Pediatr Neonatol 2008;49(3):88–93

CASE REPORT

Terminal Deletion of Chromosome 6q

Pen-Hua Su[1,2], Jia-Yuh Chen[1,2*], Suh-Jen Chen[1,2], Kai-Chi Yang[2]

[1]*Department of Pediatrics, Division of Neonatology, Chung Shan Medical University Hospital, Taichung, Taiwan*
[2]*Department of Pediatrics, Division of Genetics, Chung Shan Medical University Hospital, Taichung, Taiwan*

Received: Oct 15, 2007
Revised: Feb 14, 2008
Accepted: Jun 25, 2008

KEY WORDS:
chromosome 6q;
deletion;
psychomotor retardation;
short stature

Terminal deletions of chromosome 6q are rare. Clinical features associated with 6q terminal deletion syndrome include psychomotor retardation, seizures, hypotonia, short neck, and facial abnormalities, as well as various case-specific anomalies. Here, we describe a girl with 6q terminal deletion syndrome and unusually short stature. Features of previously described patients are also summarized.

1. Introduction

Terminal deletions of the long arm of chromosome 6 (6q) have been associated with mental retardation, hypotonia, seizures, facial dysmorphisms, and short neck.[1–7] Isolated terminal 6q deletion has been described as a distinct syndrome, and excludes cases with interstitial deletions, deletions/duplications, ring chromosomes or more complex rearrangements. The phenotypes associated with these disorders could be the consequence of various imbalances, and these genotypes are, therefore, considered to differ significantly from the defined "6q terminal deletion syndrome".[8] To date, only 19 cases of isolated 6q terminal deletion have been reported.[1,6–12] The common findings included facial dysmorphism, short neck, psychomotor retardation, hypotonia, and seizures. Differences in deletion sizes most likely explain the variation in observed phenotypes. Unlike many other unbalanced chromosome aberrations whose phenotypes include growth retardation, the features of 6q terminal deletion are frequently nonspecific, such as intrauterine and postnatal growth retardation.

We report a patient with a 6q25.3 terminal deletion. The patient presented with psychomotor retardation, facial dysmorphism, short neck and unusually short stature, which has not been reported in previous cases of isolated terminal 6q deletion.

2. Case Report

This 14.5-year-old girl was born at term after an uneventful second pregnancy from unrelated, healthy parents. Birth weight was 2150 g (below 3rd centile), length was 48 cm (3rd centile), and head circumference was 30 cm (below 3rd centile). The

*Corresponding author. Division of Genetics, Department of Pediatrics, Chung Shan Medical University Hospital, 110 Chien-Kuo North Road, Section 1, Taichung 402, Taiwan.
E-mail: jen@csh.org.tw

©2008 Taiwan Pediatric Association

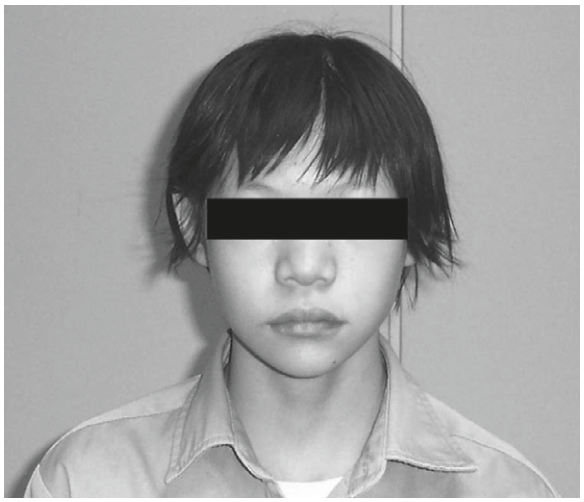

Figure 1 Craniofacial dysmorphism of patient.

