TABLE I. Clinical Symptoms in MFS55 and His Father

Symptom	MFS55	Father
Craniosynostosis	−	—
Hypertelorism	+	—
Enophthalmos	+	—
Cleft palate/bifid uvula	+	+
Malar hypoplasia	+	
Blue sclera	+	±
Ectopia lentis	−	—
Strabismus	bil.	—
Arachnodactyly	−	—
Dolichostenomelia	−	—
Pectus deformity	−	—
Scoliosis	+	—
Talipes varus	+	
Pes planus	+ (bil.)	
Camptodactyly	+ (bil. thumb)	—
Joint laxity	+	
Aortic root aneurysm	+	—
Aortic root dilatation	+	—
Arterial tortuosity	+	
Hypoplasia of arteries	+ (bil. subclavian and bil. vertebral)	
Aneurysm of other vessels	−	
Patent ductus arteriosus	−	—
Atrial septal defect	−	—
VSD	+ (double committed type, operated)	—
Bicuspid aortic valve	+	—
Chiari type I	−	
Hydrocephalus	−	
Umbilical hernia	+	
Developmental delay	−	−
MFS criteria	Not fulfilling	Not fulfilling
Others		II–III toes syndactyly, micrognathia, retrognathia, mild protruding lower bite, narrow palate

protruding bite, micrognathia, retrognathia, but a marfanoid habitus and arachnodactyly were not observed (Fig. 1A). Echocardiography indicated normal diameter of aortic annulus and sinus of valsalva. Electrocardiography and plain chest and abdominal X-ray examination did not show any abnormalities. Unfortunately further examination was not permitted.

In the literature describing somatic mosaicism of *FBN1* mutations, a propositus' mother with 43% mutant cells in lympoblasts and 51% mutant cells of fibroblasts showed joint hypermobolity, pes planus and striae distensae over the abdomen and trunk, but no other symptoms in ocular and cardiovascular systems [Montgomery et al., 1998]. Another patient's father with somatic mosaicism in blood leukocytes presented with only discreet dilatation of the ascending aorta and minimal aortic regurgitation [Collod-Beroud et al., 1999]. In the third family, the father with somatic mosaicism detected at least in his blood, saliva and semen did not show any MFS symptoms [Tekin et al., 2007]. All mosaic cases had only trace of MFS features and were apparently healthy regardless of their children with full MFS or severe neonatal MFS due to an inherited germline mutation. As for LDS, somatic mosaicism of a *TGFBR2* mutation (R537G) in a father was only briefly mentioned [Loeys et al., 2006]. The father required aortic root replacement with no craniofacial manifestations. His son showed typical LDS with the heterozygous mutation. No details of the somatic mosaicism were described. The father reported here

TABLE II. Result of Mosaic Assay

Case	Tissue	A/G allele ratio (mean ± SD)	Cells with a mutation (%)
MFS55	Blood leukocytes	1.0 ± 0.032	100
Mother	Blood leukocytes	0	0
Father	Blood leukocytes	0.35 ± 0.027	52
	Buccal cells	0.14 ± 0.010	25
	Hair follicle cells	0	0
	Nail tissues	0.21 ± 0.033	35

Ratio (%) of cells with a mutation is calculated by 200R/(1 + R). R: mean of A/G ratio.

currently does not present with any obvious vascular features of LDS, but may need careful medical attention in the future.

In conclusion, this is the first clear description of paternal somatic mosaicism of a *TGFBR2* mutation. No major symptoms were recognized in the father. The information described was quite useful for the counseling of this family including the father.

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Bilateral Perisylvian Polymicrogyria, Periventricular Nodular Heterotopia, and Left Ventricular Noncompaction in a Girl With 10.5–11.1 Mb Terminal Deletion of 1p36

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Monosomy 1p36 is a common subtelomeric microdeletion syndrome, characterized by craniofacial dysmorphisms, developmental delay, mental retardation, hypotonia, epilepsy, cardiovascular complications, and hearing impairment; deleted regions have been mapped within 10.0 Mb from the telomere in most documented cases. We report on a girl with a 10.5–11.1 Mb terminal deletion of 1p36 shown by fluorescence in situ hybridization (FISH). She had three distinct structural abnormalities: bilateral perisylvian polymicrogyria, periventricular nodular heterotopia, and left ventricular noncompaction. She died in early infancy with intractable epilepsy, progressive congestive heart failure and pulmonary hypertension. To date, this is the first case with monosomy 1p36, complicated by this combination of manifestations; she is also the first who had possibly a simple terminal deletion of 1p36 and died in early infancy. An atypically large deletion in this patient might be the basis for the development of these features and the severe clinical course. © 2008 Wiley-Liss, Inc.

Key words: monosomy 1p36; perisylvian polymicrogyria; periventricular nodular heterotopia; left ventricular noncompaction; FISH; candidate gene

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INTRODUCTION

Monosomy 1p36 is a recently recognized disorder, considered to be the most common subtelomeric microdeletion syndrome, with an estimated incidence of 1 in 5,000 [Heilstedt et al., 2003a] to 1 in 10,000 newborns [Shapira et al., 1997]. It is characterized by craniofacial characteristics including large anterior fontanel, microcephaly, brachycephaly, thickened ear helices, deep-set eyes, straight eyebrows, midface hypoplasia, flat nasal bridge, and pointed chin; neurological abnormalities including developmental delay, mental retardation, hypotonia, and epilepsy; cardiovascular complications including septal defects, patent ductus arteriosus, and dilated cardiomyopathy. Additionally there is hearing impairment, which is primarily high frequency sensorineural hearing loss [Slavotinek et al., 1999; Battaglia, 2005; Gajecka et al., 2007; Battaglia et al., 2008]. Chromosomal abnormalities in the

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syndrome include pure terminal deletions (52–67.2%), interstitial deletions (9.7–29%), derivative chromosomes (7–16.4%), and more complex rearrangements involving 1p36 (6.7–12%) [Heilstedt et al., 2003b; Gajecka et al., 2007]. Although deletion sizes range widely from 0.5 to >10.5 Mb, breakpoints cluster 3.0–5.0 Mb from the telomere (40%) and are localized within 10.0 Mb in 80% of the cases [Heilstedt et al., 2003b]. Haploinsufficiency of genes in deleted regions is postulated to cause various features of the disorder. To date, several candidate genes have been suggested; *KCNAB2* for epilepsy [Heilstedt et al., 2001], *SKI* for cleft lip/palate [Colmenares et al., 2002], *MMP23* for cranial suture closure [Gajecka et al., 2005], and *GABRD* for neuropsychiatric and neurodevelopmental abnormalities [Windpassinger et al., 2002]. On the other hand, the presence of a number of observed clinical features has had no correlation to the deletion size [Gajecka et al., 2007].

Here, we report on a girl with an atypically large 10.5 to 11.1 Mb terminal deletion of 1p36 demonstrated by FISH analysis, who had distinct structural abnormalities including bilateral perisylvian polymicrogyria, periventricular nodular heterotopia, and left ventricular noncompaction, and who died in early infancy.

