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A de novo Proximal 6q Deletion Confirmed by Array Comparative Genomic Hybridization

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Deletions of chromosome 6q, particularly in the proximal region, are relatively rare. Here, we report on a de novo interstitial deletion of (6)(q13q16.2) in a girl with facial dysmorphism, congenital hip dislocation, porencephaly, and brain atrophy. Array comparative genomic hybridization analysis showed arr 6q13q16.2(73,378,824-99,824,130), demonstrating higher resolution than the conventional cytogenetic findings, del(6)(q12q15). The clinical data were analyzed and compared with those of similar patients previously reported in the literature. *(Korean J Lab Med 2010;30:84-8)*

Key Words : *Comparative Genomic Hybridization, Chromosomes, Human, Pair 6, Chromosome Deletion*

INTRODUCTION

Deletions of the long arm of chromosome 6 are relatively rare. To date, only one case with a deletion of the long arm of chromosome 6 has been identified through standard cytogenetic analyses in Korean patients [1]. The clinical features of 6q deletions, including facial dysmorphism, mental retardation, developmental delay, and defects of the brain, heart, lungs, bones, and joints, vary with the size and location of the deleted regions [2]. Here, we report a case of interstitial 6q deletion associated with facial and skeletal anomalies, umbilical hernia, and brain defects in a female infant. The location of the chromosomal breakpoints and the size of the deleted region, previously identified by routine cytogenetics, which have limited resolution, could be confirmed using the array comparative genomic hybridization (array CGH) method that facilitates high-resolution analysis of chromosomal aneuploidy.

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CASE REPORT

The female infant was the product of the first pregnancy of a 22-yr-old woman. She was born vaginally at the 38th week and 4th day of gestation with a birth weight of 2,400 g. Details of birth head circumference and length are, however, not available. Apgar scores were 5 and 7 at 1 and 5 min, respectively. The patient had a cleft palate and sucking difficulties. Physical examination revealed a flat face, low-set ears, dislocation of both hips, and a small umbilical hernia. Brain MRI showed porencephaly of the basal ganglia and thalamus, cerebromalacia, petechial hemorrhage along the gyrus and parietal area, and brain atrophy. Routine biochemical and metabolic screenings were normal, as were renal and cardiac ultrasonographic examinations.

1. Cytogenetic analyses

Routine cytogenetic analysis performed on peripheral blood using GTG banding revealed an interstitial deletion in the long arm of chromosome 6 in all 20 cells examined (Fig. 1). The karyotype was 46,XX,del(6)(q12q15) (Fig. 2). The karyotype of both parents was normal.

Array CGH was performed with a targeted bacterial artificial chromosome (BAC) microarray (SignatureChip®; Signature Genomic Laboratories, WA, USA). Microarray analysis of 1,543 loci using 4,685 BAC clones detected an abnormality in the DNA of the peripheral blood specimen. Microarray analysis showed arr 6q13q16.2(73,378,824-99,824,130) (Fig. 3). The length of the deleted region was estimated to be approximately 26.4 Mb in size and to contain at least 59 genes that are described in the Online Mendelian Inheritance in Man (OMIM). The full extent of this deletion is unknown because it maybe larger than the region(s) represented on the SignatureChip. The nearest distal clone on chromosome 6 that was not deleted is RP11-357D6 and the nearest proximal clone that was not deleted is RP1-304O5. The break points differed from those indicated by conventional cytogenetic analysis, demonstrating the enhanced resolution of array CGH.

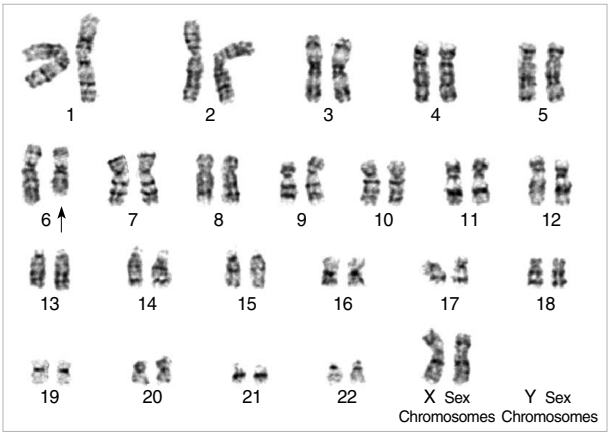

Fig. 1. The G-banded karyotype of the patient showing an interstitial deletion in the long arm of chromosome 6 (arrow).

