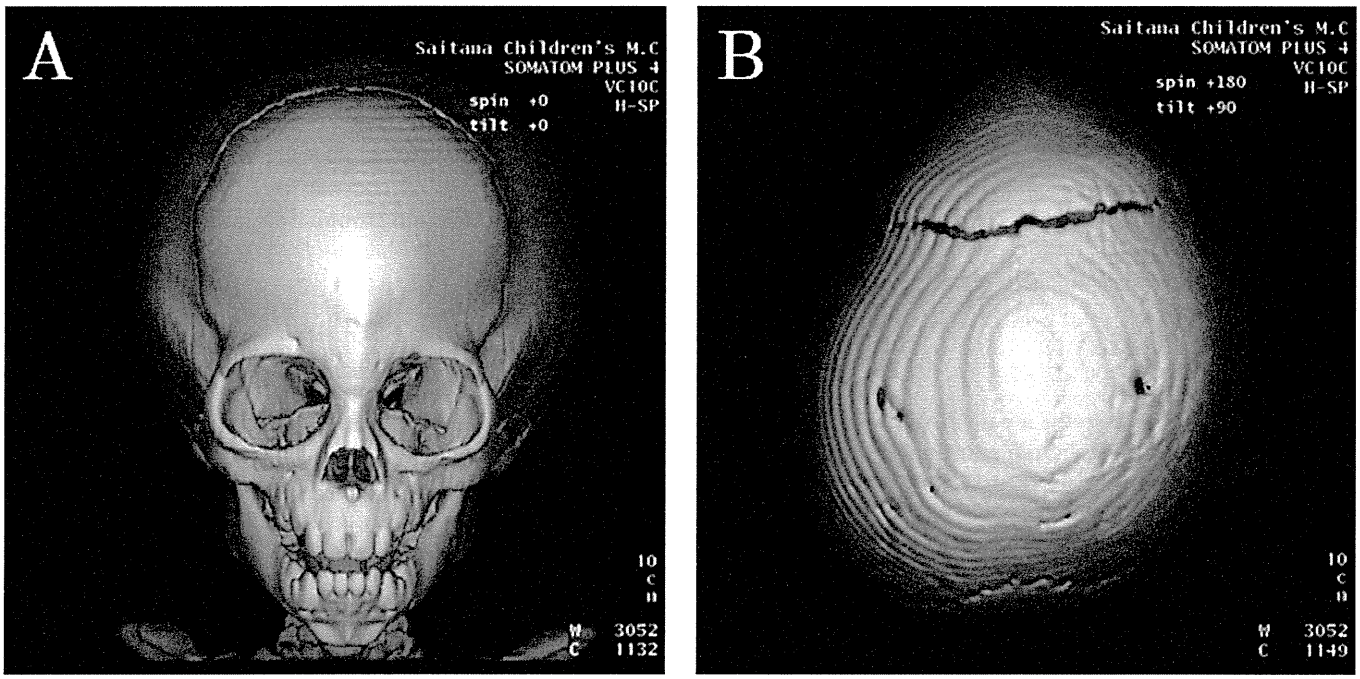

Fig. 1 Frontal (a) and top (b) views of the skull of the patient at age 11 months showing trigonocephaly, reconstructed by three-dimensional computed tomography.

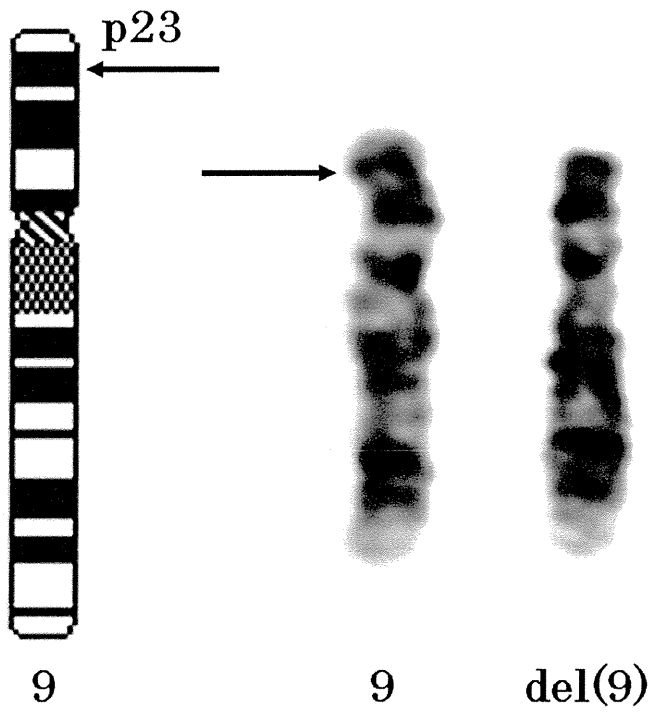

Fig. 2 G-banded partial karyotype of the patient showing a terminal deletion of chromosome 9. Arrow indicates the deletion breakpoint.

DISCUSSION

We described herein a girl patient with a terminal deletion of the short arm of chromosome 9 who had full manifestations of monosomy 9p syndrome, including distinctive craniofacial features (e.g. trigonocephaly, ptosis of the eyelids, epicanthus, upslanting palpebral fissures, flat nasal bridge, broad nasal root, low-set ears, long philtrum, thin upper lip), developmental delay, and XY sex reversal. Array CGH and FISH analyses revealed a pure terminal 9p deletion of approximately 9 Mb with the breakpoint between RP11-1134E16 and RP11-74 L16 at 9p23. *DMRT* genes, candidates for sex reversal (9p24.3), were included in the deletion in this patient.