CLINICAL REPORT

The patient, a girl, was the second child of a healthy 33-year-old mother (gravida 2, para 1) and a healthy 33-year-old nonconsanguineous father. Her sister was healthy. A fetal echocardiography showed an enlargement of the right atrium and narrowing of the right ventricle. She was delivered by spontaneous vaginal delivery at 38 weeks and 2 days of gestation. Birth weight was 2,140 g (−2.4 SD), length 48.5 cm (−0.1 SD), and OFC 30.5 cm (−1.5 SD). Apgar score was 8 both at 1 and 5 min. She showed hypotonia, tachycardia, tachypnea, and feeding difficulty, and was admitted to the neonatal intensive care unit.

Echocardiography detected two ventricular septal defects (membranous and muscular), patent ductus arteriosus, Ebstein anomaly with moderate tricuspid valve regurgitation, and left ventricular noncompaction (Fig. 1B). She had congestive heart failure and pulmonary hypertension. In spite of a treatment by furosemide and potassium canrenoate, ventricular function deteriorated gradually and pulmonary hypertension progressed.

She developed clonic seizures at age 3 days. Antiepileptic drugs (phenobarbital, valproate, carbamazepine, and lidocaine) could not control the epileptic attacks. An electroencephalography did not show significant spikes, but the background activity seemed premature for her age. A brain magnetic resonance imaging (MRI) demonstrated bilateral perisylvian polymicrogyria and periventricular nodular heterotopia (Fig. 1C). She passed newborn hearing screening (the threshold 35 dB).

When seen by us at age 27 days, she had a round face with short palpebral fissures, a depressed nasal bridge, a small mouth, a high arched palate, micro/retrognathia, and low set ears (Fig. 1A). At age 48 days, she expired with sudden cardiopulmonary arrest after feeding. An intensive resuscitation was not effective. Postmortem examinations were not performed.

MOLECULAR CYTOGENETIC INVESTIGATIONS

G-banding chromosome analysis on peripheral blood lymphocytes of the patient showed a terminal deletion of the short arm of chromosome 1, designated as 46,XX,del(1)(p36.3) (Fig. 2A). The deletion was confirmed by FISH analysis using a subtelomeric probe for 1p (ToTelVysion probe) (VYSIS, Downers Grove, IL) (data not shown). Duplication of a subtelomeric region of 1qter or other chromosomes at 1pter was excluded through all subtelomere screening using the ToTelVysion Multicolor FISH probe Panel (VYSIS) (data not shown). The parents had normal karyotypes.

To determine the extent of deletion in the 1p36 region, FISH analysis was performed using 10 BAC clones mapped to 1p36.2-p36.3 (RP11-671C15, RP11-33M12, RP11-60J11, RP11-476D13, RP11-199O1, RP11-829B14, RP11-1144L24, RP11-426M1, RP11-90N5, RP11-169K16) (Fig. 3). The deletion breakpoint was found to be localized between RP11-199O1 (10.5 Mb from the 1p telomere) and RP11-829B14 (11.1 Mb) (Fig. 2B).

DISCUSSION

The patient we have described with monosomy 1p36, suffered from progressive congestive heart failure and pulmonary hypertension, and intractable convulsions, resulting in early death. She had three distinct structural abnormalities: bilateral perisylvian polymicrogyria, periventricular nodular heterotopia, and left ventricular noncompaction. Molecular cytogenetic investigations excluded a subtelomeric rearrangement involving 1p36, and demonstrated that the deletion size was 10.5–11.1 Mb, larger than most documented cases. Haploinsufficiency of genes in this atypically large deleted segment might cause her distinct clinical characteristics. Coexistence of a non-subtelomeric complex chromosomal imbalance could not be excluded because an array-CGH analysis was not performed in the absence of a cell line or genomic DNA.

Polymicrogyria is a malformation of cortical development in which the brain surface is irregular and the normal gyral pattern replaced by multiple small, partly fused gyri separated by shallow sulci. It is

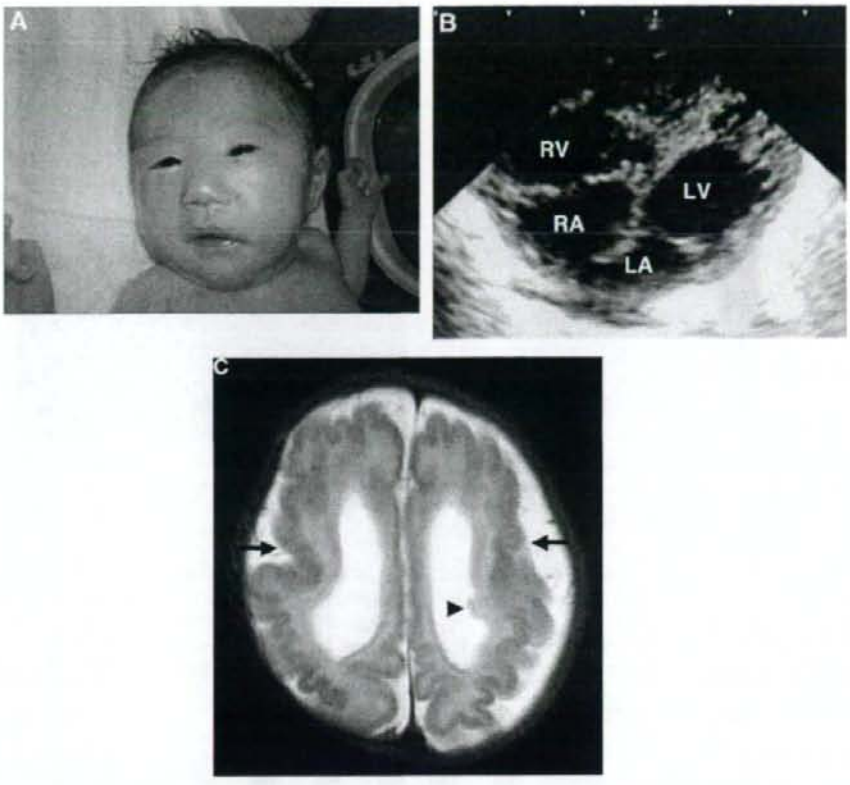

FIG. 1. **A**: Patient at age 27 days. **B**: A four-chamber view echocardiogram. Numerous prominent trabeculations and intertrabecular recesses in the apex and free wall of the left ventricle indicate left ventricular noncompaction. Apical displacement of the septal leaflet of the tricuspid valve from insertion of the anterior leaflet of the mitral valve indicate Ebstein's anomaly. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. **C**: A T2-weighted axial magnetic resonance image. Bilateral perisylvian polymicrogyria is shown as irregularly small and fused gyri, separated by shallow sulci, and cortical thickness (5 mm) from the perisylvian regions to the frontal lobes (arrows). A periventricular nodular heterotopia is shown as a lesion protruding from the wall of the left lateral ventricle with isointensity as gray matter (an arrowhead). Bilateral ventricles are enlarged. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