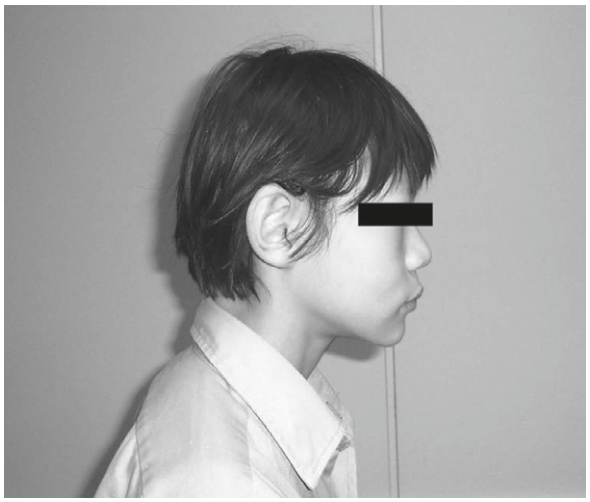

Figure 2 Large, low-set and malformed ear of patient.

first and third pregnancies had produced healthy female and male infants, respectively. Family history was unremarkable for congenital abnormalities. At age of 6 years, this girl demonstrated developmental delay and moderate hypotonia. She had head control at 4 months, rolled over at 9 months, maintained the sitting position without support at 11 months, and started to walk at 20 months. She had used single words at 15 months and had sphincter control at 36 months. However, the anterior fontanelle closed at 4 months, and the patient exhibited failure to thrive and frequent diarrhea from 2 weeks old. The patient did not experience seizures, but mental retardation was present. At the age of 9.5 years, the girl was referred to our genetic clinic for evaluation because of psychomotor retardation and short stature. Physical examination revealed severe microcephaly (head circumference, 44.5 cm), low frontal hairline, hypertelorism, depressed nasal root, bulbous tip (Figure 1), large and low-set ears (Figure 2), micrognathia, high arched palate, short neck, and joint laxity. Weight was 15 kg (below 3rd centile) and height was 117.8 cm (below 3rd centile). A radiograph of the left hand and wrist for bone age (BA) determination according to the standards of Greulich and Pyle[13] was obtained at 6.5 years of age (BA > 2 SDs below the mean for age is considered delayed). Growth hormone (GH) release was determined using clonidine and L-dopa for provocative tests. GH was measured[14] by radioimmunoassay, and the peak GH levels were 4.6 ng/mL and 5.4 ng/mL using clonidine and L-dopa tests, respectively. The level of insulin-like growth factor was 42.7 ng/mL.

Neuropsychologic testing showed mild mental retardation (IQ, 53). The girl's social interactions were good, and she was attending a school for mentally retarded children. Magnetic resonance imaging showed no significant abnormalities. Chromosome

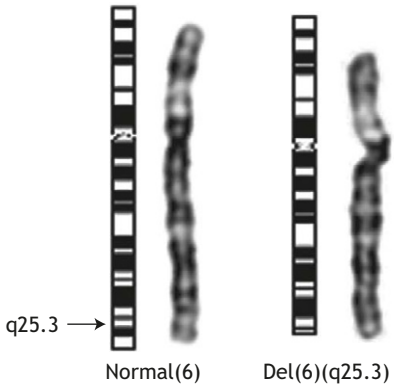

Figure 3 Chromosomal analysis showed a deletion of the long arm of chromosome 6, with a breakpoint at 6q25.3.

analysis by GTG banding showed a deletion of the long arm of chromosome 6, with a breakpoint at 6q25.3 (Figure 3). Spectral karyotyping (SKY) fluorescence *in situ* hybridization was performed using multicolor-labeled painting probes from the Applied Spectral Imaging SKY paint kit (ASI Inc., Israel) to identify chromosomal abnormalities. This revealed that no other chromosomal material was present on the aberrant chromosome 6 (Figure 4). Comparative genomic hybridization was performed to define the breakpoints and also revealed that the aberrant chromosome 6 had a breakpoint at 6q25.3 (Figure 5). According to these data, the final karyotype was defined as 46,XX,del(6)(q25.3 → qter). The parental karyotypes were normal.

After the patient reached 10 years 8 months old, she was treated with a standard dose (0.3 mg/kg/week) of GH. After 4 years of treatment, her growth rate, monitored as rate of change in body height, was 6 cm/year. At this writing, her BA is 10 years and menarche has not yet occurred.