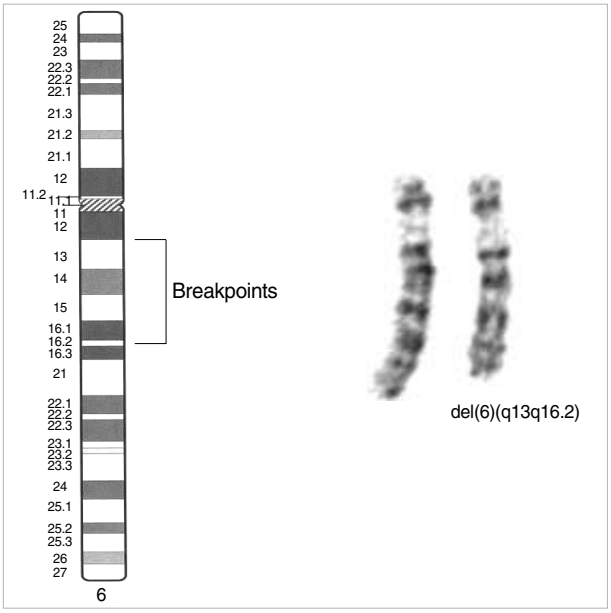

Fig. 2. Partial karyotype and idiogram of the normal and deleted chromosome 6.

DISCUSSION

Deletions of the long arm of chromosome 6, which were first described in 1973 by Mikkelsen et al. [3], are relatively rare. Fewer than 100 cases have been reported worldwide [4]. The anomalies involve multiple organ systems, and include facial dysmorphism and defects of the brain, heart, lungs, bones, and joints. The majority of patients also showed developmental delay. Clinical manifestations of 6q deletions vary according to the size and location of the deleted regions. Using conventional cytogenetic methods, Hopkin et al. [2] proposed three phenotypic groups associated with 6q deletions, namely, proximal

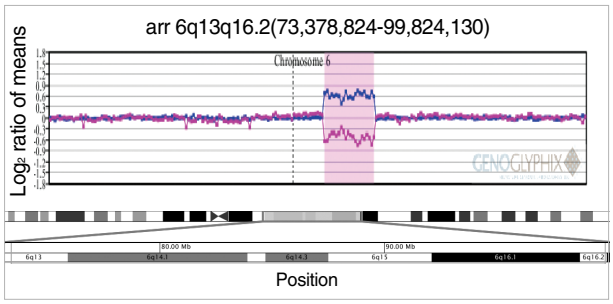

Fig. 3. Results of the array CGH analysis of chromosome 6. The pink line represents the patient-to-control fluorescence intensity ratios; the dark blue line represents dye-reversed control-to-patient fluorescence ratios. Microarray analysis showed a single-copy loss of the long arm of chromosome 6 at bands q13 through q16.2, which is 26.4 Mb in size.

Table 1. Comparison of clinical findings of proximal 6q deletion previously described in the literature and the patient presented here

Major findings	McNeal et al., 1977 [6]	Young et al., 1985 [7]	Yamamoto et al., 1986 [8]	Slater et al., 1988 [9]	Lonardo et al., 1988 [10]	Turleau et al., 1988 [11]
Break points	q13 q15	q13 q15	q13 q15	q11 q15	q13 q15	q14 q16.2
Facial dysmorphism	+*	+	+	+	+	+
Brain anomalies	+	+	+	–†	–	+
Scoliosis	+	+	+	–	–	–
Long slender finger	–	–	–	+	–	–
Clinodactyly	+	–	–	–	+	+
Single palmar crease	+	+	–	–	+	-
Umbilical hernia	+	–	+	+	+	+
Inguinal hernia	–	+	–	-	–	–
Pes planus	+	–	+	+	–	–
Hypotonia	+	+	–	+	–	–
Hypermobile joints including dislocated hip	+	+	+	+	+	–
Cardiac defect	+	–	+	–	+	–
Genital anomalies	–	–	–	+	+	–
Renal anomalies	+	–	–	–	–	–

	Valtat et al., 1992 [12]		Gershoni-Baruch et al., 1996 [13]	Romie et al., 1996 [14]	Kumar et al., 1997 [15]	Presented patient
	Case 1	Case 2				
Break points	q14 q16	q14 q16	q13 q15	q11 q15	q13 q14.2	q13q16.2
Facial dysmorphism	+	+	+	+	+	+
Brain anomalies	–	–	–	+	+	+
Scoliosis	–	–	–	–	+	–
Long slender finger	–	–	–	–	+	–
Clinodactyly	–	–	–	–	+	–
Single palmar crease	–	–	+	–	+	–
Umbilical hernia	–	–	+	+	+	+
Inguinal hernia	–	–	–	–	–	–
Pes planus	–	–	–	–	+	–
Hypotonia	-	+	+	+	+	–
Hypermobilen joints including dislocated hip	–	–	+	–	+	+
Cardiac defect	–	–	–	–	+	–
Genital anomalies	–	–	+	–	+	–
Renal anomalies	–	–	+	–	–	–

*feature present; †not present or not stated.