classified into malformations due to abnormal cortical organization according to the revised classification for malformations of cortical development, and the most common type is centered in the perisylvian regions [Barkovich et al., 2005]. Various causes of polymicrogyria have been proposed; including extrinsic effects such as disruption of the fetal vascular supply and genetic factors suggested by familial cases (autosomal dominant, autosomal recessive, or X-linked inheritance) and associated chromosomal abnormalities (deletions of 1p36, 1q44, 9p24pter, 13q14.1q31.2, and 22q11.2; duplications of 11q12q13 and 22q11.2) or congenital malformation syndromes (Adams-Oliver syndrome, Aicardi syndrome, Shprintzen-Goldberg syndrome, MICRO syndrome, and oculo-cerebro-cutaneous syndrome) [Robin et al., 2006]. Roll et al. [2006] identified a missense mutation within the first sushi domain of the *SRPX2* gene (Xq28) in a male patient with rolandic seizures and bilaretal posterior perisylvian polymicrogyria and his female relatives with mild mental retardation or unaffected carrier status. They also found another missense mutation in *SRPX2* in affected members of a 3-generation French family with rolandic seizures, oral and speech dyspraxia, and mental retardation. Robin et al. [2006] reviewed 32 patients with deletion 22q11.2 and polymicrogyria, and found that the cortical malformation consisted of perisylvian polymicrogyria with variable severity and frequent asymmetry (predisposition for the right hemisphere). They proposed that polymicrogyria in deletion 22q11.2 might be a sequela of abnormal embryonic vascular development (due to haploinsufficiency of a gene expressed in vascular tissue perfusing an embryonic brain), rather than a primary brain malformation (due to haploinsufficiency of a gene expressed in an embryonic brain and regulating

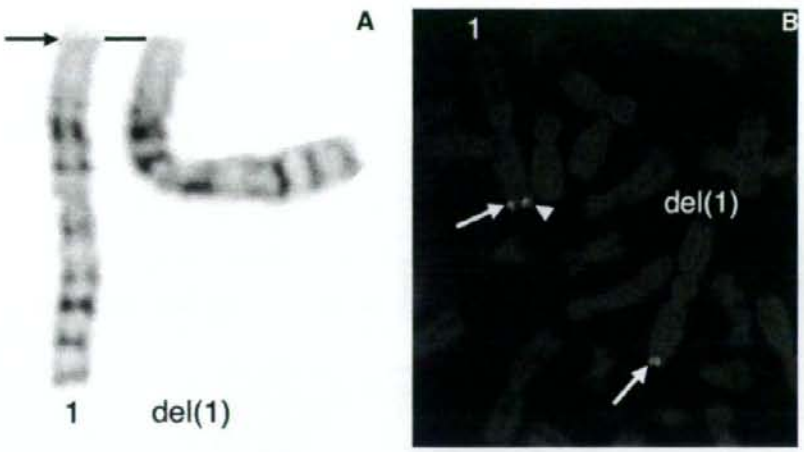

FIG. 2. **A**: G-banded partial karyotype. The breakpoint is indicated on normal chromosome 1 by an arrow. **B**: FISH analysis using clones RP11-199O1 and RP11-829B14. Two signals for the RP11-829B14 probe are observed: one on the normal chromosome 1 and one on the deleted chromosome 1 (arrows, green). One signal for the RP11-199O1 probe is observed on the normal chromosome 1 (arrowhead, orange), but none on the deleted chromosome 1. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

cortical development). Although polymicrogyria seems to be an occasional malformation in monosomy 1p36 (4/9 in unpublished data by Dobyns [Robin et al., 2006]; 10/50 in a review by Gajecka et al. [2007]), neither detailed clinical reports nor deletion mapping of these cases have been published. Ribeiro et al. [2007] reported on a girl with bilateral symmetrical perisylvian polymicrogyria and a terminal deletion of 1p accompanied by a terminal duplication of 1q designated as

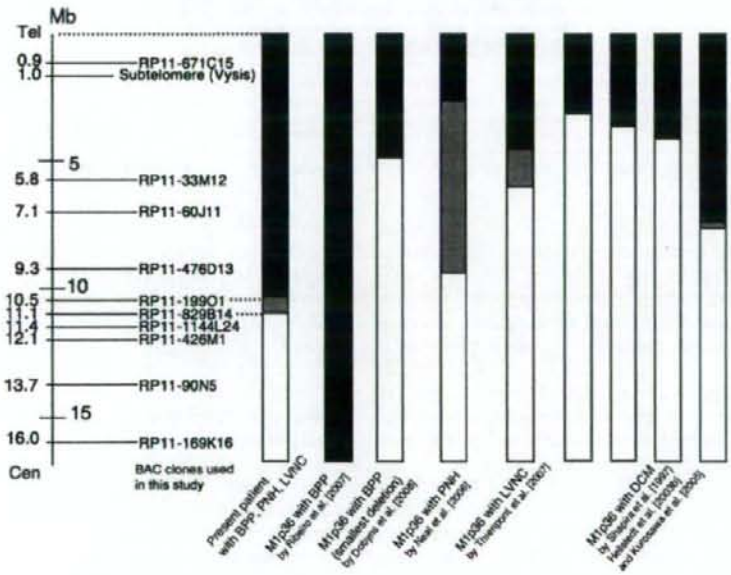

FIG. 3. Deletion maps of the 1p36.21-p36.33 region. The black areas denote the monosomic regions and the white areas the disomic regions. The gray areas denote the dosage unknown regions where the breakpoints should exist [Shapira et al., 1997; Heilstedt et al., 2003b; Kurosawa et al., 2005; Neal et al., 2006; Ribeiro et al., 2007; Thienpont et al., 2007; Dobyns et al., 2008]. BPP, bilateral perisylvian polymicrogyria; PNH, periventricular nodular heterotopia; LVNC, left ventricular noncompaction; DCM, dilated cardiomyopathy; M1p36, monosomy 1p36.

46,XX,der(1)(qter → p36.13::q42.3 → qter) (Fig. 3). She had a mild facial dysmorphism, macrocephaly, and small muscular ventricular septal defects. She also showed axial hypotonia, facial diplegia, visual impairment with nystagmus, focal motor epilepsy controlled by sodium valproate, and severe developmental delay. Recently, Dobyns et al. [2008] reported a large series of patients with polymicrogyria associated with structural chromosomal rearrangements, demonstrating 1p36.3, 2p16.1-p23, 4q21.21-q22.1, 6q26-q27, and 21q21.3-q22.2 as polymicrogyria loci with incomplete penetrance and variable expressivity. The deletion sizes of 13 patients with monosomy 1p36 ranged from 4.8 to 10.9 Mb (Fig. 3), and none of eight patients with interstitial deletions retaining the distal 1 Mb had polymicrogyria. Dobyns et al. [2008] hypothesized that a candidate gene might be localized between 1.0 and 4.8 Mb from the telomere. Also, they observed a right-dominant asymmetry resembling polymicrogyria associated with deletion 22q11.2, suggesting a common pathology leading to polymicrogyria in both disorders.