Since Alfi et al. (1973) first reported 9p monosomy syndrome it has been established as a chromosomal deletion syndrome on the basis of G-banding cytogenetic analysis. Breakpoints in most patients with the syndrome, either with a pure terminal deletion or with a deletion associated with an unbalanced chromosome segment, reside around band 9p21-p23 (Huret et al. 1988). Recent advances in molecular techniques have allowed us to study precise correlations between the phenotype and karyotype/genotype associated with this syndrome. Wagstaff and Hemann (1995) first defined the critical region for 9p monosomy syndrome, including trigonocephaly, based on a boy with cryptic 9p monosomy, who was found to have a 9p deletion of approximately 11.6 Mb that included the region from D9S286 (9p24.1) to D9S162 (9p22.1); this deletion was associated with a translocation between 3p and 9p. Christ et al. (1999) studied 24 patients with 9p deletions (terminal deletions with or without unbalanced translocation), all of whom showed the consensus 9p-deletion phenotype (including trigonocephaly), and found that the minimum common deleted region is 16.1 Mb from D9S285 to the 9p terminal. Subsequently, several reports have been published that further define the critical region for the syndrome (Kawara et al. 2006; Faas et al. 2007; Hauge et al. 2008; Swinkels et al. 2008; Shimojima and Yamamoto 2009). Although, along with these works, some genes such as *CER1*, *TYRP1* and *PTPRD* have been postulated as possible candidate genes, no gene has yet been identified as conclusively responsible for the syndrome (Shimojima and Yamamoto 2009).

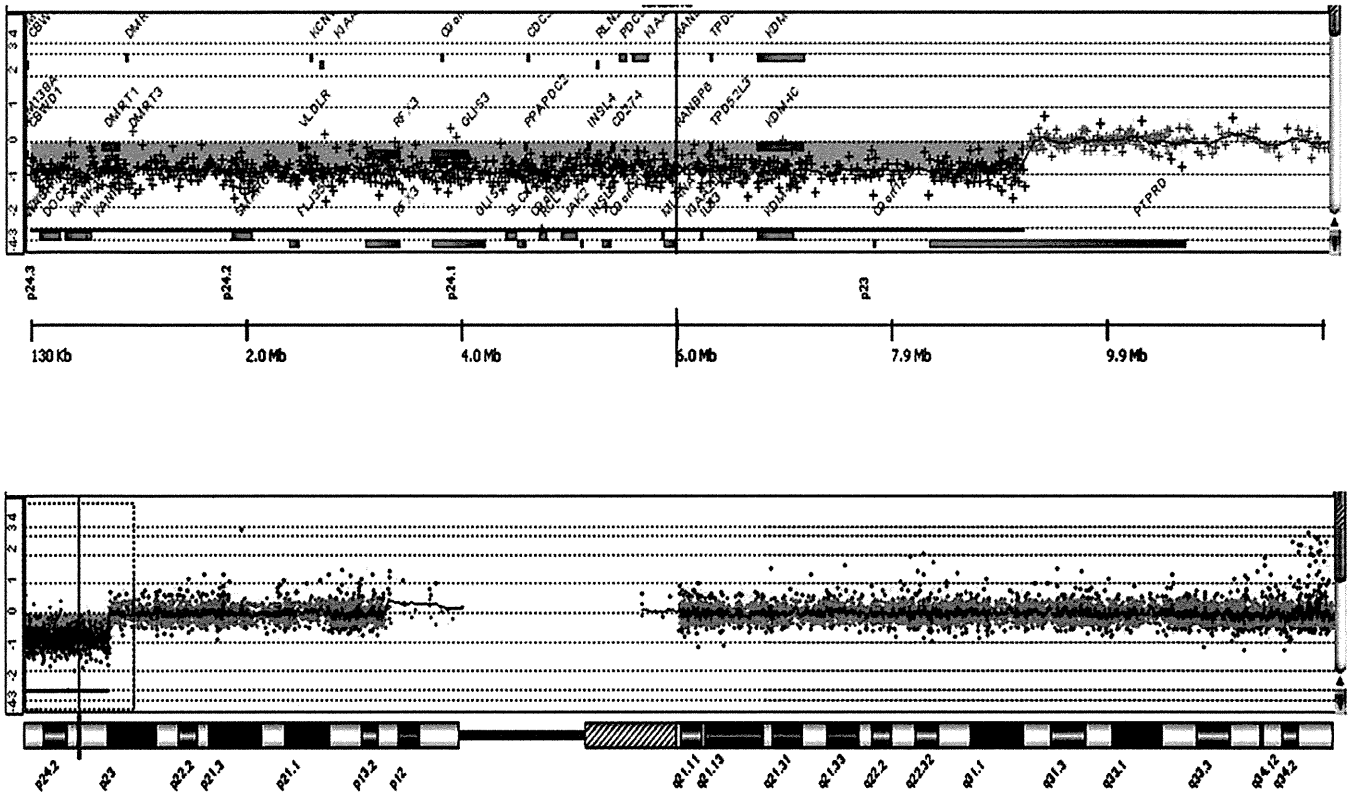

Fig. 3 Oligonucleotide array-CGH result of the patient. Whole chromosome view (lower) and close view (upper) of chromosome 9. Note a loss of 9.17 Mb of the terminal region of chromosome 9p.

Table 1 Fluoresence in situ hybridization (FISH) results using bacterial artificial chromosome clones and a subtelomeric probe around distal 9p

Probe name	Locus	Chromosome band	Distance from 9p terminal(Mb)	Signal on del(9p)
9p subtelomeric probe	–	9p24.3	–	–
RP11-143 M15	DMRT1	9p24.3	0.81	–
RP11-590E10	DMRT2	9p24.3	0.97	–
RP11-79 K3	–	9p24.1	7.30	–
RP11-29B9	D9S286	9p24.1	7.90	–
RP11-1134E16	D9S2000	9p23	8.99	–
RP11-74 L16	D9S912	9p23	9.26	+
RP11-176P17	D9S144	9p23	9.50	+
RP11-87N24	D9S168	9p23	10.47	+
RP11-58B8	–	9p23	11.60	+
RP11-382H24	D9S267	9p23	13.00	+

The distance from 9p terminal was retrieved from UCSC Genome Browser (NCBI 36/hg 18).