(6q11 to 6q16), middle (6q15 to 6q25), and terminal (6q26 to 6qter) deletions. Many of the previous reports on the patients with proximal 6q deletion have revealed a high incidence of upslanting palpebral fissures and thin lips with occasional microcephaly, micrognathia, cardiac anomalies, and umbilical or inguinal hernias. Middle 6q deletions are known to be associated with hypertelorism, intrauterine growth retardation, abnormal respiration, and upper limb malformations, whereas terminal deletions are associated with retinal abnormalities, cleft palate, and genital hypoplasia [2, 5]. Moreover, on the basis of conventional cytogenetics, there have also been several patients with deletions overlapping two of the aforementioned three groups.

The patient described in the present study is the second case of proximal deletion of 6q diagnosed in the Korean population. The patient was referred for multiple anomalies, including cleft lip, flat face, low-set ears, and hip dislocation. She also had a small umbilical hernia, porencephaly, cerebromalacia, and brain atrophy. Her karyotype was 46,XX,del(6)(q13q16.2). The first-described Korean with a del(6)(q16), a 9-yr-old boy, had growth and developmental delay, brachycephaly, minor facial dysmorphism, low-set ears, a short 5th finger with clinodactyly, abnor-

mal palmar creases, cryptorchidism, small feet, and brain defects, including an arachnoid cyst and brain atropy [1]. Comparing the findings of our patient with this patient, both were found to exhibit relatively mild clinical manifestations, including typical morphological manifestations. Congenital heart malformations, which are less common in the proximal deletion group, were observed in neither of these two patients.

The deletion found in our patient was classified into the proximal groups on cytogenetics, according to the classification criteria proposed by Hopkin et al. [2]. However, the clinical manifestations of this case did not correspond exactly with the characteristics of any of the groups classified by Hopkin et al. The manifestations of our patient plus those of the 11 patients with proximal 6q deletions in the literature grouped according to the Hopkin et al are compared in Table 1 [6-15]. Facial dysmorphism was observed in all patients, indicating that facial changes are diagnostic. Six of the 12 patients, including our patient, had brain anomalies, and some genes for central nervous system development have been mapped to this region. Our patient and eight of the previously reported patients had an umbilical hernia and some had limb anomalies. Hypermobile joints were observed in seven patients, including one patient with dislocated hip, and our patient showed congenital hip dislocation. These findings, such as umbilical hernia, limb anomalies, and hypermobile joints, suggest a connective tissue dysplasia, and Warman et al. reported that the alpha-1 subunit of type IV collagen was mapped to chromosome 6q12-q13 [16]. Cardiac and renal defects were less common (4 of 11 patients) in the previously reported cases, and were also absent in our patient.

However, in the patients reported in the literature, including the Korean case, most of cytogenetic studies on 6q deletion have been performed using conventional techniques only, which have limited resolution [1, 2, 5, 17-21]. We present a case of interstitial 6q deletion analyzed by array CGH, a method that facilitates high-resolution analysis of chromosomal abnormalities.

In our patient, array CGH revealed a single-copy loss of 22 BAC clones from the long arm of chromosome 6 at bands 6q13 through q16.2, demonstrating higher resolution than the conventional cytogenetic finding, del(6)(q12-q15). As shown in this study, array CGH has become a useful diagnostic tool for the identification of chromosome abnormalities [22]. Recent studies using array CGH have shown that the enhanced resolution of this technique enables identification of the precise location of chromosomal breakpoints, the size of the deletion, and genotype-phenotype correlations [4, 22, 23]. The *EphA7* gene, which is included in the common 6q deleted region and located in 6q16.1, has been suggested to be a candidate gene for central nervous system development [4, 24]. In our patient, the deleted region contains the *EphA7* gene, and porencephaly, which results from the absence of brain development, was observed. The deleted region also contains the *COL12A1* gene at 6q 13. *COL12A1* encodes type XII collagen, which is a structural component of ligament fibrils [25]. However, the full extent of this deletion and the precise roles of the OMIM genes identified in our patient are at present unknown. Further studies are necessary in order to obtain more precise information on the relationship between genotype and phenotype.

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