Periventricular nodular heterotopia (PNH) is a malformation of cortical development characterized by the ectopic localization of neuronal nodules along the lateral ventricle, and is classified into malformations due to abnormal neuronal migration [Barkovich et al., 2005]. Mutations in *FLNA* (Xq28) cause X-linked periventricular nodular heterotopia both in females and males [Fox et al., 1998; Sheen et al., 2001]. A rare recessive form of this malformation with microcephaly is caused by mutations in the *ARFGEF2* gene [Sheen et al., 2004]. Recently, Neal et al. [2006] reported the first patient with the malformation and a 1p36.22pter deletion. The patient was a 3-year-old female with mild facial dysmorphism, a short 5th finger, overriding toes, and scoliosis. She showed severe developmental delay, hypotonia, Duane anomaly, and hearing loss. MRI revealed several periventricular nodular heterotopia along the left lateral ventricle, truncation of the rostrum of the corpus callosum, mild ventricular enlargement, and delayed myelination in the periventricular and subcortical white matter. A terminal deletion of 1p was shown through FISH analysis using a 1p subtelomeric probe (200 kb from the 1p telomeric end) and a probe for D1Z2 midi-satellite repeats (2.3 Mb). A loss of heterozygosity observed between microsatellite markers D1S468 (3.6 Mb) and D1S450 (9.6 Mb) suggested that the deleted region spanned, at most, 9.6 Mb. Whole subtelomere screening by FISH excluded subtelomeric chromosomal rearrangement involving 1p. Sequencing of the *FLNA* gene did not reveal any mutations in the coding region. Our findings would support a candidate gene for PNV localized within the deleted region (from 1pter to 3.6–9.6 Mb) of the patient reported by Neal et al. [2006] (Fig. 3).

Left ventricular noncompaction is an cardiomyopathy characterized by the persistence of numerous excessively prominent ventricular trabeculations and deep intertrabecular recesses, and the etiology is postulated to be caused by an arrest of the normal process of intrauterine endomyocardial morphogenesis [Finsterer et al., 2006; Xing et al., 2006]. This disorder is genetically heterogenous. Mutations in the genes encoding *DTNA* (18q12.1-q12.2), *TAZ* (G4.5) (Xq28), and *LDB3*/Cypher/ZASP (10q22.2-q23.3) have been identified in patients with this condition [Ichida et al., 2001; Chen et al., 2002; Vatta et al., 2003; Kenton et al., 2004; Xing et al., 2006]. It has been described in association with various neuromuscular disorders including dystrophinopathy (caused by mutations in *DMD*), dystrobrevinopathy (*DTNA*), laminopathy (*LMNA*), zaspopathy (*ZASP*), myotonic dystrophy type 1 (*DMPK*), infantile glycogenosis type II (Pompe disease) (*GAA*), myoadenylate-deaminase deficiency (*AMPD1*), several mitochondrial disorders, Barth syndrome (*TAZ*), Friedreich ataxia (Frataxin), and Charcot-Marie-Tooth disease (*PMP22*) [Finsterer et al., 2006]. It has also been described in association with non-neuromuscular genetic disorders including Ohtahara syndrome, Roifman syndrome, Noonan syndrome, Nail-Patella syndrome, Melnick needles syndrome, MIDAS syndrome, congenital adrenal hyperplasia, and several chromosomal abnormalities (Turner syndrome; deletions of 22q11.2, 5q35qter, and 1q43; a deletion of 1q43qter with a duplication of 4q31qter, and trisomy 13) [Finsterer et al., 2006; Kanemoto et al., 2006]. Mutations in *TAZ* [D'Adamo et al., 1997] and *LDB3* [Vatta et al., 2003] have also been shown to cause dilated cardiomyopathy. Dilated cardiomyopathy during infancy has been observed in 23% of patients with monosomy 1p36 [Heilstedt et al., 2003b]. In a report by Kurosawa et al. [2005], two patients with a 3.5 Mb and a 2.7 Mb deletion each had dilated cardiomyopathy without any congenital heart defects; whereas the other nine patients with a 2.5 to >8 Mb deletion, six of whom had congenital heart defects, did not have dilated cardiomyopathy. Shapira et al. [1997] and Heilstedt et al. [2003b] reported on two patients with a 4.15 Mb and a 7.26–7.50 Mb deletion respectively who each had dilated cardiomyopathy. Thienpont et al. [2007] reported the first patient with left ventricular noncompaction and monosomy 1p36. She also had multiple small muscular ventricular septal defects, which closed spontaneously by age 5 months. In the neonatal period, she showed mild hypocontractility with a fractional shortening of 25%, which progressed at age 2 months with left ventricular dilatation and a lower fractional shortening (13%). Cardiac dysfunction improved with the administration of digoxin, diuretics, lisinopril, and carvedilol. An array-CGH analysis at 1 Mb resolution showed a deletion of the terminal 4.6–5.9 Mb of 1p36 (Fig. 3).

Based on the data by Thienpont et al. and our patient and considering only the patients with left ventricular noncompaction, a candidate gene for this disorder might be localized within a region from 1p36ter to 4.6–5.9 Mb (Fig. 3). Hypothesizing that dilated cardiomyopathy and left ventricular noncompaction could have the same etiology in patients with monosomy 1p36, the candidate gene might be localized within 2.7 Mb from 1p36ter (Fig. 3). A recent large series of monosomy 1p36 by Battaglia et al. [2008] showed that 11/48 (23%) had noncomapction cardiomyopathy and 2/48 (4%) had dilated cardiomyopathy. To uncover the etiology of cardiomyopathy in monosomy 1p36, it might be meaningful to compare the two different large patient series [Heilstedt et al., 2003b; Battaglia et al., 2008] with difference ratios of non compaction-type and dilated type, in relation to ages of detection, clinical courses, and extent of deleted regions.

There have been few reports of patients with monosomy 1p36 and early death. Out of 39 patients reviewed by Slavotinek et al. [1999], there were three deaths in early infancy. A boy, originally reported by Howard and Porteus [1990], had an interstitial deletion of 1p34.1p36.1. A girl and a boy, originally reported by Hain et al. [1980], had both a deletion of 1p36pter and a deletion of 15pterq11, derived from a maternal balanced translocation. Structural heart defects were detected in 43% of patients with monosomy 1p36 in a series by Heilstedt et al. [2003b]. The most frequent defect was patent ductus arteriosus (17%), and a complex defect (Epstein anomaly) was detected only in one patient. Dilated cardiomyopathy, detected in 23% in infancy, did not worsen in any of the patients, although three of them continued medication at the time of the evaluation. Epilepsy, requiring regular anticonvulsant medications, was detected in 48% [Heilstedt et al., 2003b]. It was usually well controlled by the medications [Battaglia, 2005; Battaglia et al., 2008], but could frequently become intractable as reported in a series by Kurosawa et al. [2005] (6/11 patients needed combination therapy of anticonvulsant drugs). Feeding problems were documented in 63% in infancy (poor suck and swallow, reflux, and vomiting) and 72% had oropharyngeal dysphagia [Heilstedt et al., 2003b]. In the present patient, progressive congestive heart failure and pulmonary hypertension, resulting from complex heart defects including Epstein anomaly and left ventricular noncompaction, and intractable epilepsy appear to be the underlying factors that lead to the patient's death. The direct cause of death (sudden cardiopulmonary arrest after feeding) might be related to acute worsening of pulmonary hypertension (pulmonary hypertension crisis) or status epilepticus, triggered by milk aspiration resulting from possible oropharyngeal dysfunction.

