RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Clinical and Molecular Characterization of the 20q11.2 Microdeletion Syndrome: Six New Patients

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Manuscript Received: 28 March 2014; Manuscript Accepted: 23 October 2014

Interstitial microdeletions of 20q chromosome are rare, only 17 patients have been reported in the literature to date. Among them, only six carried a proximal 20q11.21-q11.23 deletion, with a size ranging from 2.6 to 6.8 Mb. The existence of a 20q11.2 microdeletion syndrome has been proposed, based on five previously reported cases that displayed anomalies of the extremities, intellectual disability, feeding difficulties, craniofacial dysmorphism and variable malformations. To further characterize this syndrome, we report on six new patients with 20q11.2 microdeletions diagnosed by whole-genome array-based comparative genomic hybridization. These patient reports more precisely refined the phenotype and narrowed the minimal critical region involved in this syndrome. Careful clinical assessment confirms the distinctive clinical phenotype. The craniofacial dysmorphism consists of high forehead, frontal bossing, enophthalmos, and midface hypoplasia. We have identified a 1.62 megabase minimal critical region involved in this syndrome encompassing three genes - *GDF5*, *EPB41L1*, and *SAMHD1*– which are strong candidates for different aspects of the phenotype. These results support that 20q11.2 microdeletion syndrome is a new contiguous gene deletion syndrome with a recognizable phenotype. 2014 Wiley Periodicals, Inc.

Key words: 20q11.2 deletion syndrome; 20q11.21q11.23 deletion; Anomalies of hands; Anomalies of feet; Facial dysmorphisms; Contiguous gene deletion syndrome; *GDF5*

How to Cite this Article:
Jedraszak G, Demeer B, Mathieu-Dramard M, Andrieux J, Receveur A, Weber A, Maye U, Foulds N, Temple IK, Crolla J, Alex-Cordier M-P, Sanlaville D, Ewans L, Wilson M, Armstrong R, Clarkson A, Copin H, Morin G. 2014. Clinical and molecular characterization of the 20q11.2 microdeletion syndrome: Six new patients.
Am J Med Genet Part A. 9999A:1–8.

Conflicts of interest: None.
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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2014
DOI 10.1002/ajmg.a.36882

INTRODUCTION

Interstitial microdeletions of the chromosome 20q region are rare. To our knowledge, only 17 patients have been reported in the literature to date [Fraisse et al., 1981 Petersen et al., 1987; Porfirio et al., 1987; Shabtai et al., 1993; Aldred et al., 2002; Chen et al., 2005; Geneviève et al., 2005; Callier et al., 2006; Borozdin et al., 2007; Iqbal and Al-Owain, 2007; Hiraki et al., 2011; Gervasini et al., 2013; Iourov et al., 2013; Santoro et al., 2013; Posmyk et al., 2014] and only six of these patients carried a proximal 20q11.2 deletion, with a size ranging from 2.6 to 6.8 Mb [Callier et al., 2006; Iqbal and Al-Owain, 2007; Hiraki et al., 2011; Gervasini et al., 2013; Iourov et al., 2013; Posmyk et al., 2014]. Intellectual disability, craniofacial dysmorphism, anomalies of the extremities and feeding difficulties are recurrent clinical features in these patients, suggesting a recognizable microdeletion syndrome. We report on a study of six new patients harbouring a *de novo* 20q11.21-q11.23 microdeletion; these patients presented with a suggestive phenotype. Comparison of the deleted regions in these patients allowed more precise characterization of the critical region responsible for the phenotype, and discussion of genotype/phenotype correlations.

CLINICAL REPORTS

The phenotypic features of the six new unrelated patients and the five previously reported patients with 20q11.2 microdeletion are summarized in Table I. Clinical data and informed consents were obtained from all patients or their legal representatives.