We compared deleted segments in all reported cases of 9p monosomy that were evaluated using molecular techniques (Fig. 4). Patients without trigonocephaly were not included in this comparison because penetrance of trigonocephaly might not be 100% and therefore considered unsuitable for use in phenotype mapping. While we could not find a common region that was shared by all patients, the segment from D9S912 to RP11-439I6, which is approximately 1 Mb, was deleted in the vast majority of the patients. There are only two patients who have a deletion that does not include this 1-Mb segment. The case reported by Kawara et al. (2006) had a more proximal interstitial deletion of 4.7 Mb at 9p22.3-p23. The chromosomal rearrangement in this patient was highly complex and

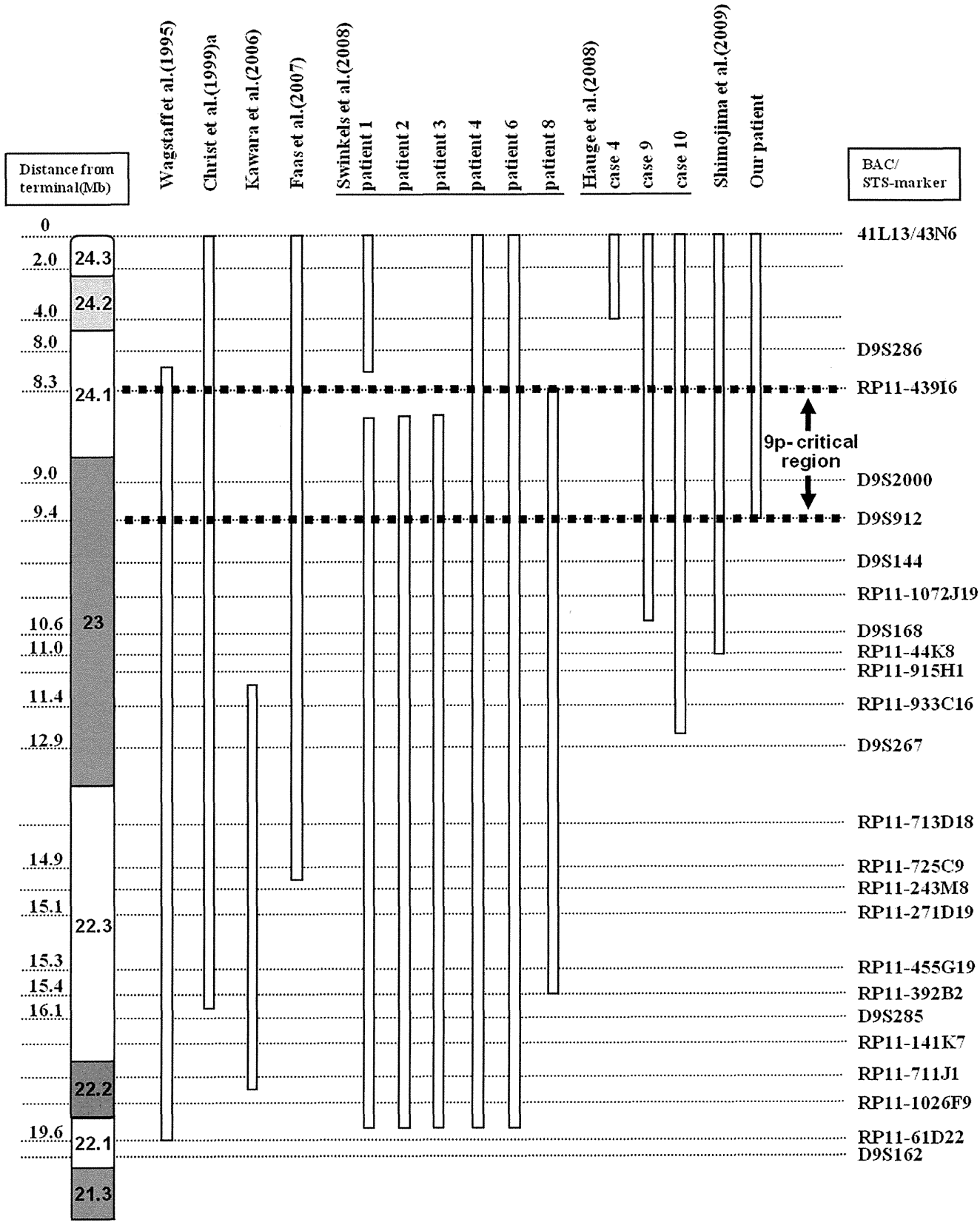

Fig. 4 Schematic map of the 9p deletion of reported cases of 9p monosomy, including the present case, evaluated using molecular analyses such as fluoresence in situ hybridization (FISH) and/or array comparative genomic hybridization. Open bars represent the presumed maximum extent of the deletion in each patient. a: the minimum common deleted region shared by 24 patients.

involved seven breakpoints on chromosomes 2 and 9. The patient, Case 4, reported by Hauge et al. (2008) showed a tiny terminal deletion of no more than 4 Mb. The karyotype of this patient was der(9)t(9;15) with a trisomic region from 15q(15q25-qter) that was translocated onto 9p24. That these two patients did not carry pure deletions of 9p may be noteworthy. Complex chromosome rearrangements are likely to have cryptic genome imbalance not only around the breakpoints but also at regions apart from the breakpoints. The altered chromosome constitution associated with unbalanced translocations might influence gene expression on the derivative chromosomes possibly through epigenetic modifications (Harewood et al. 2010). Obviously, it is preferable to choose pure terminal or interstitial deletion patients for genotype-phenotype mapping. In view of this preference and on the basis of comparison of deleted segments among patients with pure terminal or interstitial 9p deletion, including the present patient, we suggest the critical region for 9p monosomy syndrome, including trigonocephaly, might be a segment from D9S912 to RP11-439I6 of approximately 1 Mb. Of course, there are other possibilities: (i) the presence of multiple loci responsible for the syndrome and (ii) the presence of modifying factors that are located in different regions of the genome (Hauge et al. 2008). Further studies, such as using exome sequencing to screen cytogenetically normal patients with the 9p monosomy syndrome phenotype or with isolated trigonocephaly, might be necessary to identify the responsible gene for trigonocephaly of the 9p monosomy syndrome.

ACKNOWLEDGMENT

This study was funded in part by a grant from the Ministry of Health, Labour and Welfare, Japan, and from Kawano Masanori Memorial Foundation for Promotion of Pediatrics.