In conclusion, the present patient is the first case with monosomy 1p36 complicated by three distinct structural abnormalities: bilateral perisylvian polymicrogyria, periventricular nodular heterotopia, and left ventricular noncompaction and is also the first that had a simple terminal deletion of 1p36 and died in early infancy. A 10.5–11.1 Mb deletion, which was detected through FISH analysis and larger than most documented cases, would be related to development of this combination of manifestations and the serious clinical course.

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Research Letter

Pre- and Postnatal Overgrowth in a Patient With Proximal 4p Deletion

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To the Editor:

Terminal and interstitial deletions encompassing 4p16 result in Wolf–Hirschhorn syndrome (WHS) and the Pitt-Rogers-Danks syndrome (PRDS) [Wright et al., 1998]. A more proximal, interstitial deletion involving p16.1-p14 shows a distinct clinical entity without overlapping features with WHS and/or PRDS, and is characterized by long face, upslanting palpebral fissures, epicanthal folds, large lax lips, high-arched palate, micrognathia, prominent nose, tall and thin body habitus, broad hands and feet, and varying degrees of mental retardation [White et al., 1995; Tonk et al., 2003]. At least 22 cases of 4p16.1–p12 deletion have been reported [reviewed by Tonk et al., 2003], 17 of whom had a 4p16.1–p14 deletion with a common clinical profile [Romain et al., 1985; Fryns et al., 1989; Davies et al., 1990; Ishikawa et al., 1990; Chitayat et al., 1995; White et al., 1995; Innes et al., 1999; Tonk et al., 2003] (Table I). Here we report a girl with mental retardation, overgrowth and mild facial anomalies, who has a de novo 46,XX,del(4)(p16.1p15.2). A well-proportioned overgrowth pattern in our patient seems distinctive in comparison to reported features of patients with the proximal 4p deletion syndrome.

The patient, a 24-year-old female Han Chinese, was born at full-term to a 26-year-old G1P1 mother who reported an unremarkable pregnancy and nondiabetic history. Consanguinity of the parents was denied. Family history was negative for tall habitus: the body weight/height of her father, mother and a sister was 67 kg/175 cm, 49 kg/165 cm, and 43 kg/160 cm, respectively. Birth weight of the patient was 3,550 g (75th centile), length 61 cm (>97th centile) and OFC 37 cm (>97th centile). She has always been taller than the Chinese age-cohorts since birth. She raised her head at age 6 months, spoke at 15 months and walked at 3 years. She was diagnosed in her early childhood to have mental retardation by a local pediatrician and never attended school except for kindergarten. She has been able to care for herself since she was a teenager. On physical examination at age 23 years, her height was 181 cm (>97th centile), weight 74 kg (>97th centile) and OFC 58 cm, facial length 19 cm, and she had the following facial abnormalities: square-jawed face, epicanthal folds, prominent nose with overhanging tip, short philtrum, high-arched palate and hypoplastic earlobes (Fig. 1a,b). She has a tall, thickset and proportionate habitus without broad hands and feet. Her carpal bone age was advanced during her childhood and adolescence, but the recent radiographic findings at age 24 years were normal. Her first menstruation appeared at age 12 years, then it came regularly, and her secondary sexual characteristics developed normally. Psychometric testing showed moderate mental retardation with estimated IQ of 50, with poorer performance in calculations. Clinical manifestations of the patient including her facial gestalt did not fit to those for any of generalized overgrowth syndromes, such

Lingqian Wu and Zhigao Long contributed equally to this work.

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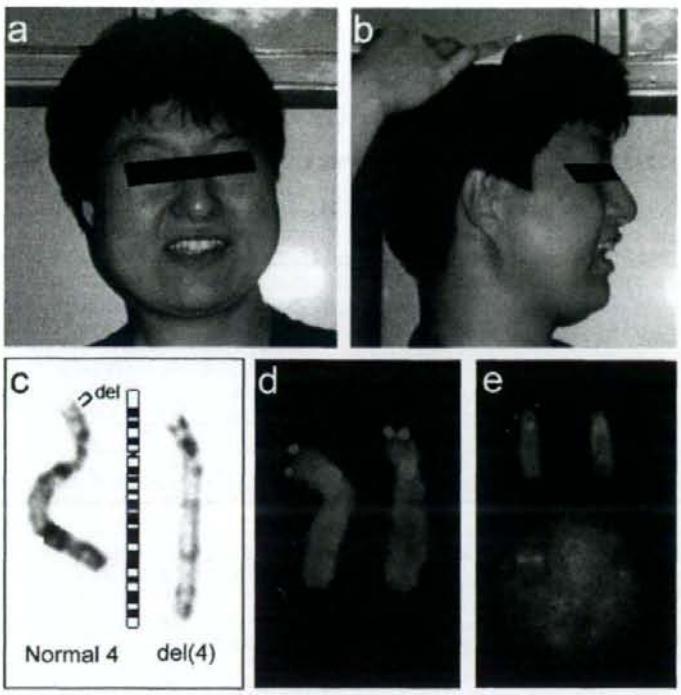

FIG. 1. A girl with a proximal 4p deletion. **a,b**: Facial appearance at age 23 years, showing well-developed, square-jawed face with hypoplastic earlobe. **c**: GTG-banded partial karyotype, showing del(4)(p16.1p15.2). **d,e**: FISH analysis using a BAC clone RP11-1150D2, showing signals in both normal and derivative chromosomes 4, and using a BAC clone RP11-29N16, showing a signal only in normal 4p and only one signal in an interphase cell.

as Weaver, Sotos, Simpson-Golabi-Behmel, Seip-Berardinelli, Perlman, Nevo, MOMO, Marshall-Smith, Beckwith-Wiedemann or Bannayan-Riley-Ruvalcaba syndromes [Douglas et al., 2003]. Thus, it is most likely that her overgrowth is constitutional and associated with a chromosomal deletion below.

High-resolution GTL-banding showed a 46,XX, del(4)(p16.1p15.2) karyotype (Fig. 1c). Fluorescence in situ hybridization (FISH) analysis with 11 BAC clones mapped to 4pter–4p14 [Kondoh et al., 2003] revealed that GS-36p21, RP11-1150D2 (Fig. 1d), 261G12 and 24K3 were retained, but RP11-29N16 (Fig. 1e), 77N9, 46O17, 79N22, 116N19, 192P23, and 106M4 were deleted. These results indicated that the WHS critical region is not deleted and that the proximal and distal deletion breakpoints are located in the regions between UCSC coordinate chromosome 4 nucleotide 24,549,727 and 24,551,523 and between nucleotide 6,504,169 and 6,504,249, respectively. Therefore, the deletion is assigned to an 18-Mb region (nt. 6,504,169–24,551,523) at 4p16.1–p15.2. The karyotypes of her father, mother and sister were normal.