Patient 1

Patient 1 was a 15-year-old boy, the second child of unrelated healthy parents with no family history of malformation. He was born at 41 weeks of gestation (WG) after an uneventful pregnancy. At birth, he weighed 3,030 g (45^{th} centile) and presented with global hypotonia, poor movements, a right supernumerary nipple, facial dysmorphism (Fig. 1 and Table I) and anomalies of the extremities (Figs. 2 and 3, and Table I). The subsequent course was marked by delayed psychomotor acquisitions with moderate intellectual disability. At age 15, he was unable to read or write despite management in a specialized school, and he was unable to dress by himself. He had mild features of autism spectrum disorder such as hand and finger biting, avoidance of eye contact, and social difficulties. Changes in facial dysmorphism were noted during the follow-up with the disappearance of microretrognathia and short philtrum, and the appearance of deep-set eyes and midface hypoplasia (Fig. 1). Growth was within normal range with a height of 180 cm (90^{th} centile), weight of 75 kg (90^{th} centile) and head circumference of 59 cm (90^{th} centile) at the age of 15. Hearing tests showed a 50 dB deficit on the right side. Ophthalmological examination, visual evoked potentials, electroencephalogram, brain MRI, electrocardiogram, abdominal ultrasound and echocardiography were normal.

Patient 2

Patient 2 was a 5.5-year-old boy with no family history of malformation. He was born at 40 WG after a pregnancy without medical supervision. Birth weight was 2,700 g (20^{th} centile). He presented with global hypertonia, anomalies of both hands and feet, and facial dysmorphism (Table I). Anomalies of the extremities consisted of fifth finger clinodactyly, left-sided single transverse palmar crease, and talipes varus. The subsequent course was marked by severe psychomotor and language delay: he began sitting over 1 year of age, waking independently at the age of 3 years, and spoke his first words over 5 years of age. When he was 5.5 years old, height was 107.6 cm (9^{th} centile), weight was 21.6 kg (50^{th}–75^{th} centile) and head circumference was 53 cm (50^{th} centile). Facial dysmorphism consisted of facial asymmetry, frontal bossing, deep-set eyes, midface hypoplasia, and short philtrum. Ophthalmological examination showed intermittent strabismus. Hearing testing was normal. No other malformations were detected.

Patient 3

Patient 3 was a 6-year-old boy with no family history of malformation. He was born at 39 WG after a pregnancy without medical supervision with a birth weight of 3,385 g (75–90^{th} centile). At birth, he presented with global hypotonia, anomalies of the extremities (Fig. 2 and Table I), mild pectus carinatum and facial dysmorphism (Fig.1 and Table I). The subsequent course was marked by developmental delay: he was able to sit from the age of 1 year and able to walk independently from the age of 2.5 years. Language was more severely affected: the first single words appeared at the age of 2 years 3 months. He was able to read a few words from the age of 6 years after management in a specialized school. At the age of 6 years, height was 104 cm (0.4^{th}–2^{nd} centile), weight was 15.9 kg (0.4^{th}–2^{nd} centile) and head circumference was 50.5 cm (2^{nd}–9^{th} centile). X-rays of the extremities showed shortening of proximal and middle phalanges of second fingers, shortening of the middle phalanges of fifth fingers, and eleven pairs of ribs. He did not present any hearing anomalies or other malformations.

Patient 4

Patient 4 was a 2.5-year-old boy born at 32 WG after a spontaneous triplet trichorionic triamniotic pregnancy. At birth, weight was 1,210 g (2^{nd} centile) and head circumference was 27.5 cm (2^{nd}–9^{th} centile). He presented with global hypotonia, facial dysmorphism (Fig. 1 and Table I) and anomalies of the extremities (Fig. 2 and Table I). The first weeks of life were marked by feeding difficulties and oesophageal reflux requiring gastrostomy. At the age of 8 months, facial dysmorphism consisted of sparse hair, broad and high forehead, hypertelorism, mild downslanting palpebral fissures, deep-set eyes, midface hypoplasia, short philtrum, microretrognathia, and small ears. When he was 2.5 years old, height was 86.5 cm (9^{th}–25^{th} centile), weight was 11.7 kg (9^{th} centile) and head circumference was 48 cm (2^{nd} centile). Facial dysmorphism had changed with disappearance of microretrognathia and appearance of hypoplastic alae nasi and long columella (Fig. 1). The subsequent course was marked by severe psychomotor retardation: he was unable to stand at 2.5 years of age and was delayed in oral language (limited to three words at the age of two years). Growth was normal. At birth, brain MRI showed delayed myelination and thickening of the ventricles. He presented no hearing impairment or other malformations.