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CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

A Clinical Study of Patients With Pericentromeric Deletion and Duplication Within 16p12.2–p11.2

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Manuscript Received: 16 July 2012; Manuscript Accepted: 8 August 2013

The short arm of chromosome 16 is rich in segmental duplications that result in chromosomal rearrangements through non-allelic homologous recombination. Several syndromes resulting from microdeletions or microduplications in this region have been reported. The chromosome 16p12.2–p11.2 deletion syndrome, 7.1- to 8.7-Mb [OMIM#613604] is characterized by minor facial anomalies, feeding difficulties, a significant delay in speech development, and recurrent ear infections. Reciprocal duplications of 16p12.2–p11.2 have been reported in some patients with autism. We identified a patient with a 16p12.2–p11.2 deletion and a patient with a 16p12.2–p11.2 duplication using oligonucleotide SNP array. The patient with the deletion showed severe developmental delay without autism. The patient with the deletion shared clinical features with previously reported patients. The patient with the duplication showed mild developmental delay and autism. She had dysmorphic features including a round face, a large mouth, and relative macrocephaly. We reviewed the reports of the two syndromes and compared the clinical manifestations. The 16p12.2–p11.2 duplication syndrome is a new syndrome with autism spectral disorders and dysmorphic features.

Key words: 16p12.2–p11.2 deletion; 16p12.2–p11.2 duplication; SNP array; chromosomal aberration

How to Cite this Article:
Okamoto N, Fujii T, Tanaka J, Saito K, Matsui T, Harada N. 2013. A clinical study of patients with pericentromeric deletion and duplication within 16p12.2–p11.2.
Am J Med Genet Part A 9999:1–7.

INTRODUCTION

Several recurrent copy number variations are known in the pericentromeric region of chromosome16p. This region is rich in segmental duplications that result in chromosomal rearrangements through non-allelic homologous recombination.

Weiss et al. [2008] identified a novel, recurrent microdeletion, and a reciprocal microduplication at 16p11.2 with susceptibility to autism spectrum disorders (ASD) which appeared among approximately 1% of cases. Kumar et al. [2008] reported more patients. Chromosome 16p11.2 deletion syndrome [MIM#611913] (29.5–30.1 Mb) is observed in about 1% of patients with ASD [Fernandez et al., 2010].

Bochukova et al. [2010] identified five patients with overlapping deletions at 16p11.2 including *SH2B1* which is associated with leptin and insulin signaling. In three of these patients, a 220-kb deletion (28.73–28.95 Mb) was inherited from an obese parent and segregated with severe early-onset obesity without developmental problems. The other two patients showed a de novo 1.7-Mb deletion at 16p11.2 extending through the proximal 593-kb region of 16p11.2. The two patients had mild developmental delay and severe early-onset obesity. Bachmann-Gagescu et al. [2010] identified 31 patients with deletions of the *SH2B1*-containing region and supported the association of developmental delays and obesity.

Girirajan et al. [2010] suggested a 2-hit model in a recurrent 520-kb heterozygous microdeletion of 16p12. Probands with the 16p12.1 microdeletion were more likely to have additional large deletions or duplications, and the clinical features of individuals with the 16p12 deletion and additional CNV were distinct from and/or more severe than those with the 16p12.1 microdeletion only.

Conflict of interest: none.
Grant sponsor: Ministry of Health, Labor and Welfare in Japan.
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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2013
DOI 10.1002/ajmg.a.36217

The chromosome 16p12.2–p11.2 deletion syndrome 7.1- to 8.7 Mb [MIM#613604] is distinct from 16p11.2 deletion syndrome. Hernando et al. [2002] reported the first case of multiple congenital anomalies associated with a deletion of 16p11.2 confirmed by array comparative genomic hybridization (CGH). Ballif et al. [2007], Battaglia et al. [2009], and Hempel et al. [2009] reported on further patients with a 16p12.2–p11.2 deletion. Minor facial anomalies, feeding difficulties, a significant delay in speech development, and recurrent ear infections are common symptoms of the 16p12.2–p11.2 deletion syndrome.

Reciprocal duplications of 16p12.2–p11.2 have been reported in some patients with mild to severe intellectual disability, ASD, and dysmorphic features [Engelen et al., 2002; Finelli et al., 2004; Ballif et al., 2007; Tabet et al., 2012; Barber et al., 2013]. The 16p12.2–p11.2 duplication syndrome shows variable phenotype.

We have identified a patient with a 16p12.2–p11.2 deletion and a patient with 16p12.2–p11.2 duplication using a high density oligonucleotide SNP array. The patient with deletion shared clinical features with previously reported patients. The patient with the duplication showed ASD and dysmorphic features. The duplicated region did not include the 16p11.2 region carrying susceptibility to autism. We reviewed and discussed the clinical manifestations of the two 16p12.2–p11.2 chromosomal aberrations.

CLINICAL REPORT

Patient 1 (16p12.2–p11.2 Deletion)

The 3-year-old male proband was the first-born child of a 26-year-old mother and a 30-year-old father, both healthy and non-consanguineous. After an uncomplicated pregnancy, he was born at 37 weeks of gestation by induced delivery. His length was 53 cm (90th centile). His birth weight was 1,770 g (25th centile). After birth, cardiac murmur was noticed. Echocardiography revealed VSD. Cardiac surgery was carried out successfully at 6 months of age. His developmental milestone was delayed. He showed muscle hypotonia. Head control was achieved at 10 months of age. He sat unsupported at 2 years of age. Independent walking was not possible. He spoke no meaningful words. His global development quotient was 20 at 2 years of age. Autistic features were not seen. He showed common clinical features of the 16p12.2–p11.2 deletion syndrome (Table I). Physical examination identified dysmorphic