Chitayat et al. [1995] reported three cases of the proximal 4p deletion syndrome and proposed 4p15.33–p15.2 as the minimal deleted segment for this syndrome, which was later supported by Innes et al. [1999]. However, our patient has a deletion encompassing the 4p16.1–p15.2 region, and there have been five reported cases of a deletion similar to our patients [Davies et al., 1990; White et al., 1995; Innes et al., 1999; Tonk et al., 2003]. All of these five cases shared several clinical features that include a long face, epicanthal folds, distinctive nose, thick lower lip, tall and thin habitus and moderate mental retardation. Thus, Tonk et al. [2003] suggested that the critical region for the proximal 4p deletion syndrome can be narrowed to a region from 4p16.1 to p15.2. As all reported cases that had a 4p16.1–p15.1 deletion manifested all typical features of this syndrome (Table I), the critical region should be confined to 4p16.1–p15.1. By a review of breakpoints of 4p16.1–p14 deletions in reported patients (Table I), we found that the tall habitus is most likely attributed to 4p16.1–p15.32 deletion, probably implying the presence of a negative control mechanism against tall status or overgrowth.

Overgrowth and other features in our patient merit comments. According to the information from Table II, 82% (14/17) of patients with a 4p16.1–p14

TABLE 1. Clinical Features of 18 Reported Cases of 4p16.1–4p14 Deletion

	Reported patients with deletion [references]							
	4p16.1–p15.2, present case	4p16.1–p15.2, 5 cases [1–4]	4p16.1–p15.1, 4 cases [2]	4p16.1–p14, 1 case [2]	4p15.33–15.2, 3 cases [5,6]	4p15.32–p14, 2 cases [2,7]	4p15.32–p15.2, 1 case [8]	4p15.2–14, 1 case [5]
Long face	–	+ + – + –	+ + + +	+	+ + +	+ –	?	+
Upslanted fissures	–	+ + ? + –	+ + + +	+	– ? ?	+ +	?	?
Epicanthal folds	+	+ + ? + –	+ + + +	+ +	– + –	+ +	–	+
Distinctive nose	+	+ + – – –	+ + + +	+ +	– – +	– –	?	–
High or cleft palate	+	– – ? + –	+ + + +	+ +	– + +	– –	+	+
Thick lower lip	–	+ + ?+ +	+ + + +	+ +	– + +	– +	+	–
Micrognathia	– (macrognathia)	– – – + –	+ + + +	+ +	– + +	+ –	+	+
Broad, short neck	–	– – – + –	–	+ +	– ? ?	– +	?	?
Broad hands and feet	–	– – ? + –	+ + + +	+ +	– + –	– –	?	+
Tall, thin habitus	Tall but symmetric	+ + + + +	+ + + +	+ +	+ – +	+ +	–	–
Mental retardation								
Mild	–	+ +	–	–	+	–	+	
Moderate	+	+ +	+ + + +	–	+ +	+ +		+
Severe	–	+ –	+	–	–			

1, White et al. [1995]; 2, Tonk et al. [2003]; 3, Innes et al. [1999]; 4, Davies et al. [1990]; 5, Chitayat et al. [1995]; 6, Romain et al. [1985]; 7, Fryns et al. [1989]; 8, Ishikawa et al. [1990]. ?, no available data.

deletion had a tall, thin stature, while the habitus of our patient was tall and well-proportioned, rather than thin, and began prenatally. In addition, her face was not long but her jaw was well developed. These features seem distinctive among the reported manifestations for the proximal 4p deletion syndrome, and might be attributed to possibly different extent of deletion between our and other patients with del(4)(p16.1p15.2), although our findings remain inconclusive as this is a single case and a possible role of genetic background within the family cannot be ruled out. Based on a familial transmission and reproductive fitness of the syndrome reported previously, as well as a possible reproductive capacity in our patient, we must exercise a caution when counseling patients with this condition [Tonk et al., 2003].

According to information from the Gene Predictions in the UCSC database, there are several candidate genes in the deleted segment that may explain the overgrowth in the present patient. Among them, the *SLC2A9* and *BAPX1* genes may play a role in the development and survival of chondrocytes in cartilage matrices and in skeletal development, respectively. The *FGFBP1* gene encoding fibroblast growth factor binding protein 1 may have a function similar to that of *FGFR3*, the gene for fibroblast growth factor receptor 3, which regulates endochondral ossification [Deng et al., 1996]. Moreover, the *PPARGC1A* gene (chr4: 23,402,742–23,500,798) that is located near the proximal breakpoint of the 18-Mb deleted region in our patient may involve in regulating cellular cholesterol homoeostasis and development of obesity.

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Patient Report

Mirror duplication of chromosome 21 with complete phenotype of Down syndrome

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Key words Down syndrome, FISH analysis, mirror duplication, pseudo isodicentric chromosome.

The mirror (reverse tandem) duplication of chromosome 21 is a rare chromosomal aberration. Several cases have been described,[1,2] but only a few of them demonstrated chromosome breakpoints in detail using cytogenetic and/or molecular techniques.[2] The Down syndrome critical region (DSCR) is a chromosome 21 segment containing genes responsible for many features of Down syndrome (DS), and is located on 21q22.2–q22.3.[3,4]

We here report a patient with mirror duplication of chromosome 21, whose karyotype was 46,XX, psu idic(21)(q22.3). Clinically, the patient is completely compatible with DS and does not have any finding caused by monosomy for 21q22.3 region.

Case report

The patient, a 2-year-old Japanese girl, was the second of two children of non-consanguineous healthy parents. Her mother and father were 34 and 39 years old, respectively, at the time of her birth. She was born at 38 weeks of gestation at a weight of 3132 g (mean) and length of 49.0 cm (mean). Pregnancy and delivery were uneventful. The patient had hyperbilirubinemia at the age of 3 days, and was given phototherapy for 3 days. Because of heart murmur and her facial expression suggestive of DS, she was referred to Nagasaki University Hospital at the age of 5 days. Because the patient fulfilled more than 13 of 25 items in Jackson's checklist (Table 1),[5] she was clinically diagnosed as DS. Cardio-echography indicated tetralogy of Fallot (TOF), small atrial septal defect, and pulmonary infundibular and valvular stenosis. The patient has been taking diuretics since 22 months of age. When examined at 2 years of age her weight was 11.45 kg (+0.2 SD) and height was 79.9 cm (−1.4 SD), and her total developmental quotient was 60. She did not have complications of Bethlem myopathy or infectious susceptibility. Data from her ordinary biochemical investigations and thyroid hormone examinations were within the normal range.