3. Discussion

Clinical descriptions of patients with 6q terminal deletions have been reported since 1975. Many rearrangements involving the terminal region of chromosome 6 have been documented, including interstitial deletions, unbalanced translocations and ring chromosomes, as well as isolated terminal deletions.[1,6–12,15–22] Bertini et al[8] defined the "6q terminal deletion syndrome" as a new syndrome characterized by specific craniofacial dysmorphisms, short neck, and neurologic manifestations, along with various nonspecific malformations. These common phenotypes are individually present in many chromosomal syndromes, but considered together, they are valuable for the identification of 6q terminal deletion syndrome.

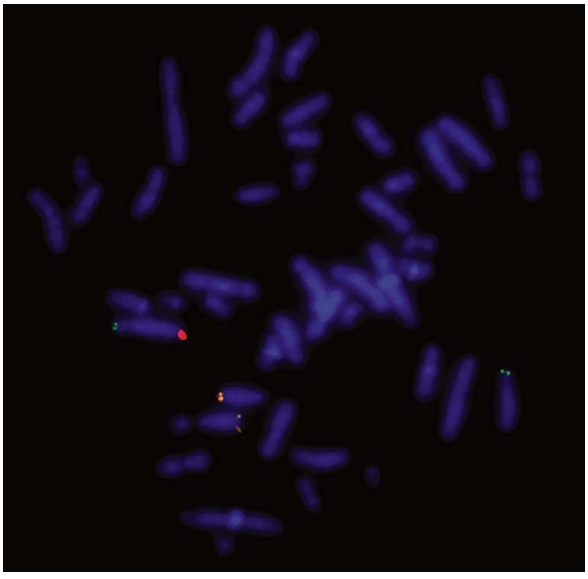

Figure 4 Spectral karyotyping fluorescence *in situ* hybridization indicated that no other chromosomal material was present on the aberrant chromosome 6.

Microcephaly is a common feature present in almost all patients.[8] The ears are large and malformed, and micrognathia, a high arched palate, long philtrum and short neck are also reported consistently.[8] Our patient shared these significant craniofacial anomalies. It is interesting to note, however, that our patient did not have a "fish-like" mouth. Frequently observed neurologic manifestations include psychomotor retardation, hypotonia, and seizures.[8] Although our patient presented with moderate psychomotor retardation (IQ, 53) and joint hyperextensibility, she had neither seizures nor brain anomalies such as dilatation of ventricles, agenesis or hypoplasia of the corpus callosum. Previous reports have suggested that vertebral anomalies and congenital heart and retinal defects are relatively common in patients with 6q deletions,[1,3,6,7] but we failed to identify these features in our patient. Features documented in previously described patients, in comparison with the current case, are summarized in the Table.

It is interesting that growth retardation has often been associated with distal deletions of 6q,[23] but is not included in the characteristics of isolated 6q