TABLE I. Clinical Findings in Patients with 16p12.2–p11.2 Deletion Syndrome

		Ballif et al. [2007]						
	Hernando et al. [2002]	Subject 1	Subject 2	Subject 3	Subject 4	Battaglia et al. [2009]	Hempel et al. [2009]	Present patient 1
Size of deletion [Mb]		8.7	7.1	7.8	7.8	8.2	7.7	7.7
Age of diagnosis	5 months (died)	13 years 8 months	13 years 9 months	3 years 1 month	2 years 19 months	6 years	13 years 3months	3years
Gender	M	F	F	F	F	F	M	M
Delay in motor development		+	+	+	+	+	+	+
Hypotonia		+	−	+	+	+	+	+
Intellectual disability		+	+	+	+	+	+	+
Severe speech delay		+	+	+	+	+	+	+
Autism spectrum disorders		−	−	−	−	−	−	−
Growth								
Height (centile)		3rd	<3rd	25–50th	25th	50th	50th	10–25th
Weight (centile)		3rd	10–25th	50th	3rd	25th	50th	3rd
Head circumference (centile)		10th	25th	25th	8th	30th	50th	10th
Facial appearance								
Flat face	+	+	+	+	−	+	+	+
High fore head/frontal bossing	+	+	−	+	+	−	+	+
Downslanting palpebral fissures		+	+	+	+	−	−	+
Epicantal folds		+	−	+	+	−	−	−
Deep set eyes		+	−	−	+	+	+	−
Low-set, malformated ears	+	+	−	+	+	+	+	+
Small mouth							+	−
Micrognathia	+						−	
Congenital cardiac anomalies	+	+	−	−	+	−	−	+
Gastrointestinal problems								
Feeding difficulties		+	+	+	+	+	+	+
Gastro esophageal reflux		+	+	+	+	−	−	−
Hands								
Single palmar creases		+	+	+	−	+	−	−
Camptodactyly		+	+	−	−	−	−	−
Other problems								
Recurrent ear infections		+	+	+	+	+	+	+
Hearing impairment		+	−	−	−	−	+	−

features, including a flat face, downslanting palpebral fissures, low-set posteriorly rotated ears, and a thin upper lip vermilion (Fig. 1). Hearing and visual acuity were normal. His weight was 9.3 kg (−1.9 SD), and his length was 82.6 cm (−0.9 SD). His head circumference was 46.5 cm (−1.1 SD). Routine laboratory tests were normal. Neuroradiological analysis revealed no significant abnormalities. Conventional cytogenetic examination of G-banded chromosomes from peripheral blood lymphocytes was normal. Microarray analyses were performed to reveal submicroscopic chromosomal aberrations.

Patient 2 (16p12.2–p11.2 Duplication)

The patient, a 9-year-old girl, was born to non-consanguineous healthy Japanese parents. Her family history was unremarkable. She was born at 38 weeks' gestation. Her birth weight was 3,200 g. Her gross development was delayed. She started to walk independently at 18 months old. Her development in speech and social interaction were retarded. At 4 years of age, she was diagnosed with ASD. G-banded karyotyping revealed a normal female karyotype. Brain MRI was normal. EEG showed epileptic discharges, but she was free from epileptic seizures. She visited our hospital for further medical studies. Her dysmorphic features included a round face, a flat nasal bridge, full cheeks, a wide philtrum, a wide mouth, a pointed chin, fetal pads on fingers and toes, and generalized hypertrichosis (Fig. 2). Her height, weight, and head circumference were 119 cm (−2.3 SD), 22.8 kg (−1.2 SD), and 54.2 cm (+1.5 SD), respectively. Relative macrocephaly was noted. She had difficulties with daily activities. In addition, impaired social interaction, poor social skills, and strict adherence to routine behaviors were noted. She was again diagnosed with ASD according to the DSM–VI criteria. Her DQ was 76 according to the standard Japanese method. Recently, her communication skill improved. Microarray analyses were performed to reveal submicroscopic chromosomal aberrations.

MATERIALS AND METHODS

With written informed consent, genomic DNA was obtained from blood leukocytes. A copy number analysis was performed using the CytoScan HD Array (Affymetrix, Santa Clara, CA) which features 2.7 million genetic markers covering the whole human genome. Genomic DNA of the patients was diluted to 50 μg/μl and processed according to the protocol (Affymetrix Cytogenetics Copy Number Assay User Guide) supplied by Affymetrix. The data were analyzed with the Chromosome Analysis Suite software (Affymetrix).

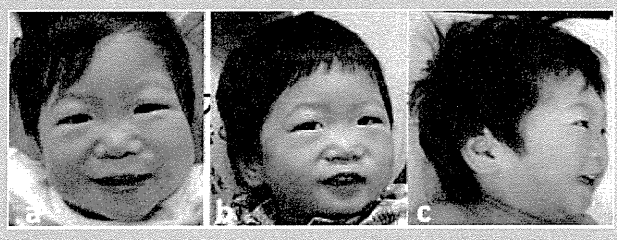

FIG. 1. a,b,c: Facial appearance of Patient 1 with the 16p12.2–p11.2 deletion at 2 years of age. He shows dysmorphic features, including a flat face, downslanting palpebral fissures, low-set posteriorly rotated ears, and a thin upper lip vermilion. (Permission for presentation has been obtained from his parents).

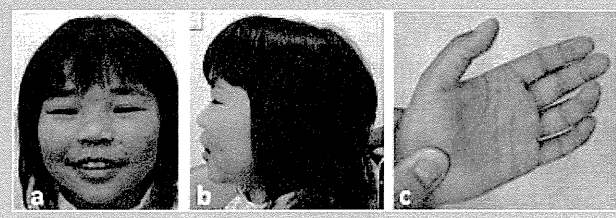

FIG. 2. a,b: Facial appearance of Patient 2 with the 16p12.2–p11.2 duplication. Her features included a round face, a flat nasal bridge, full cheeks, wide philtrum, a wide mouth, and a pointed chin. c: Fetal pads of the fingers were observed. (Permission for presentation has been obtained from her parents).