TABLE I. Clinical Features of Reported Patients with 20q11.2 Deletions

	Present study											
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Calliers' Case	Iqbals' Case	Hirakis' Case	Gervasinis' Case	Posmyks' Case	SUMMARY
	15 y. male	5.5 y. male	6 y. male	2.5 y. male	20 y. female	2 m. female	4 y. female	2 y. male	18 m. male	9 y. female	2 y. female	6 males/5 females
Craniofacial dysmorphism												
High forehead	+	+	+	+	+	+	+	+	−	−	+	9/11
Frontal bossing	+	+	+	−	+	−	+	−	−	−	−	5/11
Deep-set eyes	+	+	+	+	+	+	+	+	+	+	+	11/11
Hypertelorism	+	−	−	+	−	−	+	−	+	−	+	4/11
Midface hypoplasia	+	+	+	+	+	−	+	−	+	+	−	8/11
Short philtrum	+	+	−	−	+	−	+	−	+	−	−	5/11
Ear anomalies	+	−	−	+	−	+	+	+	+	+	+	8/11
Anomalies of the extremities												
Brachydactyly	+	−	+	−	+	−	−	−	−	−	−	3/11
Finger clinodactyly	+	+	+	−	−	−	+	−	+	−	+	6/11
Camptodactyly	+	−	−	+	−	−	−	−	+	−	+	4/11
Talus valgus	+	+	−	+	+	−	+	+	+	−	−	7/11
Adductus thumbs	+	−	+	−	−	−	−	−	−	−	−	2/11
Neurology												
Hypotonia	+	−	+	+	−	+	−	−	−	−	+	5/11
Development delay	+	+	+	+	+	+	+	+	+	+	+	11/11
Behavior troubles	+	ND	−	−	−	−	+	+	+	+	−	5/10
Otherfeatures												
Neonatal feeding difficulties	+	+	−	+	+	+	+	+	+	+	+	10/11
Intra-uterine growth retardation	−	−	−	+	−	+	+	+	+	+	+	7/11
Cardiopathy	−	−	−	−	+	+	+	−	+	+	+	6/11
Ocular anomaly	−	+	−	−	+	−	+	+	+	−	+	6/11
Brain malformation	−	−	−	+	−	+	+	+	+	−	ND	5/10
Hearing impairment	+	−	−	−	+	−	ND	+	+	ND	−	4/9

ty.: years; m.: months; ND: not determined.

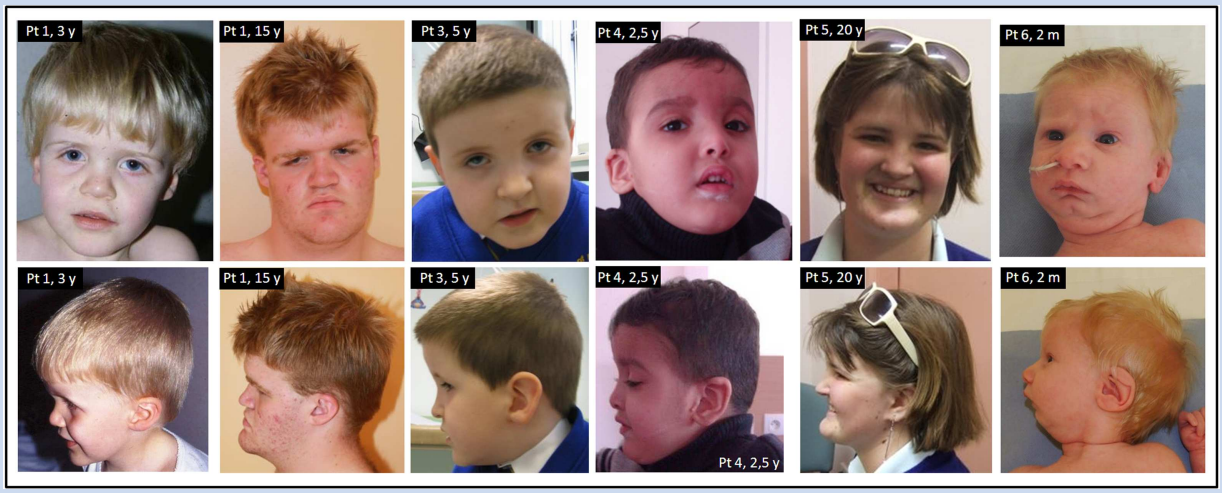

FIG. 1. Facial dysmorphism. Common facial features are broad and high forehead with frontal bossing, deep-set eyes, midface hypoplasia and ears anomalies. Patient 6 also had a microretrognathia.