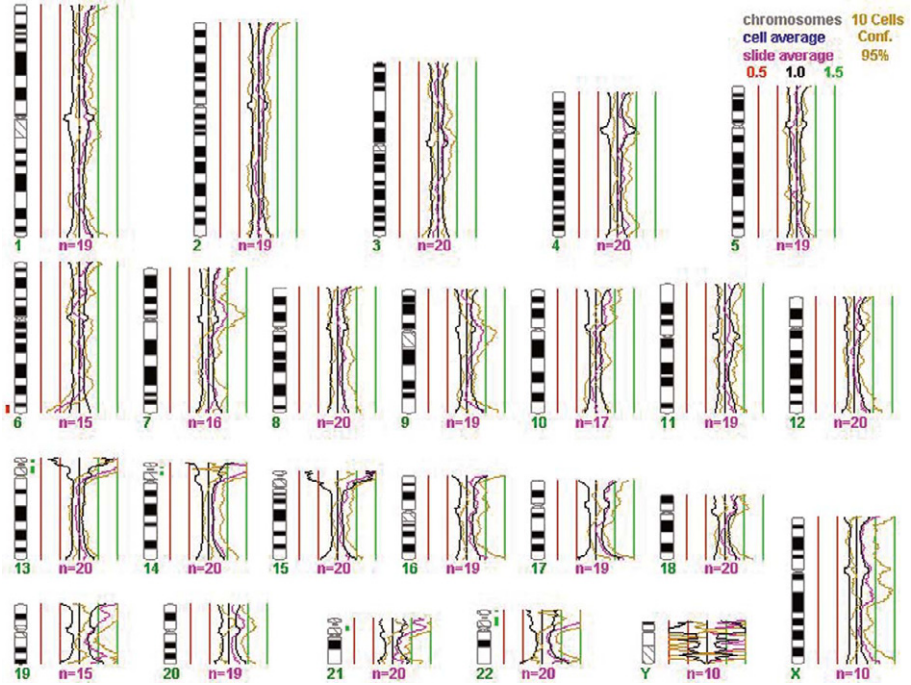

Figure 5 Comparative genomic hybridization was performed to define the breakpoints and revealed that the aberrant chromosome 6 had a breakpoint at 6q25.3.

Table Comparison of patients (n=12) with deletion 6q25–qter

	De novo												n (%)
	Milosevic and Kalicanin[9]	Liberfarb et al[12]	Bartoshesky et al[11]	Rivas et al[15]	Stevens et al[16]	Valtat et al[20]	Valtat et al[20]	Meng et al[19]	Evers et al[21]	Hopkin et al[1]	Koh and Boles[22]	Present case	
Cytogenetic studies	+	+	+	+	+	+	+	+	+	+	+	+	
FISH analysis	–	–	–	–	–	–	–	–	+	–	–	+	
Sex	M	F	M	F	M	F	M	F	M	M	F	F	M:F=6:6
Proband age	2 yr	14 mo	20 mo	5 yr	2 yr	9 d	10 yr	2 yr	2 yr	2 yr	10 d	9.5 yr	
Birth height (cm)		51.5			48	46			48	55.5		48	
Birth weight (g)		3300	2670	2250	2870	2280		1800	2570	2600		2150	
Head girth (cm)		31.5			32	30.5			33	44		30	
Craniofacial													
Microcephaly	+	+	+	+	+	+		+	+			+	9 (75)
Brachycephaly				+									1 (8)
Dolichocephaly									+				1 (8)
Trigonocephaly								+	+		+		3 (25)
Asymmetric head				+									1 (8)
Flat occiput			+										1 (8)
Prominent metopica				+				+					2 (17)
Sloping forehead						+				+	+		3 (25)
Low frontal hairline												+	1 (8)
Nose													
Broad nasal bridge	+	+	+	+	+		+	+				+	8 (67)
Prominent nasal bridge	+	+	+		+			+		+			6 (50)
Anteverted nares				+						+	+		3 (25)
Bulbous nasal tip	+		+	+	+		+		+	+			7 (58)
Depressed nasal root												+	1 (8)
Ears													
Increased size	+		+	+	+	+		+					6 (50)
Malformed/dysplastic	+		+			+		+	+	+		+	7 (58)
Low or apparently low-set	+		+					+		+			4 (33)
Posteriorly rotated			+	+						+			3 (25)
Oral													
Micrognathia	+	+	+		+	+	+	+			+	+	9 (75)
Large mouth				+			+						2 (17)
Downturned corner/ “fish-like” mouth	+		+	+		+	+	+		+			7 (58)
High-arched palate	+						+	+				+	4 (33)
Cleft palate			+					+	+				3 (25)
Long philtrum			+	+	+	+	+	+		+		+	8 (67)

Contd.