RESULTS

The SNP array analysis confirmed aberrations on the short arm of chromosome 16. The karyotype of Patient 1 was 46, XY, arr 16p12.2p11.2(21,306,156–29,053,253) × 1 (hg19) (Fig. 3). The deletion size was 7.7 Mb. The segment contained OMIM disease genes (*OTOA*, *SCNN1G*, *SCNN1B*, *COG7*, *EARS2*, *PALB2*, *IL4R*, *IL21R*, *CLN3*, *TUFM*, *SH2B1*, *ATP2A1*, and *CD19*). The karyotype of Patient 2 was 46, XX, arr 16p12.2p11.2 (21,516,366–28,234,120) × 3 (hg19) (Fig. 4). The duplication size was 6.7 Mb. The segment contained OMIM disease genes (*OTOA*, *SCNN1G*, *SCNN1B*, *COG7*, *EARS2*, *PALB2*, *IL4R*, and *IL21R*). The duplicated region of Patient 2 was smaller than the deleted region of Patient 1. *SH2B1*, *ATP2A1*, and *CD19* were not included in the duplication. These copy number variations were confirmed by FISH analysis (Fig. 5). In both families, the parents did not have the abnormalities.

DISCUSSION

The chromosome 16p12.2–p11.2 deletion syndrome 7.1 to 8.7 Mb [MIM#613604] (21.4 to 29.3 Mb) is a new syndrome resulting from non-allelic homologous recombination. The deleted segment is distal to the 16p11.2 deletion syndrome region and is distinguished from the 16p11.2 deletion syndrome which is associated with autism [Kumar et al., 2008; Marshall et al., 2008].

Hernando et al. [2002] reported the first case of multiple congenital anomalies associated with a deletion of 16p11.2 confirmed by array CGH. The male infant showed severe intrauterine growth retardation and dysmorphic features. The patient died at the age of 5 months due to cardiac disease. Ballif et al. [2007] identified a recurrent de novo pericentromeric deletion of

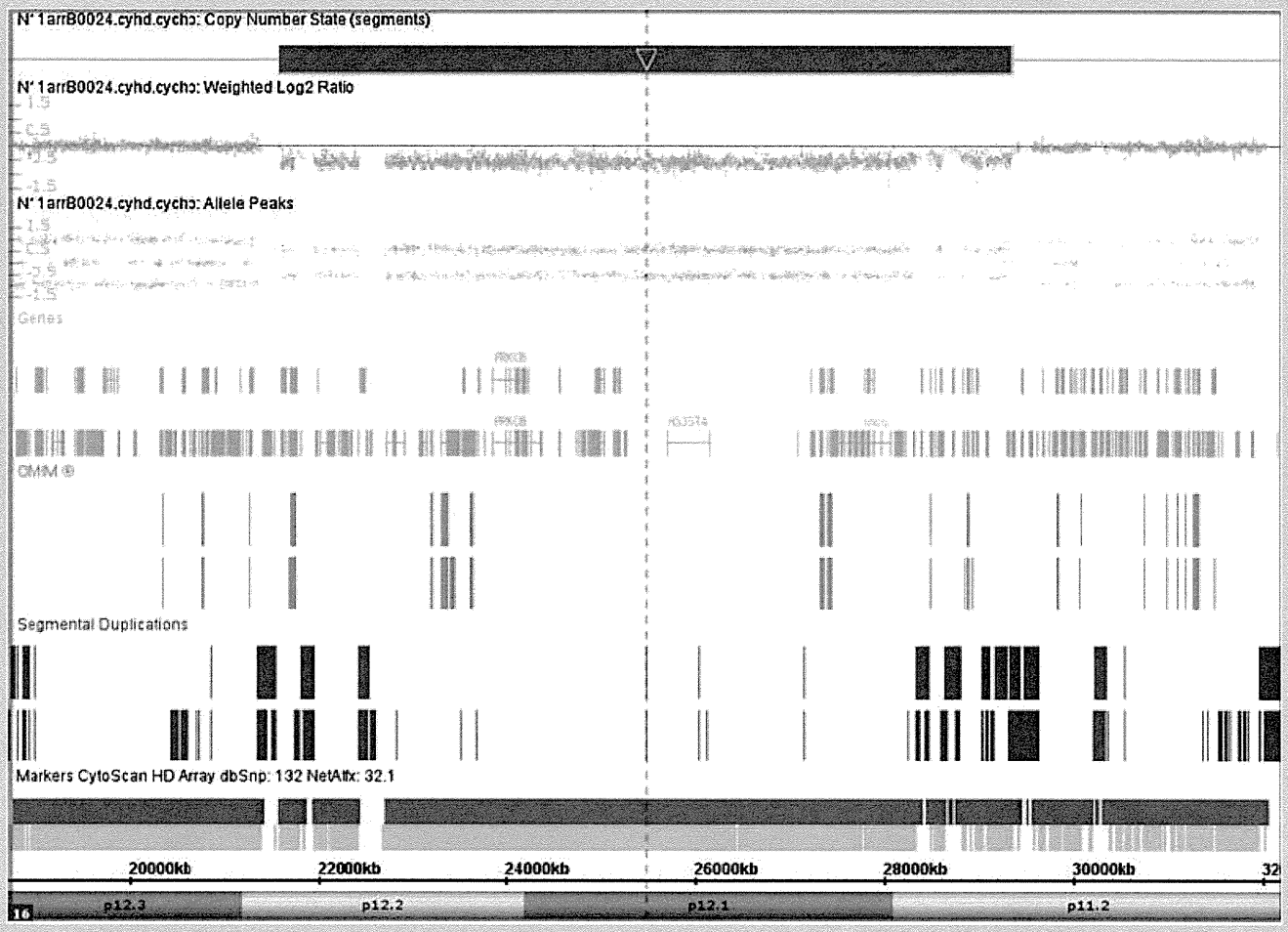

FIG. 3. Results of the SNP array analysis of Patient 1. The red bar indicates the 16p12.2–p11.2 deletion. The deletion size was 7.7 Mb. The segment contained OMIM disease genes (*OTOA, SCNN1G, SCNN1B, COG7, EARS2, PALB2, IL4R, IL21R, CLN3, TUFM, SH2B1, ATP2A1,* and *CD19*).

16p12.2–p11.2 in four individuals with developmental disabilities by array-CGH. The four patients had common clinical features. Battaglia et al. [2009] and Hempel et al. [2009] reported on further patients with a 16p12.2–p11.2 deletion.