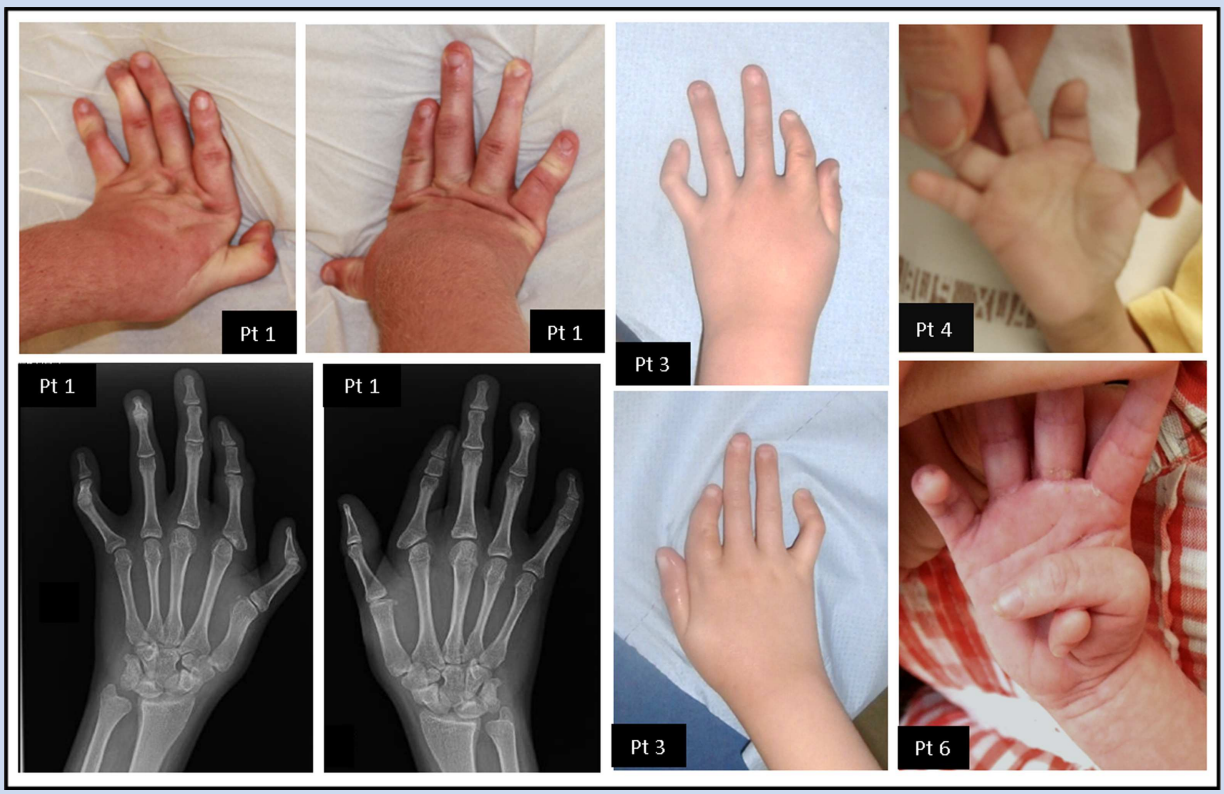

FIG. 2. Hand anomalies in Patients 1, 3, and 6. Hand anomalies. Common features are 2nd (3rd) and 5th fingers brachydactyly, camptodactyly and clinodactyly. Patient 6 had right pre-axial polydactyly and long fingers.

