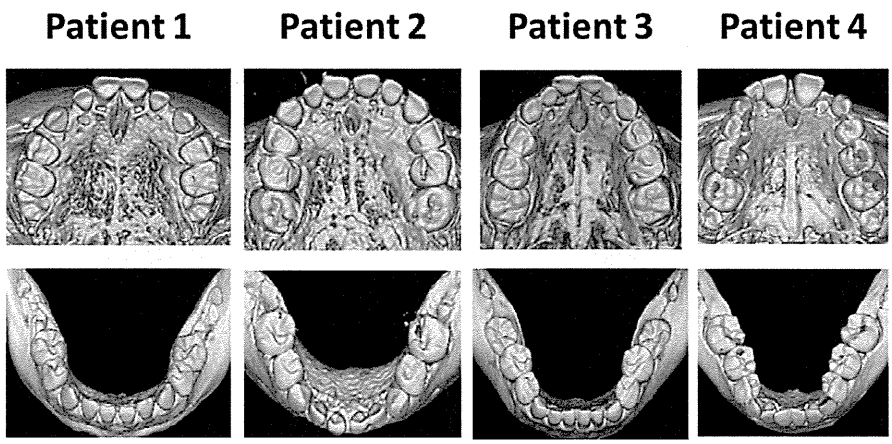

Fig. 3 Multi-detector row computed tomography (MDCT)-synthesized upper and lower dental arches in all four patients. Small dental arches are noted in three patients (patients 2, 3 and 4). Patient 2 exhibited a U-shaped dental arch in the maxilla and narrow dental arch in the mandible; Patients 3 and 4 exhibited narrow dental arches in the maxilla and rectangle arches in the mandible.

Table 4 Tooth size measurements in four patients

Patient	1		2		3		4	
	Right	Left	Right	Left	Right	Left	Right	Left
Maxillary								
Primary teeth								
Central incisor	0.54	0.54	−1.08	−0.54	−0.45	−0.45		
Lateral incisor	−2.00	−1.78	−1.56	−1.56	−2.44	−2.44	−0.49	
Cuspid	−1.22	−0.98	−1.22	−1.71	−0.73	−0.73	−0.98	−0.24
First molar	−2.39	−2.61	−2.17	−1.96	−1.09	−0.87	−0.43	−0.43
Second molar	−3.33	−3.16	−3.68	−3.51	−1.93	−1.58	−1.05	−0.53
Permanent teeth								
Central incisor							0.24	0.98
First molar							−1.95	−1.95
Mandibular								
Primary teeth								
Central incisor	0.31	0.00	−0.31	0.00	−1.00	−0.67		
Lateral incisor	1.21	1.52	0.00	−0.30	−0.83	−1.39		
Cuspid	0.31	0.31	−0.31	−0.63	−0.33	0.00	1.00	1.33
First molar	−1.30	−1.52	−1.30	−1.30	−0.60	−0.40	0.20	0.00
Second molar	1.04	1.04	−1.88	−1.46	0.00	−0.20	0.98	1.18
Permanent teeth								
Central incisor							−0.56	−0.83
Lateral incisor							−0.51	0.00
First molar							1.50	1.83

Tooth size represents the distance from the medial to the distal. Unit, S.D.

(RASopathies), including Noonan syndrome, CFC syndrome and Costello syndrome. However, a detailed investigation about craniofacial and dental findings has not yet been done. Recently, Goodwin et al. (2012) studied craniofacial and dental development in CFC syndrome based on 32 patients as the first large cohort study and found characteristic findings of the syndrome, including macrocephaly, convex facial profile, malocclusion with open bite, posterior cross bite, dental crowding, and high-arched palate. Among these features of CFC syndrome, macrocephaly, convex facial profile, malocclusion and high-arched palate were features noted in our patients with Costello syndrome as well. Unfortunately, as the evaluations of CFC syndrome by Goodwin et al. were mainly based on physical examination, more detailed evaluation regarding, such as dental arches, tooth size, and relationships between craniofacial, dental and skeletal structures have not been fully provided.

