PURE INTERSTITIAL DUPLICATION OF CHROMOSOME 7q (7q31.2→q33) IN A 4-YEAR-OLD GIRL WITH GROWTH RESTRICTION, SHORT STATURE, SPEECH DELAY AND INTELLECTUAL DISABILITY

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Summary: *Pure interstitial duplication of chromosome 7q (7q31.2→q33) in a 4-year-old girl with growth restriction, short stature, speech delay and mental retardation:* We report the cytogenetic and molecular characterization of a 22.3-Mb pure interstitial duplication of chromosome 7q, dup(7)(q31.2→q33) in a 4-year-old girl with growth restriction, short stature, speech delay, inguinal hernia, strabismus and intellectual disability. We speculate that the gene dosage increase effect of the *ING3* and *LEP* genes may be partially responsible for the phenotype of growth restriction and short stature in this patient.

Key-words: 7q31.2→q33 – Chromosome 7q duplication – *ING3* – *LEP* – Growth restriction – Strabismus.

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INTRODUCTION

Clinical cases with pure partial trisomy of 7q are rare. To date, at least 18 cases have been reported (20). Novales *et al*. (17) suggested that three possible distinct clinical syndromes can be established according to three segments, namely 7q21 or q22→q31, 7q31→qter and 7q32→qter, and the patients with dup(7)(q21 or q22→q31) are associated with more abnormalities than those with dup(7)(7q31→qter) or dup(7)(7q32→qter). Here, we present a case where the smallest portion of the long arm of chromosome 7 (7q31.2→q33) is duplicated with some distinct clinical manifestations.

CLINICAL REPORT

The 4-year-old girl was the first child of healthy and non-consanguineous parents. When she was born, the mother was 28 and the father 32 years old. The family history was unremarkable. She was delive-

red at 38 weeks of gestation with a body weight of 2,492 g (< 3rd centile), a length of 44 cm (< 3rd centile), a head circumference of 33.5 cm (15-50th centile) and a chest circumference of 30.5 cm (5th centile). She underwent herniorrhaphy for bilateral inguinal hernias at 15 months of age. When examined at 16 months of age, she manifested hypotonia, developmental delay, unstable gait, mild horizontal nystagmus, convergent strabismus of the right eye and craniofacial dysmorphism including macrocephaly, frontal bossing, hypertelorism, epicanthic folds, a depressed nasal bridge, micrognathia, a short neck and low-set ears (Fig. 1). Her body weight was 10 kg (50th centile) and length 71 cm (< 3rd centile). When examined at 2 years of age, she was found to have intellectual disability, speech delay, language difficulties and poor weight gain. Her body length was 79.6 cm (< 3rd centile), head circumference 49.1 cm (90-97th centile) and body weight 10 kg (10th centile). The findings of brain computed tomography scans and abdominal and heart ultrasound were unremarkable. Cytogenetic