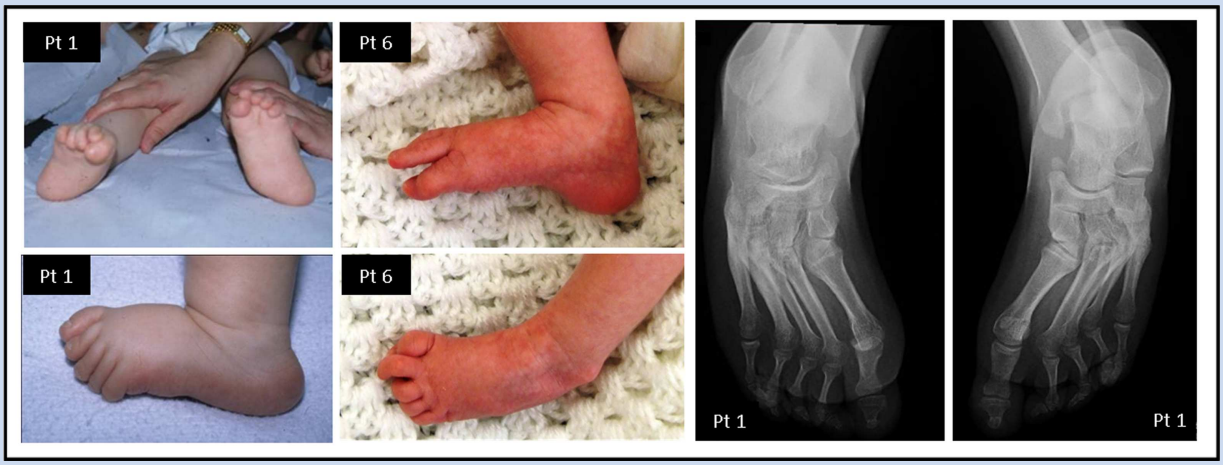

FIG. 3. Feet anomalies in Patients 1 and 6. Patient 1 had bilateral talus valgus and hallux adductus. Patient 6 had long and overlapping toes.

Patient 5

Patient 5 was a 20-year-old woman with no family history of psychomotor delay or malformation. She was born at term after an uneventful pregnancy. At birth, weight was 3,000 g (10^{th} centile) and length was 51 cm (50^{th} centile). Multiple congenital anomalies were diagnosed, including total anomalous pulmonary venous return requiring surgical treatment in the first week of life, bilateral congenital talus valgus, hip dysplasia, right sacroiliac pit and covered anus and facial dysmorphism (Fig. 1 and Table I). The subsequent course was marked by mild developmental delay. No delay of motor acquisitions was observed. Language developed from the age of 3–4 years, and reading and writing were acquired only from the age of 8 years, after intensive management in a specialized school. Precocious puberty and an excessive weight gain were noted during adolescence due to food-seeking behavior. At the age of 20, she was able to read and write, had a job and lead a relatively independent life. Height was 157 cm (10^{th}–25^{th} centile), and weight was 57 kg (25^{th}–50^{th} centile). Changes in facial dysmorphism were noted: the midface hypoplasia became more obvious with time. She also had tapered fingers and narrow calves. Dermatological examination revealed multiple melanocytic naevi and lentigines. Ophthalmological examination revealed unilateral astigmatism and ptosis. Hearing tests showed bilateral high frequency hearing loss. She had no other obvious malformations.

Patient 6

Patient 6 was a 2-month-old girl. Prenatal ultrasound found mild intra-uterine growth restriction and oligohydramnios from 27 WG. She was born at 39 WG with a birth weight of 2,268 g (0.4^{th}–2^{nd} centile). She presented with global hypotonia, facial dysmorphism (Fig. 1 and Table I) and digital anomalies (Fig. 2 and 3, and Table I). During the first two months of life, she experienced feeding difficulties with failure to thrive in a context of gastroesophageal reflux and seizures. When she was two months old, weight was 2,900 g (0.4^{th}–2^{nd} centile) and head circumference was 35 cm (0.4^{th}–2^{nd} centile). Her hand malformations consisted of right pre-axial polydactyly and long fingers. She had long, overlapping toes (Fig. 3). Brain MRI showed atrophy of the left hemisphere, and unilateral end-stage periventricular leukomalacia. Echocardiography revealed atrial septal defect, mitral incompetence and pulmonary hypertension. She had no other obvious malformations.