We used MDCT as a substitute for cephalometric, panoramic and dental cast studies. To our knowledge, this is the first study of thorough craniofacial and dental evaluation by using MDCT in Costello syndrome. As intellectual disability is common in Costello syndrome, these conventional cephalometric, panoramic and dental

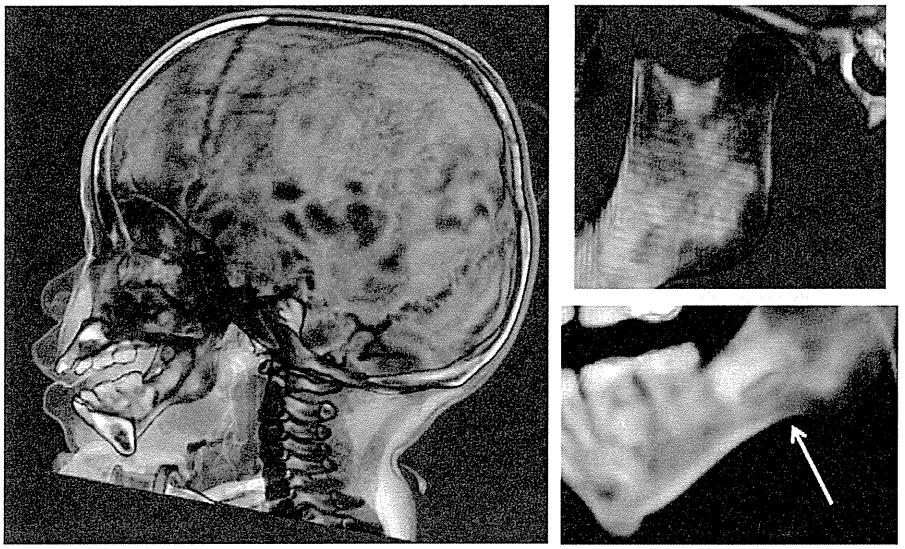

Fig. 4 Multi-detector row computed tomography (MDCT)-synthesized lateral radiograph (left) and close view of mandible (right) of Patient 3 at age of 6 years. Note the macrocephalic skull with hypoplastic facial bones (left). Mandibular anomalies are also noted, characterized by thick and flat head of the condylar process, short condylar neck, narrow mandibular notch (right upper) and antegonial notching (right lower).

Table 5 Lateral cephalometric analysis with MDCT of four patients

Patient	1	2	3	4
Skeletal				
Convexity	7.85	3.47	5.29	0.50
A-B plane	−0.12	−0.95	−1.78	0.76
SNA	4.06	−1.78	−1.78	−1.21
SNB	0.42	−2.89	−2.61	−1.14
Facial angle	−1.39	−1.54	1.39	0.53
SNP	−1.14	−2.99	−3.13	−1.56
Y axis	0.00	−0.15	−0.45	−0.84
SN-S·Gn	0.06	1.68	3.29	1.40
Mandibular plane	1.18	0.00	0.74	0.94
Gonial angle	0.77	−1.23	0.29	0.93
GZN	−0.12	2.33	2.51	2.09
FH to SN	−0.38	1.97	3.98	2.16
Dental				
U-1 to FH plane	2.37	−2.62	−0.31	4.44
U-1 to SN plane	3.12	−1.10	−2.41	3.02
L-1 to mandibular	1.17	4.94	−1.88	−1.28
Interincisal	−3.04	−2.04	0.80	−2.41
Occlusal plane	2.36	1.17	−0.69	−1.23

Unit, S.D.

cast studies are often difficult to perform, especially in the infantile period when patients tend to show marked irritability. MDCT is a useful tool for precise evaluation of craniofacial and oral manifestations in multiple congenital anomaly/intellectual disability syndromes (Hirai et al. 2011).

In conclusion, characteristic craniofacial and oral features frequently noted in patients with Costello syndrome might be true/relative macrocephaly with facial bone hypoplasia, gingival hypertrophy, malocclusion, occlusal attrition, small dental arches, microdontia, and convex face. Craniofacial and dental abnormalities are common in Costello syndrome patients and comprehensive dental care should be provided from early infancy.

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CASE REPORT

Patient with terminal 9 Mb deletion of chromosome 9p: Refining the critical region for 9p monosomy syndrome with trigonocephaly

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ABSTRACT **We describe a patient with typical manifestations of 9p monosomy syndrome, including trigonocephaly and sex reversal. Array comparative genomic hybridization (CGH) revealed a 9p terminal deletion of approximately 9 Mb with the breakpoint at 9p23. We compared the deleted segments of 9p associated with reported cases of 9p monosomy syndrome with trigonocephaly. We did not identify a region that was shared by all patients; however, when only pure terminal or interstitial deletions that did not involve material from any other chromosome were compared, we identified a segment from D9S912 to RP11-439I6 of approximately 1 Mb that was deleted in every patient. We propose that this 1-Mb segment might be the critical region for 9p monosomy syndrome with trigonocephaly.**

