Korean J Lab Med 2010;30:318-24
DOI 10.3343/kjlm.2010.30.3.318

A Girl with 15q Overgrowth Syndrome and dup(15)(q24q26.3) that Included Telomeric Sequences

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Distal 15q trisomy or tetrasomy is associated with a characteristic phenotype that includes mild to moderate intellectual disability, abnormal behavior, speech impairment, overgrowth, hyperlaxity, long face, prominent nose, puffy cheeks, pointed chin, small ears, and hand anomalies (mainly arachno- and camptodactyly). We present the case of a 13-yr-old girl with the main clinical features of 15q overgrowth syndrome and a 46,XX,dup(15)(q24q26.3)[117]/46,XX[3].ish dup(15)(q24q26.3)(SNPRN+,PML+,subtel++,tel++) de novo karyotype. The findings in this case are consistent with those in the previous distal 15q trisomy cases that presented with overgrowth and mental retardation. Further, the rearranged chromosome had a double set of directly oriented telomeric and subtelomeric sequences. *(Korean J Lab Med 2010;30:318-24)*

Key Words : *Chromosome 15, Distal 15q duplication, 15q overgrowth syndrome, Interstitial telomere*

INTRODUCTION

Since the first report of a 15q22 → qter duplication by Fujimoto et al. [1], at least 71 other cases of similar or smaller distal 15q imbalances have been described, including 5 cases involving aborted fetuses. Such duplications or partial trisomies are usually caused by unbalanced reciprocal translocations, intrachromosomal duplications, or recombination within a pericentric inversion [2-6]. In addition to the 71 cases, 12 sporadic cases (including 2 cases involving aborted fetuses) of 15q distal tetrasomy have also been described; among these, 10 had an extra neocentric marker and 2 had a triplication [6-8]. The phenotype-genotype correlations observed in these cases resulted in the delineation of the 15q overgrowth syndrome, which is caused by the increased dosage of 15q25-q26 and is primarily manifested as mild to severe intellectual disability, language impairment, abnormal behavior, tall stature, macrodolichocephaly, long face, puffy cheeks, prominent chin, cardiac defects, renal abnormalities, camptodactyly, and other minor limb anomalies [2-6]. This phenotype appears to be independent of the parental origin of the surplus 15q [4]. We report the case of a tall female teenager with mental retardation, learning disabilities, and a dir dup(15)(q24q26), a phenomenon that enabled us to review the phenotype in 17 "pure" instances; i.e., instances without a concomitant euchromatic imbalance (Table 1) [2-6, 9-18], and to summarize the rearrangements responsible for the 15q overgrowth syndrome (Supplementary material available upon request: a Table with the 85 cases reviewed here and a

Received : December 4, 2009 Manuscript No : KJLM09-140
Revision received : February 5, 2010
Accepted : February 25, 2010
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ISSN 1598-6535

Table 1. Cytogenetic and clinical findings in 16 patients with a "pure" distal 15q duplication*