METHODS

Chromosomal analyses were performed for all patients after obtaining informed consent according to local legislation in each country. Conventional karyotypes, FISH and quantitative PCR analyses were performed according to standard methods on samples of peripheral blood lymphocytes. Array CGH analyses were performed using a 44 K array for Patients 1 and 3 (Agilent Technologies, Santa Clara, CA, USA), 180K array for Patient 4 (Agilent Technologies, Santa Clara, CA, USA), and a 60 K array (Bluegnome ISCA Cytochip, Cambridge, UK) for Patients 2 and 5. A SNP array using an Affymetrix GeneChip 6.0 array (Affymetrix, Santa Clara, CA, USA) was performed for Patient 6. Confirmation of these results and investigation of inheritance were performed by analysing parental samples when available, using quantitative PCR (Patients 1 and 4), FISH analyses (Patients 2, 3, and 5), or karyotype (Patient 6).

DNA sequence information for patients is presented according to the UCSC Genome Browser (http://genome.ucsc.edu/; February 2009 Assembly, hg19).

RESULTS

Cytogenetics analyses were performed to explore a malformation syndrome in each case. No anomalies were found on conventional karyotypes. Array CGH analyses found a microdeletion of the 20q11.2 chromosomal region in all patients, with sizes ranging

from 2.24 Mb to 7.7 Mb (Table II). Array-CGH also excluded the involvement of another chromosomal imbalance in the phenotype. Patients 1 to 4, who had a very similar phenotype, allow us to define a minimal critical region measuring 1.62Mb (33,962,025–35,580,928)(hg19) (Fig. 4). This region encompasses 29 genes according to the UCSC Genome Browser. Three of these genes are referenced in the OMIM database: *GDF5*, *EPB41L1* and *SAMHD1*. All breakpoints of the deleted regions were unique, suggesting that these deletions were not generated by a non-allelic homologous recombination mechanism. The deleted region in Patient 5 did not include *EPB41L1*, and the deleted region in patient 6 did not include *GDF5*, as showed in Figure 4.

The *de novo* occurrence of the deletions was confirmed for Patients 1, 2, 4, 5 and 6 by cytogenetic analysis of their parents. An inherited form could not be excluded in Patient 3: the mother did not carry the deletion and the father could not be tested.

DISCUSSION

We report on six new patients with a 20q11.2 microdeletion. They shared common clinical features with previously reported patients. Array CGH analyses refined the minimal critical deleted interval to a 1.62 Mb region.

Only five patients with *de novo* interstitial 20q11.2 deletions have been previously reported, and their cytogenetic results are summarized in Figure 4 [Callier et al., 2006; Iqbal and Al-Owain, 2007; Hiraki et al., 2011; Gervasini et al., 2013 ; Posmyk et al., 2014]. Another patient reported by Iourov et al. [2013] harboured a more proximal deletion, with a different phenotype, and will be excluded from the discussion.

Comparison of the clinical data of our 6 patients and those of the five previously reported patients support the idea that the 20q11.2 microdeletion causes a recognizable clinical phenotype. Ten of the 11 patients presented with anomalies of the extremities. Both hands and feet were affected with extremely variable degrees of severity. The most common signs in these patients were finger clinodactyly (6/11), camptodactyly (4/11), brachydactyly (3/11) and feet malposition (7/11). The anomalies observed in Patient 1 can be classified as type A2 brachydactyly and those of Patient 3 can be classified as type C brachydactyly. Two patients presented with pre-axial polydactyly associated with other distal anomalies; only Patient 6 presented with isolated pre-axial polydactyly. Surprisingly, the patient reported by Gervasini et al. [2013] had no anomaly of the extremities. Ten of the 11 patients presented with feeding difficulties and failure to thrive during the first weeks of life. Associated gastrointestinal anomalies were observed in 6 patients, including gastroesophageal reflux, pyloric stenosis and oesophageal hiatus hernia. Psychomotor delay was present in all 11 patients: moderate to severe delay in both motor and language acquisitions were noted in 10 patients. Only Patient 5 presented with mild intellectual disability. A recognizable craniofacial dysmorphism was suggested, which comprised of high forehead, enophthalmos, abnormal ears, short philtrum and microretrognathia in infants. Microretrognathia had resolved in the oldest patients and, inversely, the chin became more prominent and midface hypoplasia became more apparent. Furthermore, patients with 20q11.2 microdeletion exhibit occasional findings of variable growth (7/11), behavioral disorders (5/10), hearing impairment (4/9) and inconsistent malformations of the heart (6/11), eye (6/11) and brain (5/10) were also noted (Table I).