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Cytogenetic analysis

On chromosome analysis of cultured peripheral blood lymphocytes the karyotype was 46,XX,psu idic(21)(q22.3) (Fig. 1). To validate trisomic/monosomic regions of the abnormal chromosome 21 precisely, we performed fluorescence *in situ* hybridization (FISH) using 12 BAC clones that were mapped to 21q22.2–q22.3

Table 1 Jackson's checklist

	Present patient	Previously reported patients (ref. 2)		
		A	B	C
Brachycephaly	+	+	+	+
Oblique eye fissure	+	+	+	+
Epicanthic eye fold	+	+	+	+
Blepharitis, conjunctivitis	+	ND	ND	ND
Brushfield spots (iris color)	−	−	−	−
Nystagmus	+	−	−	−
Flat nasal bridge	+	+	+	+
Mouth permanently open	−	−	−	−
Abnormal teeth	ND	−	ND	−
Protruding tongue (macroglossia)	+	−	+	−
Furrowed tongue	+		ND	+
High-arched palate	+	+	−	+
Narrow palate	+	+	−	+
Folded ear (right, left)	−/−	−/−	−/+	−/−
Short neck	+	+	+	+
Loose skin of neck	−	ND	−	ND
Short and broad hands	+	+	+	+
Short fifth finger (right, left)	+/+	+/+	−/−	−/−
Incurved fifth finger (right, left)	−/−	+/+	−/−	−/−
Transverse palmar crease (right, left)	−/−	−/−	−/−	−/+
Gap between first and second toes (right, left)	−/−	+/+	+/+	+/+
Congenital heart defect	+(TOF)	−	+(TOF)	+(VSD)
Heart murmur	+	−	+	+
Joint hyperflexibility	−	−	−	+
Muscular hypotonia	+	+	+	+
Total	16	12	12	15

ND, not done; TOF, tetralogy of Fallot; VSD, ventricular septal defect. A, B and C correspond to patients. TY, LI and AL, respectively, in reference 2.

Table 2 Cytogenetic and molecular analysis of idic(21)(q22.3) chromosome

Chromosome	BAC clone name	Gene symbol	Genomic location		Copy number			
			Start	End	Present patient	Previously reported patients (ref. 2)		
						A	B	C
21q22.12		RUNX1	35081968	35182857				
21q22.13		CLDN14	36754790	36760595				
21q22.2	RP11–137J13		39627180	39780344	3			
21q22.2	RP11–419K6		40647060	40865029	3			
21q22.2	RP11–1000A5		41000852	41204567	3			
21q22.3		478D2 (*D21S42*)				3	3	3
21q22.3	RP11–113F1		42507241	42689355	3			
21q22.3		*CBS*	43346371	43369493				
21q22.3		*CRYAA*	43462209	43465982		2	3	3
21q22.3		*CSTB*	44018259	44020687				
21q22.3	RP11–466A11		44000835	44208698	3			
21q22.3	RP11–113I8		44158888	44352211	3			
21q22.3	RP11–867D1		44478890	44695209	3			
21q22.3		*AIRE*	44530190	44542528				
21q22.3		*PFKL*	44544357	44571683		1	2	3
21q22.3	RP11–323F14		44822749	45022308	1			
21q22.3	RP11–53E17		44865246	45041136	1			
21q22.3	RP11–16B19		44958870	45143207	1			
21q22.3		*ITGB2 (CD18)*	45130313	45165232		1	1	3
21q22.3	RP11–581A12		45395635	45584697	1			
21q22.3		*COL6A1*	46226090	46249391		1	1	1
21q22.3		*COL6A2*	46342469	46374147				
21q22.3	RP11–135B17		46756339	46932616	1			
21q22.3		*S100B*	46842958	46849424		1	1	1

A, B and C correspond to patients. TY, LI and AL, respectively.

region (according to Human GenomeBrowser May 2004 version: http://genome.ucsc.edu/cgi-bin/hgGateway?db=hg11; Table 2; Fig. 2). FISH clearly showed that the breakpoint of inverted duplication of the psu idic(21) chromosome was mapped between RP11-867D1 and RP11-323F14. And duplicated and deleted regions were 44.4 Mb and 2.1 Mb in extent, respectively.

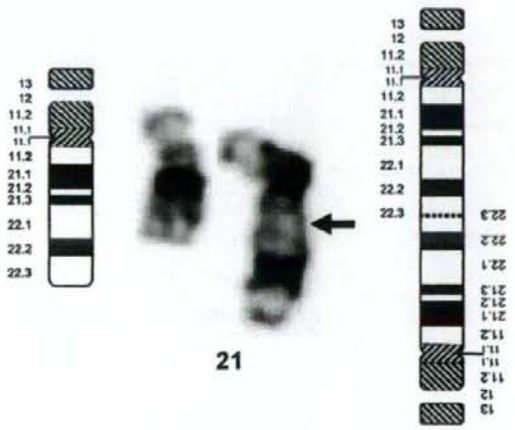

Fig. 1 Chromosome analysis according to G-banding in the present case; 46,XX,psu idic(21)(q22.3).

Discussion

Patients with mirror duplication of chromosome 21 have been infrequently reported. Either a reciprocal translocation or an exchange between the arms of the chromosome or sister chromatids has been postulated to cause such mirror duplication.[2] Unfortunately, chromosome breakpoints were determined in

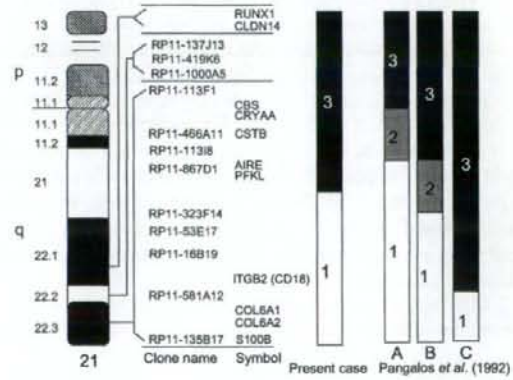

Fig. 2 Cytogenetic and molecular analysis of chromosome 21q of the present patients in comparison to those of the previously reported patients. A, B and C correspond to patients. TY, LI and AL, in reference 2. Numbers in columns at right side indicate copy numbers.

detail in only a few cases. Pangalos *et al.* reported three patients with mirror duplication who had the breakpoints at 21q22.3,[2] as in the present patient. More detailed analysis, however, indicated that chromosome breakpoints were variable among those including the present patient (Table 2; Fig. 2).

The present patient, as well as patient B described by Pangalos *et al.*, had TOF. Barlow *et al.* reported association of the region around the *PFKL* gene on 21q22.3 with TOF.[6] Although the detailed information is not available, similarity of chromosomal organization between the two patients (Table 2; Fig. 2) may confirm the report by Barlow *et al.*

In addition to the present patient, all three patients reported by Pangalos *et al.* were phenotypically DS, and monosomy of distal 21q22.3, ranging from the telomere to *PFKL*, apparently had no significant effect on the expression of DS phenotype. Based on analysis of genotype–phenotype correlation of the present case, the region from RP11-323F14 to RP11-135B17 does not appear to play an important role for the phenotype of DS. Monosomy in the present patient involved three genes: *ITGB2 (CD18)*, *COL6A1*, and *COL6A2* (Fig. 2). The mutations of *ITGB2* gene and *COL6A1*/*COL6A2* gene are responsible for leukocyte adhesion deficiency and Bethlem myopathy, respectively.[7,8] However, since both gene products work as a heterodimer, the monosomic state would not influence the protein structure. Therefore it is not surprising that the present patient lacked symptoms suggestive of infectious susceptibility or myopathy. Likewise, the present patient lacked any other phenotypic feature suggestive of monosomy 21q22.3, such as large ears, high nasal bridge, or retromicrognathia, which have been described in other reports.[9]

As discussed here, mirror duplication of chromosome 21 can provide an opportunity to precisely determine phenotype–genotype correlation. Further accumulation of these cases and detailed cytogenetic and molecular analysis are warranted.