Table Continued

	De novo												*n* (%)
	Milosevic and Kalicanin[9]	Liberfarb et al[12]	Bartoshesky et al[11]	Rivas et al[15]	Stevens et al[16]	Valtat et al[20]	Valtat et al[20]	Meng et al[19]	Evers et al[21]	Hopkin et al[1]	Koh and Boles[22]	Present case	
Eyes													
Downsloping palpebral fissures			+					+					2 (17)
Upsloping palpebral fissures	+						+						2 (17)
Epicanthic folds	+		+			+	+	+			+	+	7 (58)
Hypertelorism/telecanthus			+				+	+		+		+	5 (42)
Esotropia	+	+	+		+				+				5 (42)
Extremities													
Abnormal hands/feet	+	+		+	+	+		+	+		+		8 (67)
Abnormal dermatoglyphics	+	+	+			+		+					5 (42)
Musculoskeletal													
Short neck	+		+	+		+		+	+			+	7 (58)
Scoliosis			+					+					2 (17)
Sacral dimple		+							+	+			3 (25)
Dysplastic hip(s)	+		+								+		3 (25)
Shield chest								+					1 (8)
Muscular hypotrophy				+									1 (8)
Muscular hypertrophy											+		1 (8)
Joint laxity												+	1 (8)
Congenital heart defects	+	+	+			+		+	+	+	+		8 (67)
Gastrointestinal													
Feeding problems		+	+						+	+			4 (33)
Umbilical or inguinal hernias	+			+	+								3 (25)
Genitourinary													
Hydronephrosis	+									+			2 (17)
Micropenis			+										1 (8)
Cryptorchidism			+						+				2 (17)
Neurologic manifestation													
Psychomotor retardation	+	+	+	+	+			+	+			+	8 (67)
Seizures		+						+	+				3 (25)
Hypotonia	+	+	+	+			+	+		+	+	+	9 (75)
Retinal abnormalities								+		+			2 (17)
Brain anomalies													
Hydrocephalus										+	+		2 (17)
Aqueductal stenosis											+		1 (8)
Enlarged ventricles								+	+				2 (17)
Cystic areas				+									1 (8)

+ = present; − = absent; FISH = fluorescence *in situ* hybridization; M = male; F = female.

deletion syndrome.[8] To our knowledge, GH deficiency has never previously been reported in a patient with 6q deletion. There have also been no reports on the effects of GH treatment in these patients. During 5 years of follow-up of our patient, there was a significant increase in the rate of change of body height from 3.8 cm/year to 6 cm/year before and after GH replacement, respectively. The cost–benefit of GH therapy in a girl with chromosome anomaly and moderate mental retardation is controversial, but the body image confidence benefit is significant.

To correlate phenotype with genotype, Hopkin et al[1] divided 6q deletions into three groups: (1) group A [del (6)(q11q16)], showing microcephaly, up-slanting palpebral fissures, thin lips, micrognathia, heart malformations and hernia; (2) group B [del (6)(q15q25)], showing intrauterine growth retardation, hypertelorism, upper limb malformations and respiratory problems; and (3) group C [del (6)(q25qter)], showing retinal abnormalities, cleft palate and genital hypoplasia. The common findings in all three groups were mental retardation, ear anomalies, hypotonia, and postnatal growth retardation. Bertini et al[8] described band q25 as the most common location for breakpoints in patients with 6q terminal deletions. However, it has to be noted that 6q26 is a region characterized by a common fragile site, FRA6E (6q26), and that the fragility extends over a large region ranging from 6q25.3 to 6q26 (3.6 Mb).[24] Because all fragile sites are characterized by a delayed replication time, this common feature may be related to their potential role in causing constitutional chromosomal deletions.

In summary, this patient had a 6q25.3 deletion, typical craniofacial abnormalities, mental retardation, and growth retardation. GH replacement was observed to increase height and may be beneficial in similar patients. We, therefore, suggest that: (1) high-resolution chromosome analysis is necessary in patients with mental retardation combined with growth retardation, because the 6q telomeric region, like most telomeres, stains lightly with G-banding, and small rearrangements are, therefore, difficult to detect; and (2) the necessity for recombinant human GH replacement must be decided after long-term follow-up and a GH provocation test.