Dysmorphic features including flat face, feeding difficulties, significant delay in speech development, and recurrent ear infections are common symptoms of the 16p12.2–p11.2 deletion syndrome. Some patients have anxiety, irritability, hyperactivity, short attention ability, and introverted behavior. However, ASD is not described in the patients. Patient 1 shared many of the clinical findings in these reports (Table I). Our result further confirmed that the 16p12.2–p11.2 deletion is responsible for a distinct multiple congenital anomalies and intellectual disability (MCA/ID) syndrome without autistic features.

The distal breakpoint of these patients was 21.4 Mb from the 16p telomere. The proximal breakpoints of these patients were 28.3–29.3 Mb from the 16p telomere and differed in the 16p11.2 region. The distal and the proximal breakpoint of Patient 1 was 21.3 Mb and 29.1 Mb from the 16p telomere, respectively.

Some disease-causing genes are included in the deleted region. Hempel et al. [2009] speculated that heterozygosity of the *OTOA* gene may cause hearing impairment in some patients. Herterozygous deletion of *CD19* may lead to recurrent ear infections. Patient 1 had recurrent ear infections. Routine laboratory investigations revealed no immunological abnormalities. Deletions encompassing the *SH2B1* gene were recently reported in early-onset obesity [Bochukova et al., 2010]. Although the *SH2B1* gene was deleted in Patient 1, he was not obese due to feeding difficulties. We should be careful for the later onset obesity.

Reciprocal duplications of 16p12.2–p11.2 have been reported in some patients with ASD and dysmorphic features [Engelen et al., 2002; Finelli et al., 2004]. However, the precise boundaries of the duplication were not defined because they were studied only by standard cytogenetic techniques. Tabet et al. [2012] reported two monozygotic twins carrying a de novo 16p12.2–p11.2 duplication of 8.95 Mb (21.28–30.23 Mb) encompassing both the 16p11.2 and 16p12.2–p11.2 regions. The twins exhibited ASD, severe intellectual disabilities, and dysmorphic features,

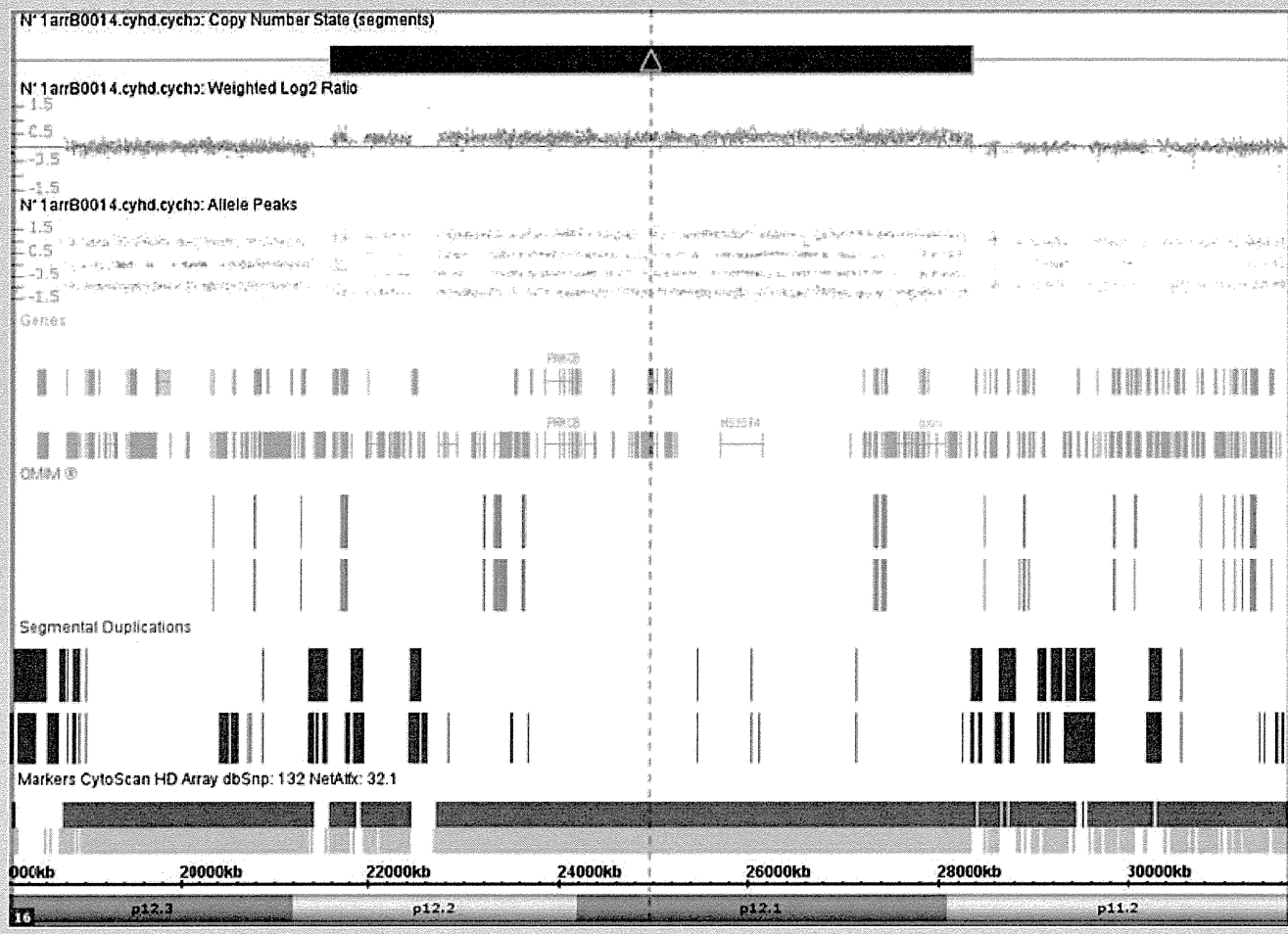

FIG. 4. Results of the SNP array analysis of Patient 2. The blue bar indicates the 16p12.2–p11.2 duplication. The duplication was 6.7 Mb. The segment contained OMIM disease genes (*OTOA*, *SCNN1G*, *SCNN1B*, *COG7*, *EARS2*, *PALB2*, *IL4R*, and *IL21R*). The duplicated region of Patient 2 was included in the deleted region of Patient 1. *SH2B1*, *ATP2A1*, and *CD19* were not included in the duplication.

including a triangular face, deep-set eyes, a large and prominent nasal bridge, and a tall, slender build. Barber et al. [2013] reported further two patients with duplication. One patient was a girl of 18 with autism, moderate ID, behavioral difficulties, dysmorphic features, and 7.71 Mb duplication. Another patient had 7.81 Mb duplication, speech delay, and obsessional behavior as a boy and, as an adult, short stature, macrocephaly and mild dysmorphism. Barber et al. [2013] suggested that the 16p12.2–p11.2 duplication syndrome is a recurrent genomic disorder with a variable phenotype.