Key Words: 9p monosomy, craniosynostosis, critical region, sex reversal, trigonocephaly

INTRODUCTION

Monosomy 9p syndrome [MIM 158170] is a rare but well-known chromosomal deletion syndrome characterized by distinct craniofacial features (including trigonocephaly), various systemic anomalies, developmental retardation, and occasional sex reversal in XY patients (Huret et al. 1988). Since Alfi et al. (1973) first described a patient with the syndrome, more than 100 patients, most with terminal deletions with breakpoints around 9p21-p23 based on chromosome G-band analysis, have been reported. Recent advances in molecular/cytogenetic techniques allow attempts to map the loci responsible for cardinal features of the syndrome, especially trigonocephaly and sex reversal. While *DMRT* genes, which map to the most terminal 9p24.3 band, have been elucidated as the genes responsible for sex reversal (Raymond et al. 1998; Ogata et al. 2001; Barbaro et al. 2009), no gene has yet been identified as definitively responsible for trigonocephaly. Moreover, previous studies have been inconsistent with regard to identification of the 9p regions that are responsible for trigonocephaly (Wagstaff and Hemann 1995; Christ et al. 1999; Kawara et al. 2006; Faas et al. 2007; Hauge et al. 2008; Swinkels et al. 2008; Shimojima and Yamamoto 2009). Here, we describe a patient with a terminal 9p deletion of approximately 9 Mb who has the typical clinical manifestations of 9p monosomy syndrome, including trigonocephaly and sex reversal.

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CLINICAL REPORT

The girl patient was born by cesarean section after 38-week gestation to a 30-year-old gravida 2, para 1 mother and a 31-year-old father, both Japanese, healthy, and unrelated. The patient's birth weight was 2864 g (−0.5 SD), length 49.5 cm (+0.2 SD), and occipitofrontal head circumference 35.5 cm (+1.5 SD). The patient had a healthy older sister. The patient was referred to us at the age of 11 months because of developmental delay and skull deformity. The notable craniofacial features were trigonocephaly, ptosis of the eyelids, epicanthus, upslanting palpebral fissures, flat nasal bridge, broad nasal root, long philtrum, thin upper lip, and low-set ears. A skull computed tomography scan with 3D reconstruction confirmed trigonocephaly with metopic suture synostosis (Fig. 1). Fronto-orbital advancement with cranial reshaping was performed when she was 1 year and 3 months old. She showed normal female external genitalia. When the patient was 2 years old, an abdominal ultrasonography revealed a uterus, but no ovary or testis was detected. A test of human chorionic gonadotropin load suggested the existence of testis, while luteinizing hormone-releasing hormone load test revealed primary hypogonadism. She weighed 14 kg (−1.7 SD) and was 100.2 cm tall (−1.9 SD) at 5 years of age. Her development was moderately delayed, and her IQ was estimated to be around 40 with the Tanaka–Binet Intelligence Scale at the age of 6 years.

G-banding analysis at a resolution of 550-bands on metaphase chromosomes obtained from phytohemagglutinin-stimulated lymphocyte cultures from the patient revealed a distal deletion of the short arm of chromosome 9 with a breakpoint at 9p23 and an XY sex chromosome constitution (sex reversal) (Fig. 2). Her parents were chromosomally normal. Fluorescence *in situ* hybridization (FISH) using whole-chromosome painting probes for chromosome 9 and a subtelomeric probe for the short arm of chromosome 9 (both from Vysis/Abbott Molecular Inc., Des Plaines, IL, USA) revealed that the abnormal chromosome 9 did not contain translocated material from another chromosome. To further define the extent of the deleted region in 9p, we performed an array comparative genomic hybridization (CGH) analysis using the Agilent Human Genome 244 K CGH kit (Agilent Technologies, Santa Clara, CA, USA). The result showed a hemizygous 9.17 Mb terminal deletion of chromosome 9p and no other apparent pathogenic copy number variation was identified in the whole genome (Fig. 3). Her karyotype was designated as 46,XY,del(9)(p23).arr 9p23 (194 193-9 169 072)x1 dn. FISH analyses with bacterial artificial chromosome (BAC) clones spanning the region from 9p23 to 9p24 refined the breakpoint between the clones RP11-1134E16 (D9S2000) and RP11-74 L16 (D9S912) (Table 1). BACs containing *DMRT1* and *DMRT2*, both candidate genes for sex reversal (9p24.3), were confirmed to be in the deleted segment of 9p in the patient.