References

1. Hopkin RJ, Schorry E, Bofinger M, et al. New insights into the phenotypes of 6q deletions. *Am J Med Genet* 1997;70:377–86.
2. Knight SJL, Regan R, Nicod A, et al. Subtle chromosomal rearrangements in children with unexplained mental retardation. *Lancet* 1999;354:1676–81.
3. Lorda-Sanchez I, Lopez-Pajares I, Roche MC, et al. Cryptic 6q subtelomeric deletion associated with a paracentric inversion in a mildly retarded child. *Am J Med Genet* 2000;95:336–8.
4. Colleaux L, Rio M, Heuertz S, et al. A novel automated strategy for screening cryptic telomeric rearrangements in children with idiopathic mental retardation. *Eur J Hum Genet* 2001;9:319–27.
5. Anderlid BM, Schoumans J, Anneren G, et al. Subtelomeric rearrangements detected in patients with idiopathic mental retardation. *Am J Med Genet* 2002;107:275–84.
6. Stevenson DA, Brothman AR, Carey JC, et al. 6q subtelomeric deletion: is there a recognizable syndrome? *Clin Dysmorphol* 2004;13:103–6.
7. Eash D, Waggoner D, Chung J, Stevenson D, Martin CL. Calibration of 6q subtelomere deletions to define genotype/phenotype correlations. *Clin Genet* 2005;67:396–403.
8. Bertini V, De Vito G, Costa R, Simi P, Valetto A. Isolated 6q terminal deletions: an emerging new syndrome. *Am J Med Genet A* 2006;140:74–81.
9. Milosevic J, Kalicanin P. Long arm deletion of chromosome no. 6 in a mentally retarded boy with multiple physical malformations. *J Ment Defic Res* 1975;19:139–44.
10. Hagemeijer A, Hoovers J, Smit EME, Bootsma D. Replication pattern of the X chromosomes in three X/autosomal translocations. *Cytogenet Cell Genet* 1977;18:333–48.
11. Bartoshesky L, Lewis MB, Pashayan HM. Developmental abnormalities associated with long arm deletion of chromosome no. 6. *Clin Genet* 1978;13:68–71.
12. Liberfarb RM, Atkins L, Holmes LB. Chromosome 6q– and associated malformations. *Ann Genet* 1978;21:223–5.
13. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford: Stanford University Press, 1959.
14. Parks JS, Hypopituitarism. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*, 17th ed. Philadelphia: WB Saunders, 2004:1850–1.
15. Rivas F, Ruiz C, Rivera H, Moller M, Serrano-Lucas JI, Cantu JM. *De novo* del(6)(q25) associated with macular degeneration. *Ann Genet* 1986;29:42–4.
16. Stevens CA, Fineman RM, Breg WR, Silken AB. Report of two cases of distal deletion of the long arm of chromosome 6. *Am J Med Genet* 1988;29:807–14.
17. McLeod DR, Fowlow SB, Robertson A, Samcoe D, Burgess I, Hoo JJ. Chromosome 6q deletions: a report of two additional cases and a review of the literature. *Am J Med Genet* 1990;35:79–84.
18. Oliveira-Duarte MH, Martelli-Soares LR, Sarquis-Cintra T, Machado ML, Lison MP. Distal monosomy of the long arm of chromosome 6 (6q25–6qter) inherited by maternal translocation t(6q;17q). *Ann Genet* 1990;33:56–9.
19. Meng J, Fujita H, Nagahara N, Kashiwai A, Yoshioka Y, Funato M. Two patients with chromosome 6q terminal deletions with breakpoints at q24.3 and q25.3. *Am J Med Genet* 1992;43:747–50.
20. Valtat C, Galliano D, Mettey R, Toutain A, Moraine C. Monosomy 6q: report on four new cases. *Clin Genet* 1992;41:159–66.
21. Evers LJM, Schrander-Stumpel CTR, Engelen JJM, et al. Deletion of the long arm of chromosome 6: two new patients and literature review. *Clin Genet* 1996;50:138–44.
22. Koh S, Boles RG. Cerebral aqueductal stenosis as a presentation of deletion 6q25–qter. *Clin Genet* 1998;53:317–8.
23. Sukumar S, Wang S, Hoang K, et al. Subtle overlapping deletions in the terminal region of chromosome 6q24.2–q26: three cases studied using FISH. *Am J Med Genet* 1999;87:17–22.
24. Denison SR, Callahan G, Becker NA, Phillips LA, Smith DI. Characterization of FRA6E and its potential role in autosomal recessive juvenile parkinsonism and ovarian cancer. *Genes Chromosomes Cancer* 2003;38:40–52.