Molecularly defined patients with the 16p12.2–p11.2 duplication syndrome are summarized in Table II. Facial features of the 16p12.2–p11.2 duplication syndrome are different among patients. Common dysmorphisms reported by Barber et al. [2013] included a depressed, broad or large nasal bridge, upslanting or narrow palpebral features, hypertelorism, and a long or tented philtrum. Patient 2 had dysmorphic features characterized by a round face, a flat nasal bridge, full cheeks, a wide philtrum, a wide mouth, a pointed chin, generalized hypertrichosis, and fetal finger pads. She

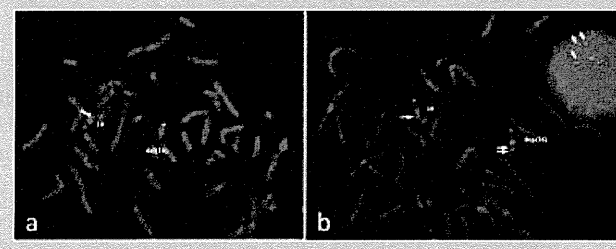

FIG. 5. A FISH analysis was performed to confirm the copy number changes. a: The red signal covering RP11-281K19 (*RBBP6*) [chr16:24,439,760–24,647,914] was deleted in patient 1. b: The red signal covering RP11-281K19 (*RBBP6*) was duplicated in Patient 2. The green signal indicates the 16q24.3 subtelomeric probe, GS-240G10. Arrows indicate RP11-281K19 (*RBBP6*).

TABLE II. Clinical Findings in Patients with 16p12.2–p11.2 Duplication Syndrome

	Finelli et al. [2004] Patient 1	Ballif et al. [2007] Subject 5	Tabet et al. [2012] Patient 2 (MZ twin)	Tabet et al. [2012] Patient 3 (MZ twin)	Barber et al. [2013] Patient 1	Barber et al. [2013] Patient 2	Present patient 1
Size of duplication [Mb]	8	5.7 Mb triplication, 1.1 Mb duplication	8.95	8.95	7.71–8.07	7.81–8.37	6.7
Age of diagnosis	25 years	10 years	17 years	18 years	15 years	45 years	9 years
General							
Gender	M	F	M	M	F	M	F
Development/neurological							
Developmental delay	+	+	+	+	+	+	+
Intellectual diability	Severe	Severe	Severe	Severe	Moderate	+	Mild
Epilepsy	+				−	−	−
EEG abnormalities	+				−		+
Autism spectrum disorders	+	+	+	+	+	−	+
Obsessive behavior	+				+	+	+
Stereotype behavior	+	+	+	+	+		
Social problems	+	+	+	+	+		−
Growth							
Height	<3rd centile	−3 to −4 SD	normal	normal	<*P*25	0.4th centile	−2.3 SD
Weight	<3rd centile	−2 SD	−2 SD	−1 SD	<*P*25		−1.2 SD
Head circumference	25th centile	−1 SD	−1 SD	−1 SD	<*P*50	Macro	1.5 SD
Facial appearance							
Round face		+	−	−			+
Triangular glabella		−	+	+			−
Promient glabella		−	+	+	+		−
Depresssed/large/broad nasal bridge	+	+	+	+	+		+
Upslanting palpebral fissures		−	+	+			−
Deep set eye		−	+	+			−
Hypertelorism	+	+	+	+			−
Nystagmus/Strabisums		+	+	+	+	+	−
Anteverted nares		+			+		−
Upper lip anomaly	+	+			−		−
Low set ears	−				−		+
Wide/large mouth	+	+					+
Full cheeks		+					+
Micro/retrognathia		−	−	−	−	+	−
Finger/hand anomalies	+	Fetal pads	+	+	−	Brachydactyly	Fetal pads
Generalized hypertrichosis							+

shared some features with other reported patients. Fetal finger pads have been found in one of the patients reported by Ballif et al. [2007]. Our results further support the evidence that ID, ASD, dysmorphic features, short stature, and anomalies of the hands and fingers are common in the 16p12.2–p11.2 duplication syndrome. However, intellectual disabilities in Patient 2 were very mild. Her communicating skill improved after 8 years old. Duplication in our patient did not include the 16p11.2 region carrying susceptibility to ASD and *SH2B1*. We suppose that differences in the proximal breakpoint may contribute to the severity of intellectual disabilities. Increased dosage of one or more genes in the duplicated region might contribute to ASD.

Delay in motor development is a constant feature of the 16p12.2–p11.2 deletion syndrome. Early development of the twins reported by Tabet et al. [2012] was normal, with walking at 15 months. The patient reported by Barber et al. [2013] walked at 13 months. Patient 2 started to walk independently at 18 months old. Delay in motor development is not considered to be a serious problem in the 16p12.2–p11.2 duplication syndrome.

Barber et al. [2013] suggested that the duplications *Polo-like kinase 1* (*PLK1*) might have an effect on neuronal development and microcephaly in human. However, one of the patients reported by them had macrocephaly and our patient also had relative macrocephaly.

We posit that the 16p12.2–p11.2 duplication is a new clinical entity with ASD due to non-allelic homologous recombination. The deletion is a MCA/ID syndrome. More patient studies will be needed to further define the syndrome.

ACKNOWLEDGMENTS

We thank for the family for their cooperation. This study was supported by the Health and Labor Research Grants in 2012 by Ministry of Health, Labor, and Welfare in Japan.