At least three genes included in the common deleted region could probably be responsible for a part of the associated phenotype. Growth/Differentiation factor 5 (*GDF5*) – OMIM 601146–encodes a secreted growth factor that plays a regulatory role in embryonic skeletal and joint development in mice and chicks by modulation of the BMP pathway [Storm and Kingsley, 1996; Merino et al., 1999]. Mutations of this gene induce various syndromes characterized by skeletal malformations, depending on the site of the mutations and their consequences for protein function [Temtamy and Aglan, 2008; Mundlos, 2009]. There is evidence that haploinsufficiency of *GDF5* is the mechanism responsible for type C brachydactyly, as all the reported mutations are frameshift or missense heterozygous mutations leading to loss of function of the protein [Everman et al., 2002; Yang et al., 2008]. All patients, except for Patients 1 and 3, presented with more variable associations of anomalies of the extremities, suggesting another molecular pathogenesis in the case of entire *GDF5* deletions. Patient 6 harbored a deletion that did not encompass *GDF5*, and she presented with a different phenotype of the extremities with unilateral pre-axial polydactyly and long fingers. The patients reported by Hiraki et al. [2011] and Posmyk et al. [2014] also presented with pre-axial polydactyly, suggesting the possible implication of another unknown genetic factor located in this chromosomal region. Some heterozygous *GDF5* mutations are associated with hearing impairment, probably due to abnormalities of middle ear bones. This possibly explains the hearing impairment observed in four patients. *GDF5* may also have

TABLE II. Summary of the Deleted Region (hg19)

Patient	Microarray	Deleted region	Size	Inheritance
1	Agilent 44K	chr20:33,962,025-36,768,739	2.8 Mb	de novo
2	ISCA Cytochip 60K	chr20:32,945,492-37,263,920	4.3 Mb	de novo
3	Agilent 44K	chr20:33,834,793-37,945,599	4.1 Mb	not determined
4	Agilent 180K	chr20:33,097,682-35,580,928	2.48 Mb	de novo
5	ISCA Cytochip 60K	chr20:32,118,663-34,361,435	2.24 Mb	de novo
6	AffymetrixGeneChip 6.0	chr20:34,194,054-41,958,122	7.7 Mb	de novo

Array CGH results of patients with deletion 20q11.2.