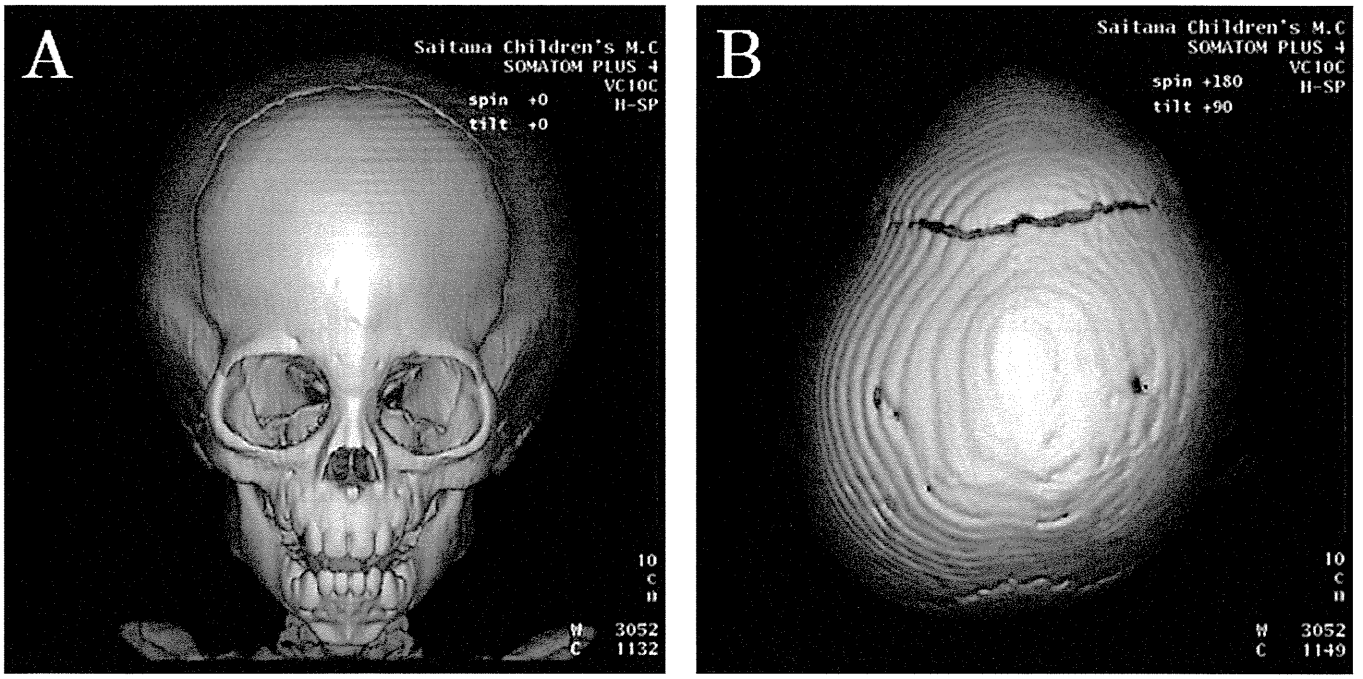

Fig. 1 Frontal (a) and top (b) views of the skull of the patient at age 11 months showing trigonocephaly, reconstructed by three-dimensional computed tomography.