	Coco and Penchaszadeh [9]	Yip et al. [11]	Chandler et al. [12]	Abe et al. [13]	Okubo et al. [14]	Faivre et al. [15]	Roggenbuck et al. [16]			Bonati et al. [17]	Kant et al. [18]	Tatton-Brown et al. [6]				Present case	Distal 15q duplication [2-6]
							Case 1 Twin 1	Case 2 Twin 2	Case 3		Case A	Family A		Family B			
												Case II-3	Case III-2	Case II-2	Case II-6		
Sex/Age	M / 20 mo	M / 9 mo	F / 13 yr 4 mo	F / 9 mo	M / 5 yr	M / 22-wk fetus	F / 1 d†	F / 4 yr 6 mo	M / 21 mo	M / 4 yr 8 mo	F / 3 yr 4 mo	F / adult	M / 18 mo	F / 38 yr	M / 33 yr	F / 13 yr 10 mo	
Duplicated segment	15q22→qter	15q21→qter	15q24→qter	15q24.3→q26.3	15q25→qter	15q25→qter	15q24→q26.3	15q24→q26.3	15q24→q26.3	15q25.2→qter	15q26.1→qter	15q26.1→qter	15q26.1→qter	15q26→qter	15q26→qter	15q24→qter	15q2→qter
Rearrangement and occurrence	inv(15)(p1q22) mat	dir dup dn mosaic 46,XY	dir dup dn	dir dup dn	inv(15)(p11.2q25) mat	add (15)(p11)dn mosaic 46,XY	dir dup dn	dir dup dn	dir dup dn	add(15)(p11)dn	t(15;21)(26.1;p12) uk	inv(15)(p12q26.1) pat	inv(15)(p12q26.1) pat	t(14;15)(p11.2;q26) mat	t(14;15)(p11.2;q26) mat	dir dup dn mosaic 46,XX	Diverse
Mental or psychomotor retardation	+	+	+	+	+	NA	NA	+	+	+	+	NR	+	NR	NR	+	+
Defective speech		NA	+	NA	+	NA	NA	+	+	+	+	NR	+	+	+	+	+
Height		<3 percentile	NL	<3 percentile	>97 percentile	>97 percentile	NR	<3 percentile	NL	>97 percentile	97 percentile	>97 percentile	>97 percentile	>97 percentile	>97 percentile	>97 percentile	>97 percentile
OFC		NL	<3 percentile	NL	>97 percentile	NL	Anencephaly	<3 percentile	<3 percentile	<3 percentile	97 percentile	NR	>97 percentile	NL	NL	NL	>97 percentile
Long distinctive face	+	-	+	-	+	NR	NR	+	-	-	+	+	Mildly dysmorphic	+	+	+	+
Prominent or bulbous nose	-	+	-	-	-	NR	NR	-	+	-	+	+	-	+	+	+	+
Pointed or prominent chin		-	-	-	+	NR	NR	-	-	-	-	+	+	+	+	+	+
Puffy cheeks	NR	+	-	+	+	-	NA	+	-	NR	-	+	-	+	+	+	+
Congenital heart disease	-	Hypertrophic ventricular septum	Patent ductus arteriosus	Patent ductus arteriosus	NR	NR	NR	-	VSD and ASD	-	NR	NR	-	-	-	-	+
Renal anomalies	NR	-	Horseshoe	-	-	NR	NR	-	-	-	NR	Horseshoe	Right agenesis	-	-	-	+
Abnormal fingers	Short, stubby	Brachydactyly	Arachnodactyly	Syndactyly	NR	NR	NR	Syndactyly, long tapered fingers and incurved toes	Clinodactyly	NR	NR	NR	Tapered fingers, overlapping toes	Clinodactyly, overlapping toes	NR	Poly, arachno, and camptodactyly	+

*The fetus reported in ref. [10] was not included because of the lack of a detailed description; †dead.

Abbreviations: mat, maternal; dn, de novo; uk, unknown; pat, paternal; NA, not applied; NR, not reported; NL, normal; OFC, occipitofrontal circumference.

list of the corresponding additional references).

CASE REPORT

1. Case

The patient was the first child born to a 24-yr-old woman and an unrelated 28-yr-old man; family history was not a contributory factor for the patient's condition. The patient was born by cesarean delivery at the 37th week of an uneventful pregnancy; at birth, the patient's weight, height, and occipitofrontal circumference (OFC) were 3,750 g (>90th percentile), 55 cm (>97th percentile), and 37 cm (90th percentile). She had a weak cry, a reduced 1 ×1 cm anterior fontanel that showed no malformation in transfontanelar ultrasonography, a sloping forehead, palpebral fissures oriented slightly downwards and outwards, a bulbous nose with a prominent bridge and septum, puffy cheeks, a midline crease in the lower lip, micrognathia, and additional postaxial rudimentary digits and camptodactyly in both hands (Fig. 1A, B). The extra digits were removed shortly after birth, and the camptodactyly was partially corrected at 10 yr of age. She sat at 9 months of age, walked independently at 24 months, and pronounced her first words at 36 months. She was prone to lose control of vesical and anal sphincters, with sudden noises like thunder; at 11 yr, she experienced an episode of accidental immersion asphyxia. Menarche occurred at 12 yr and her menses are normal. An examination at the age of 13 yr revealed a slender habitus, thin hair, high forehead, elongated face, large nose, pointed prominent chin, pubertal development according to age, arachnodactyly, residual camptodactyly (Fig. 1C, D), and height, weight, and OFC of 170 cm (>97th percentile), 49 kg (<50th percentile), and 55 cm (80th percentile), respectively. In addition, she had chronic periodontitis and had recently been diagnosed with atopic dermatitis in the creases of the elbows and wrists. No renal anomalies were observed in a recent ultrasonography examination.

At the age of 13 yr and 5 months, she underwent a cognitive assessment based on the WISC-IV Scale [19], which yielded a total score of 40 with no discrepancy in the verbal comprehension, perceptual reasoning, working memory, and processing speed scores. In the Child Neuropsychological Assessment-ENI [20], the patient's score was similar to that for a 5- or 6-yr-old child; however, she showed greater impairment in expressive vocabulary and lesser impairment in visual perception tasks, receptive vocabulary tests, and semantic visual and verbal fluency. In spite of her attendance to a special education school since the age of 6 yr, she could only read and write a few letters, her own name, and some 1-digit numbers through rote memory. On the Adaptive Behavior Scale [21] filled out by her mother, the patient's behavior was comparable to that of a 4- to 6-yr-old child; she showed no obsessive behavior, panic or phobic disorders, nor loss of temper control.

