patients from the Literature

Patients	1	2	Tanteles et al. [2007]	Nagamani et al. [2009] Patient 3	Pirola et al. [1998]	Narahara et al. [1991] Patient 2	Sukumar et al. [1999] Patient 1	Sukumar et al. [1999] Patient 2	Caselli et al. [2007]	McLeod et al. [1990] Patient 2	Biggaard et al. [2006] Patient 1	Nowaczyk et al. [2008] Patient 1	Nowaczyk et al. [2008] Patient 2	Nowaczyk et al. [2008] Patient 3	Thienpont et al. [2010] Patient A	Thienpont et al. [2010] Patient Fp	Thienpont et al. [2010] Patient Fm
Proximal 6q band deleted	6q24.2	6q24.2	6q24.3	6q24	6q25.1	6q25.1	6q24.2	6q25.1	6q24.3	6q23	6q25	6q24.2	6q24.3	6q24.2	6q24.2	6q24.3	6q24.3
Distal 6q band deleted	6q25.2	6q25.2	6q25.2	6q25.3	6q25.3	6q25.3	6q25.1	6q25.3	6q25.1	6q25	6q25	6q24.3	6q25.2	6q24.3	6q25.1	6q25.1	6q25.1
de novo	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
Sex	M	F	M	F	F	M	M	M	F	M	F	M	F	F	M	M	F
Age	18 years	16 years 6 months	30 months	11 months	9 months	7 months	9 months	17 years	8 years 2 months	1 year 6 months	6 years	13 months	At birth	3 years			
Method of detection	Array/FISH	Array/FISH	FISH	Array	Array	HR-banding	FISH	FISH	Array rtPCR	HR-banding	Array rtPCR	BAC/PAC microsat	BAC/PAC microsat	BAC-FISH PCR	Array	Array	Array
IURG/growth delay	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Microcephaly	+	+	-	+	-	+	+	+	-	+	-	-	-	-	-	+	-
Facial features																	
Ptosis	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Downslanted palpebral fissures	+	+	-	-	-	-	-	+	+	+	-	-	-	-	-	-	-
Upslanted palpebral fissures			-	-	-	+	-	-	-	-	-	+	+	-	+	+	+
Widely spaced eyes	+	+	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-
Nasal root abnormalities			-	+	-	+	+	-	+	-	-	-	-	-	-	-	-
Low-set ears	+	+	+	+	+	-	-	-	+	+	+	+	-	-	-	-	-
Posteriorly rotated ears	+	+	-	+	-	-	-	-	+	+	+	+	-	-	-	-	-
Abnormal ear/or pits	+	+	-	-	-	-	-	+	+	+	+	+	-	-	-	+	+
Long philtrum	+	+	+	-	-	-	-	-	+	-	+	-	+	-	-	-	-
Thin upper vermillion	+	+	-	-	-	-	+	-	+	+	+	+	+	-	-	-	-
Palatal abnormalities	-	-	-	+	+	-	-	-	+	-	-	-	-	-	-	-	-
Hands and feet																	
Skin laxity	+	+	+				-	+	-	+			+	-			
Articular hyperflexibility	+	+	+					+	-	-		+	+	-			
Joint contractures	-	-	-					-	-	+			-	-			
Short hands and feet	+	+	+					+	+					-			

Patients	1	2	Tanteles et al. [2007]	Nagamani et al. [2009] Patient 3	Pirola et al. [1998]	Narahara et al. [1991] Patient 2	Sukumar et al. [1999] Patient 1	Sukumar et al. [1999] Patient 2	Caselli et al. [2007]	McLeod et al. [1990] Patient 2	Bisgaard et al. [2006] Patient 1	Nowaczyk et al. [2008] Patient 1	Nowaczyk et al. [2008] Patient 2	Nowaczyk et al. [2008] Patient 3	Thienpont et al. [2010] Patient A	Thienpont et al. [2010] Patient Fp	Thienpont et al. [2010] Patient Fm
Congenital heart disease	+	+	-	-	-	-	+	-	+	+	+	+	+	-	+	+	+
CIV/CIA/PDA	-	+	-	-	-	-	-	-	+	+	+	-	+	-	+	-	-
Aortic coartation	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
Aortic stenosis	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+
Valvular abnormality	+	-	-	-	-	-	+	-	+	-	-	+	-	-	+	+	+
Nervous system																	
Intellectual disability	+	+	-					+	+	+	+	-	-	-	+	-	-
Motor developmental delay	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-
Seizures	+	+	-	-	-	-		+	-		-	-	-	-	-	-	-
Structural brain abnormalities	-	-	-	+	+	-		-	-		-	-	-	-	-	-	-
Agensis of the corpus callosum	-	-	-	+	+			-			-	-	-	-	-	-	-
Hypotonia	+	+	+	+		-	+		-	+	-		+	-	-	-	-
Other																	
Genitourinary abnormalities	+	+	+	-	-	-	+	+	-		-	-	-	-	+	-	-
Sacral and/or anorectal anomalies	-	-	-	-	+	-			-	+	-	-	-	-		-	-
Scoliosis	+	+	-							+	-	-	-	-		-	-

Presence (+), absence (-), or not described (blank space) clinical features.