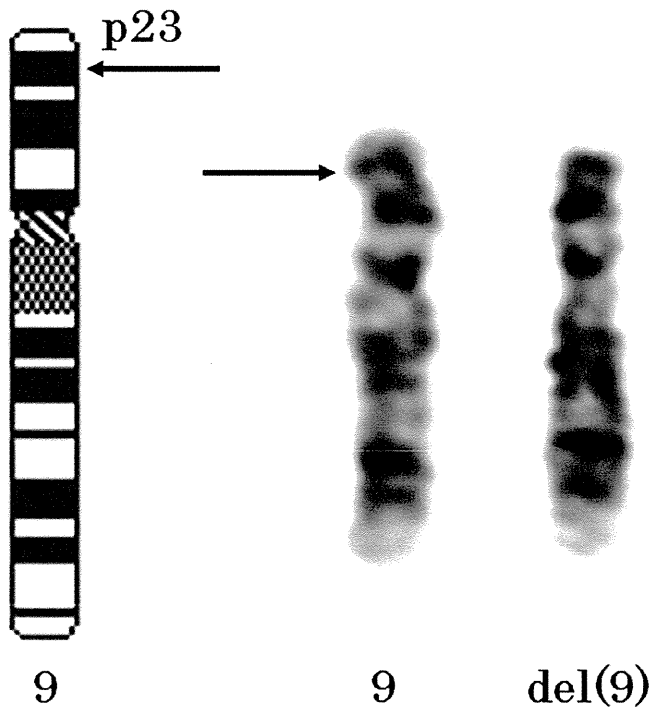

Fig. 2 G-banded partial karyotype of the patient showing a terminal deletion of chromosome 9. Arrow indicates the deletion breakpoint.

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).

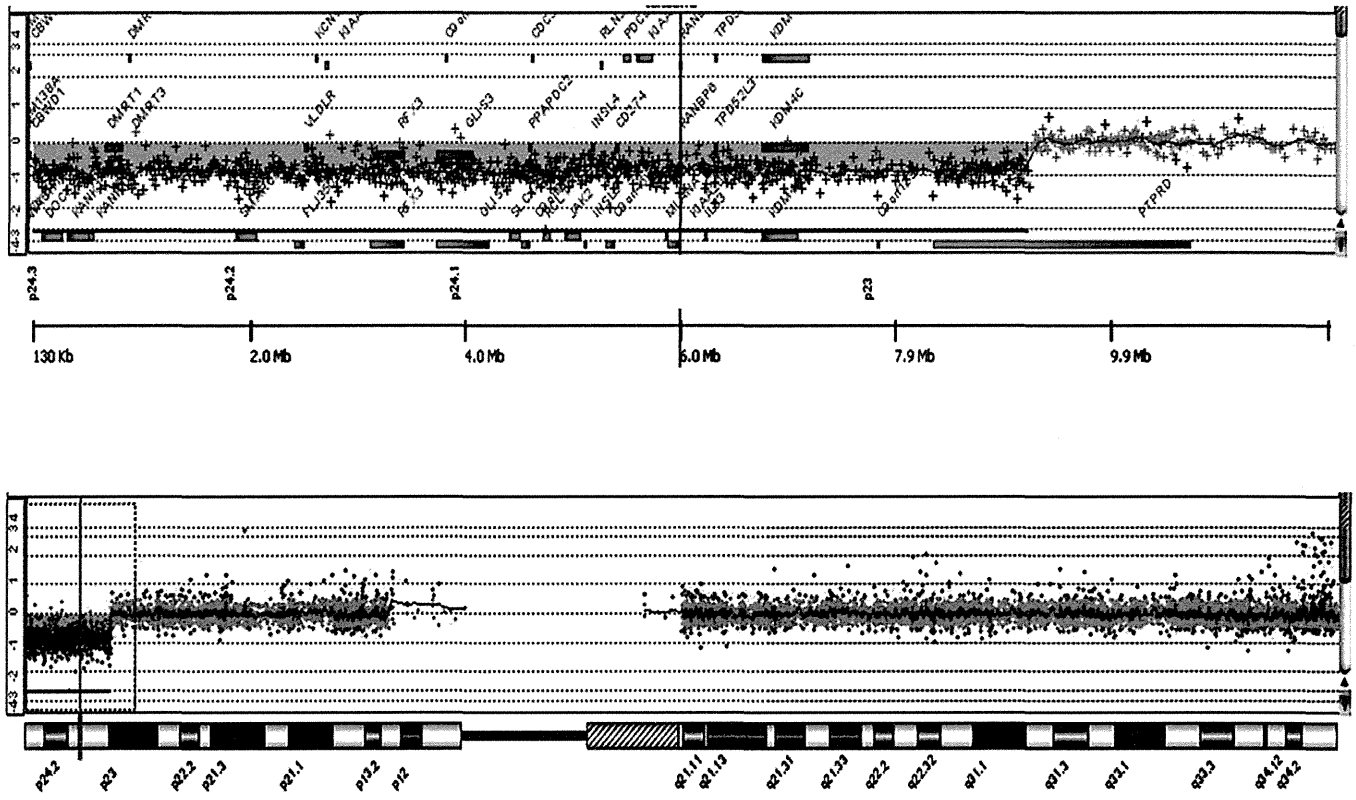

Fig. 3 Oligonucleotide array-CGH result of the patient. Whole chromosome view (lower) and close view (upper) of chromosome 9. Note a loss of 9.17 Mb of the terminal region of chromosome 9p.