2. Cytogenetic studies

The chromosomes of the patient and her parents were

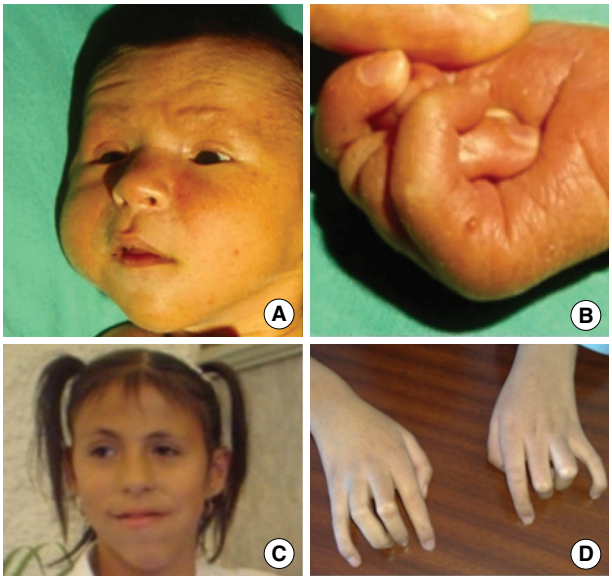

Fig. 1. Images of the patient as a newborn (A and B) and at 13 yr of age (C and D). (A) Note the sloping forehead, palpebral fissures oriented slightly downwards and outwards, bulbous nose with prominent bridge and septum, puffy cheeks, midline crease in the lower lip, and micrognathia. (B) Additional postaxial rudimentary digits and overlapping fingers in both hands. (C) Note the high forehead, elongated face, large nose, and pointed prominent chin. (D) Arachno-camptodactyly in both hands.

analyzed using preparations obtained from peripheral blood cultures. The analysis of 30 G-banded metaphases at a resolution of 550 bands revealed that the patient had a 46,XX,dir dup(15)(q24q26.3) karyotype; moreover, the duplicated chromosome had no visible satellites whereas the normal chromosome had relatively large stalks and satellites (Fig. 2A). We scored 90 more cells, and only 3 of these had the 46,XX karyotype. The parental karyotypes were normal and exhibited contrasting 15p heteromorphisms: paternal 15 chromosomes were devoid of satellites whereas the maternal chromosomes had a short arm similar to that of the patient's normal chromosome (images not shown).

FISH assays with the proband's chromosome preparations were performed using 3 probe sets: the dual-color Prader-Willi/Angelman (SNRPN) Region and the 15q subtel clone 154P1 set with probes labeled red and green, respectively (Cat No LPU 005; Aquarius Cytocell, Cambridge, UK), a pantelomeric probe labeled with digoxigenin and detected with rhodamine, and the t(15;17) (q22;q21) probe labeled with biotin/digoxigenin and detected with fluorescein isothiocyanate/rhodamine (Oncor, Gaithersburg, MD, USA, Cat No P5097-DG.5 and P5119, respectively). At least 10 metaphases were scored in each assay. The dual probe set yielded 2 subtelomeric green signals in the duplicated chromosome (one signal in each 15q26 band) and a single signal on qter of the normal homolog (Fig. 2B); the accompanying red signal for Prader-Willi/Angelman at 15q11-13 was present once in each homolog (Fig. 2B). In >20 interphases, the same pattern of 2 red and 3 green or 15q subtel signals was observed; moreover, 2 green signals were rather close or even adjacent (images not shown). The pantelomeric probe showed double hybridization on the duplicated 15q segment: 1 signal was terminal and the other interstitial at the 15q26 breakpoint junction (Fig. 2C). Finally, the t(15;17) probe confirmed that the *PML* locus at 15q22 was not involved in the duplication (images not shown). Thus, the patient's karyotype was determined to be 46,XX,dup(15)(q24q26.3) [117]/46,XX[3]. ish dup(15)(q24q26.3)(SNRPN+,PML+,subtel++,tel++) dn.