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Early View (Articles online in advance of print)

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Research Letter

Prenatal diagnosis of Costello syndrome using 3D ultrasonography amniocentesis confirmation of the rare HRAS mutation G12D†

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ABSTRACT

No Abstract.

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ARTICLE TEXT

To the Editor:

Costello syndrome (CS, OMIM #218040) is a rare disorder with a distinctive facial appearance, prenatal overgrowth, poor postnatal growth, loose skin of the hands and feet, characteristic hand position, developmental delay, papillomata, cardiac abnormalities, and tumor predisposition. *HRAS* is the only gene currently known to be causative for CS [Aoki et al., [2005]; Nava et al., [2007]; Rauen, [2007]]. Almost all of the mutations of the *HRAS* gene in CS patients which have been reported subsequently have been diagnosed after infancy [Estep et al., [2006]; Gripp et al., [2006]; Kerr et al., [2006]; Schulz et al., [2008]] except for patients presenting with severe neonatal manifestation of CS [Lo et al., [2008]]. We report on the first patient with prenatally diagnosed CS dues to the rare c.35G > A, p.G12D *HRAS* mutation.

A 31-year-old G2P1 woman was referred at 23 weeks of gestation for ultrasonography which showed polyhydramios, good fetal movement, and overgrowth with estimated body weight 1,300 g (+5.3 SD using a Japanese fetal growth curve). There was no pleural effusion, ascites or subcutaneous edema. Craniofacial features included large head

(+3.0 SD), pointed chin, full cheeks, wide nasal bridge, and low-set ears (Fig. 1A), but no macroglossia, omphalocele, hydrocephalus, or brain anomalies. The size of the abdomen was equivalent to that of a fetus at 28-31 weeks gestation. The fetal stomach could not be identified. Hepatomegaly was detected, but the other visceral organs were normal. The extremities were normal in length without deformity, although the wrists were deviated laterally.

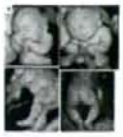

Figure 1. A: Three-dimensional ultrasound images of the fetus at 24 weeks of gestation with overgrowth and so-called "coarse face". Note his left hand presenting ulnar deviation and flexion of the wrist. B: Electropherogram of *HRAS* showing missense mutation at codon 12, c.35G > A, p.G12D. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.] [Normal View 47K | Magnified View 75K]

Cytogenetic and molecular analyses were performed after obtaining informed consent from parents. Standard chromosomes analysis by amniocentesis showed normal karyotype: 46,XY. The deletion of *NSD1* responsible for Sotos syndrome was not detected by fluorescence in situ hybridization (data not shown). By the time CS was suspected, the volume of amniotic fluid was only 1.8 ml which was frozen and stored in the clinic. To perform molecular diagnosis for CS, DNA was extracted with QIAvac vacuum manifold (Qiagen, Chatsworth, CA) from the specimen, and whole genome amplification was carried out with GenomePlex Whole Genome Amplification Kit (Sigma-Aldrich, St. Louis, MO), according to the manufacture's instructions. In this procedure, 3 ㎍ of DNA was obtained. All *HRAS* coding exons and their flanking intronic sequences were analyzed by direct sequencing on an ABI 3100 automated sequencer (Applied Biosystems, Foster City, CA), and a rare missense mutation was found, that is, c.35G > A, p.G12D (Fig. 1B).

The mother had been transported to a pediatric hospital after the fetal evaluation, and the fetus subsequently developed pleural effusion and deteriorated. He was born at 31 weeks gestation via cesarean. He weighed 2,926 g (+4.2 SD) and developed respiratory failure, severe hypoglycemia, cardiac hypertrophy and renal failure. Although he was treated in neonatal intensive care unit, he died soon after birth due to multiple organ failures. Permission for autopsy was not granted. We were unable to study the parental origin [Sol-Church et al., [2006]; Zampino et al., [2007]] because DNA samples from the mother and his 33-year-old father had not been obtained.

Prenatal overgrowth and polyhydramios were prominent in this case. Dysmorphic facial features and flexion of the wrist, imaged with striking clarity by three-dimensional (3D) ultrasonography led us to a clinical diagnosis of CS. Prenatal overgrowth syndromes include relatively few conditions, that is, Sotos syndrome, Simpson-Golabi-Behmel syndrome, Beckwith-Wiedemann syndrome, and CS. The presence of polyhydramios which occurs in over 90% of pregnancies with CS, supported by the 3D ultrasonographic imaging of facial features (broad nose, puffy cheeks, so-called "coarse" face, pointed chin, and flexion of the wrist) made the diagnosis likely. Three-dimensional ultrasonography is clearly more beneficial than two-dimensional (2D) ultrasonography in a diagnosis of genetic syndromes, since we can see overall fetal image of malformation which we hardly get with conventional 2D ultrasonography [Lee and Simpson, [2007]]. The phenotype of Noonan syndrome often overlaps with that of CS, and the prenatal findings of Noonan syndrome, polyhydramnios and so-called "coarse face" in a fetus with the T854C mutation in the *PTPN11* gene, have been reported [Levaillant et al., [2006]], although that fetus with Noonan syndrome did not develop overgrowth.

CS was diagnosed clinically in the prenatal period in monozygotic twins who died 57 days of life after birth at 30 weeks of gestation due to respiratory failure [Van den Bosch et al., [2002]]. Molecular diagnosis was not available. Neonatal deaths in two patients with CS confirmed by molecular diagnosis of G12D *HRAS* mutation were reported by Lo et al. [2008]. One patient was born at 36 weeks gestation weighing 2,950 g developed hypoglycemia, persistent and severe jaundice, persistent respiratory distress with tracheomalacia, bronchomalacia and chylothorax. The baby also had clenched hands, atrial septal defect, paroxysmal multifocal atrial tachycardia, pulmonary lymphangiectasia, and renal failure. She died at age 3 months due to respiratory failure. The other patient was a girl born at 37 weeks gestation weighing 3,115 g had hypoglycemia, rhizomelic limb shortening and flexion contractures at the wrist, hypertrophic cardiomyopathy, dysplasic pulmonary valve, atrial fibrillation, cardiac failure and persistent hyponatremia due to renal sodium leakage. She became ventilator dependent and died at 3 months of age from sepsis and renal failure. Both had pregnancies complicated by polyhydramios. Lo et al. [2008] suggested that differences in activating potential of G12D mutations in *HRAS* gene may result in severe manifestations, such as hypoglycemia, renal abnormalities, severe early cardiomyopathy, and congenital respiratory abnormalities, which result in multiple organ failure.

We believe this is the first case of prenatally diagnosed CS confirmed with molecular genetic analysis with a G12D mutation in *HRAS* gene. The mutation was not observed in previous natural history studies of CS, perhaps because of the rarity of the mutation and the fact that the patients die in early infancy. Our findings contribute to the natural history of this mutation which includes a severe clinical course. If prenatal ultrasonographic findings show both polyhydramnios and overgrowth, CS should be considered despite its rarity. Molecular diagnosis should be offered in the perinatal period without hesitation.

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