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

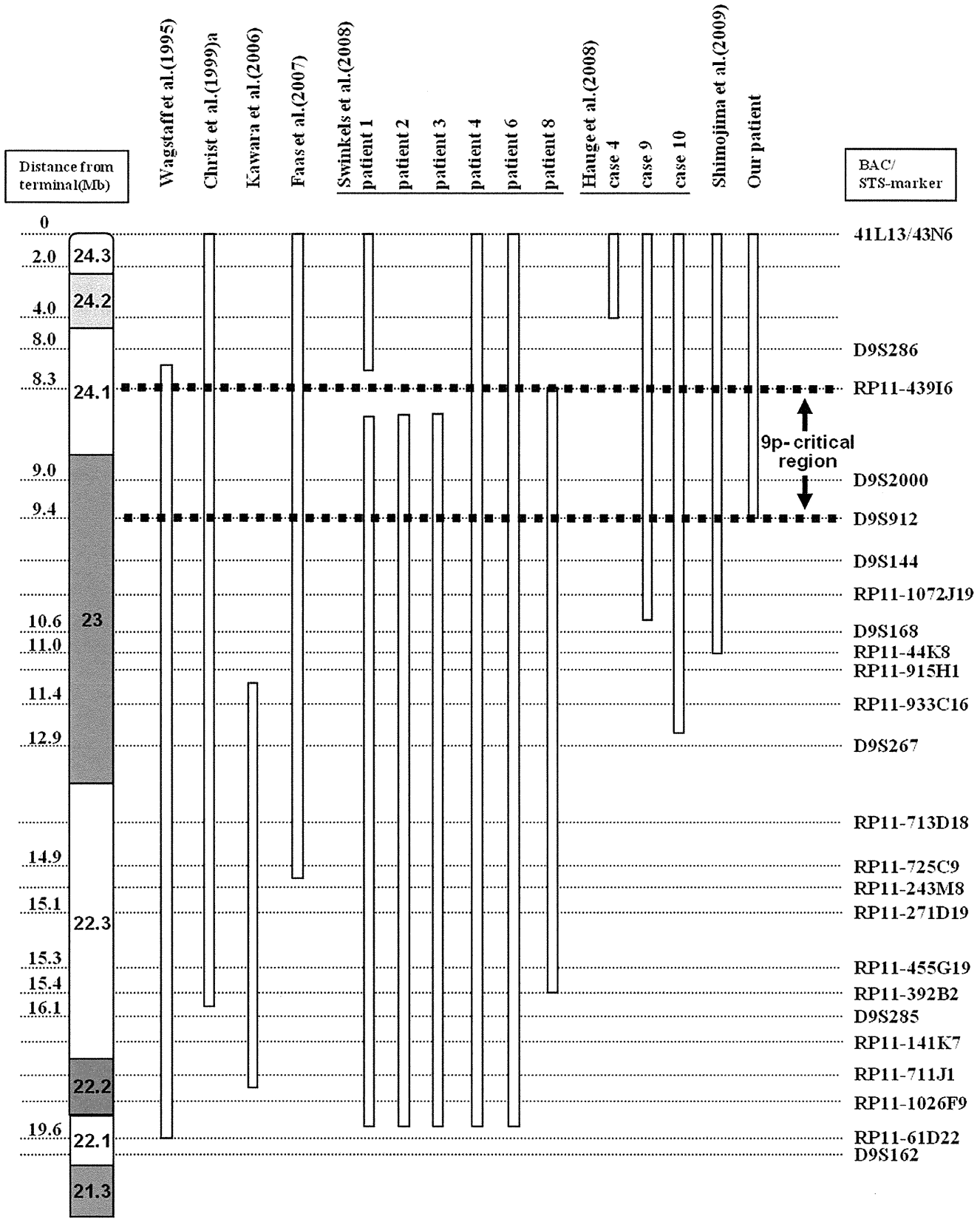

Fig. 4 Schematic map of the 9p deletion of reported cases of 9p monosomy, including the present case, evaluated using molecular analyses such as fluoresence in situ hybridization (FISH) and/or array comparative genomic hybridization. Open bars represent the presumed maximum extent of the deletion in 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.

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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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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. © 2013 Wiley Periodicals, Inc.

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

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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.

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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		+	−	−	−	−	+	−