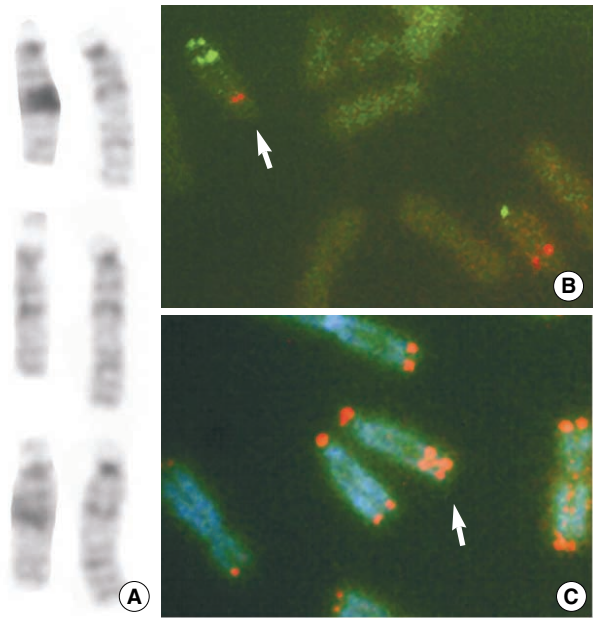

Fig. 2. The patient's dup(15)(q24q26.3). (A) 3 G-banded chromosome 15 pairs with the duplicated homolog on the right. Note the distinct satellites on the normal member. (B) A partial metaphase after FISH with the dual-color Prader-Willi/Angelman (SNRPN) Region and 15q subtel clone 154P1 probe set labeled red and green, respectively; note the double 15q subtel green signal directly oriented. (C) A partial metaphase after FISH with the pantelomeric probe (red signal); note 2 signals in the same direct orientation.

DISCUSSION

The clinical features of the present case, including moderate mental retardation, learning difficulties, tall stature, large head, and distinct facial gestalt as well as the other less common traits such as hand campto- and polydactyly, satisfy the diagnostic criteria for distal 15q overgrowth syndrome [2-6]. Similar to the findings obtained in previous cases of overgrown patients with a distal 15q overdosage [4, 6, 14, 15, 18, 22], the patient's tall stature can be reliably associated with the extra copy of the *IGF1R* (insulin-like growth factor 1 receptor) gene located at 15q26.3. While the patient's neuropsychological profile expands the spectrum of the 15q overgrowth syndrome, it fails to support the association of 15q distal duplication with autism seen in a single patient [17], nor does it verify the debatable connection between DUP25 genomic polymorphism at 15q24-q26 and panic and phobic disorders [23, 24]. However, such disorders may have been

overlooked in other cases [17]. Otherwise, distal 15q overdosage may show variable expression, as evidenced by the absence of true macrocephaly, craniosynostosis, congenital heart defect, and renal anomalies in this patient.

The comparison between the findings in 16 patients (including 1 case involving a fetus) with a "pure" 15q distal duplication (Table 1) and those in 57 cases with an "impure" duplication reveals no major phenotypic differences, except perhaps the life-span. The only death among the "pure" instances was that of an anencephalic newborn [16], whereas the oldest survivors were 33 and 38 yr old at the time of reporting [6]. In contrast, 10/52 (20%) patients born alive with an "impure" 15q duplication were dead at the time of reporting.

The chromosomal rearrangements that were more frequent in 73 patients with a 15q distal duplication (supplementary material) are 56 reciprocal translocations and 8 intrachromosomal duplications. Including the present case (Table 1), there are 7 direct 15q duplications [11-13, 16, this report] and 1 inverted [25] 15q duplication. Among the cases of direct 15q duplications, 6 (5, if a pair of twins is counted as a single event) involve the segment 15q24 → qter; moreover, the present instance appears to be the second mosaic case with a normal cell line [11] and the first 15q duplication with a documented double set of both subtelomeric and telomeric sequences. However, in the previous cases, the investigators did not specifically look for such repeat sequences. Actually, interstitial telomeres were found in a 9p duplication [26] but not in 12 terminal duplications involving diverse chromosomes [27]. In contrast, interstitial telomeric and/or subtelomeric sequences have been detected in both triplications alluded to in previous studies [7, 8], in a tandem 15q telomeric translocation [28], as well as in 9/21 (43%) translocations and rings concerning chromosomes other than chromosome number 15 [29].

The concurrence of a normal cell line along with the double set of (sub)telomeric sequences indicates that the present direct duplication most likely arose in a 46,XX zygote via an interchromosomal or interchromatid nonallelic recombination between a low-copy repeat or duplicon located in 15q24 [30, 31] and telomeric 15q sequences. Indeed, considering the occurrence of internal (TTAGGG)n sequences at duplicon boundaries, such a recombination may be a homologous one [31]. Otherwise, chromosome 15p heteromorphisms would imply that a paternal chromosome was involved in the duplication. Although a meiotic origin cannot be ruled out, it seems unlikely in the light of the requirement of a postzygotic "normalizing" deletion of the duplicated segment; however, at least 2 duplications of meiotic origin have been found in mosaic patients with a normal cell line [27, 32]. Finally, the occurrence of 5 similar dup(15)(q24q26) indicates that these duplications may indeed represent another recurrent 15q genomic disorder comparable to the t(12;15)(p13;q25) typical of congenital fibrosarcoma [30].

ACKNOWLEDGEMENTS

We thank the patient and her mother for their cooperation and Mie Ryoung Gene for translating an article from Korean. The authors do not have any conflicts of interest.

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