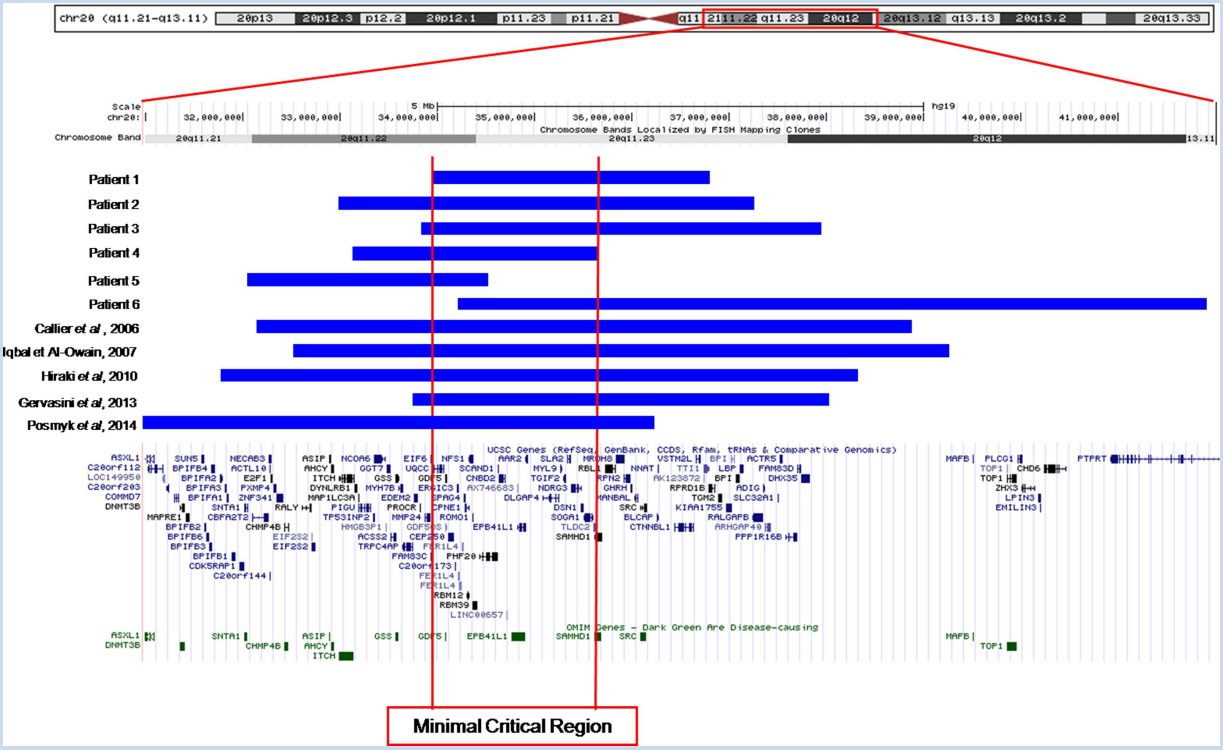

FIG. 4. Comparison of the deleted regions. Array CGH analyses refined the minimal critical region to a 1.62 Mb deletion, between 33,962,025 and 35,580,928 (hg19) (UCSC Genome Browser).

other pleiotropic effects: the influence of *GDF5* on dendrite size and morphology was demonstrated in a murine model, which could explain part of the neurological phenotype observed in these patients [Osório et al., 2013].

Erythrocyte Membrane Protein Band 4.1-Like 1 (*EPB41L1*) –OMIM 602879–is included in the critical deleted region and was deleted in ten patients. *EPB41L1* encodes a neuronal cytoskeletal protein, called 4.1 N, that binds an AMPA receptor, GLUR1, and regulates its expression at excitatory synapses [Shen et al., 2000]. A missense loss-of-function mutation of *EPB41L1* has been reported in one case of nonsyndromic intellectual disability syndrome (MRD11–OMIM 614257): the patient presented with hypotonia and severe intellectual disability but with no cerebral malformations [Hamdan et al., 2011]. It can be hypothesized that haploinsufficiency of *EPB41L1* results in decreased function of 4.1 N and is responsible for part of the neurological phenotype of patients with a 20q11.2 deletion. Patient 5 harbored a deletion that did not encompass *EPB41L1*, which could possibly explain her less severe neurological phenotype.

SAMHD1–OMIM 606754–is the third gene of interest included in the common deleted region. Bi-allelic mutations and/or deletions in *SAMHD1* have been associated with Aicardi-Goutieres syndrome [Rice et al., 2009; Leshinsky-Silver et al., 2011]. Heterozygous mutations in *SAMHD1* are also known to be responsible for a late-onset form of systemic lupus erythematosus and retinal vasculopathy with cerebral leukodystrophy [Ravenscroft et al., 2011]. Deletion of *SAMHD1* could explain the cerebral malformations (cerebral atrophy in the three first patients reported, periventricular leukomalacia in Patient 6), and the retinal dysplasia observed in the patients reported by Hiraki et al. [2011] and Posmyk et al. [2014]. While systemic lupus erythematosus has not been reported in the literature to date in any patients with 20q11.2 deletions, regular and long-term follow up would be important to identify the potential onset of systemic lupus erythematosus in these patients.

In conclusion, these findings confirm that deletion of chromosome 20q11.2 is responsible for a recognizable microdeletion syndrome comprising anomalies of the extremities, distinctive facial dysmorphism, intellectual disability, neonatal feeding difficulties and hearing impairment. We hypothesize that three genes are involved in the phenotype: *GDF5* for anomalies of the extremities and hearing impairment, *EPB41L1* for intellectual disability, and *SAMHD1* for cerebral malformation and retinal dysplasia. This study supports that the 20q11.21q11.23 microdeletion syndrome may be a newly recognized contiguous gene deletion syndrome.

ACKNOWLEDGMENTS

We wish to express our sincere gratitude to the patients and their families for their participation.

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