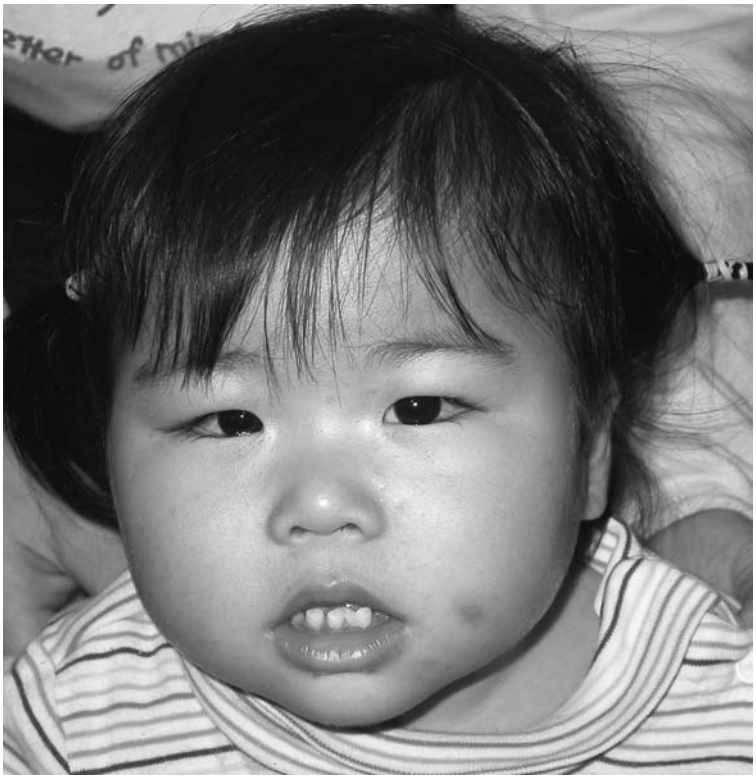

Figure 1: Craniofacial appearance of the proband at the age of 16 months

analysis revealed a *de novo* derivative chromosome 19 [der(19)], of which an aberrant chromosomal segment was inserted into the long arm of chromosome 19 at band 19q13.3 (Fig. 2). The parental karyotypes were normal. Molecular analysis using array-based comparative genomic hybridization (aCGH) with high-density oligonucleotide array (NimbleGen, Madison, WI, USA) revealed a 22.3-Mb duplication of 7q31.2→q33 (114,330,000-136,590,000) (NCBI Build 36, March 2006) (Fig. 3). No genomic imbalance was found in chromosome 19. Polymorphic DNA marker analysis determined a paternal origin of the duplication. The karyotype of the proband was 46,XX,der(19)ins(19;7)(q13.3;q31.2q33) (Fig. 2). When examined at 4 years of age, she manifested short stature, growth delay, intellectual disability, speech delay and strabismus. She weighed 14 kg (10th centile).

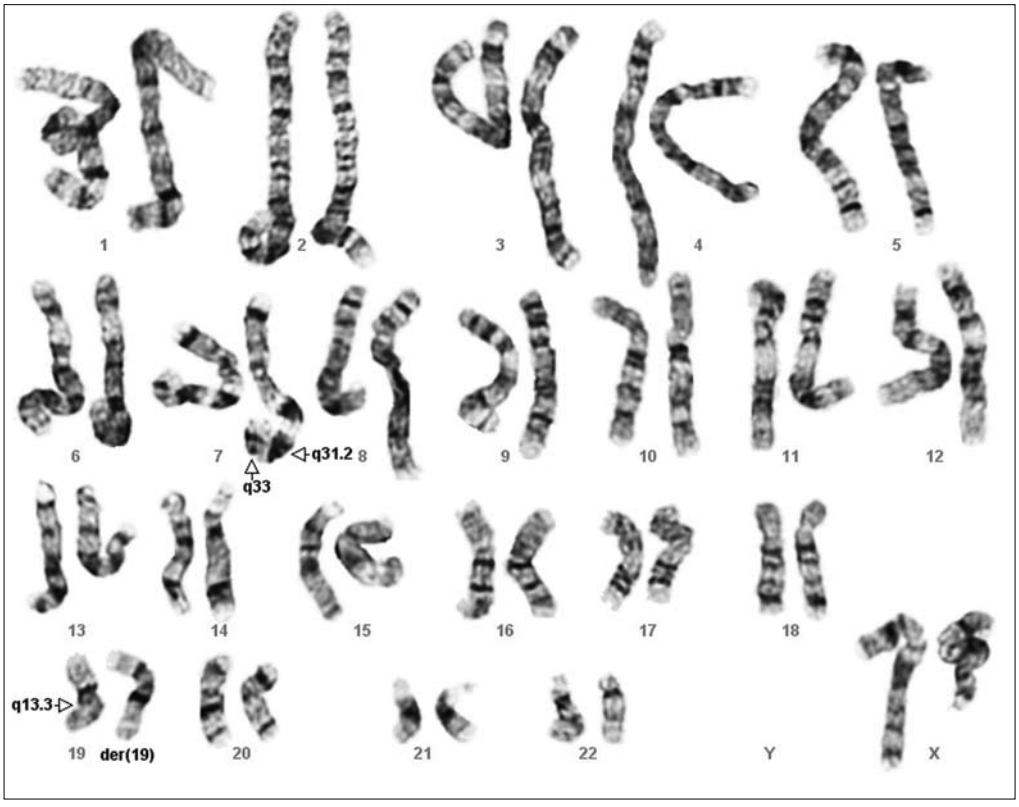

Figure 2: A karyotypes of 46,XX,der(19)ins(19;7)(q13.3;q31.3q33). Arrows on normal chromosomes 7 and 19 indicate the breakpoints.

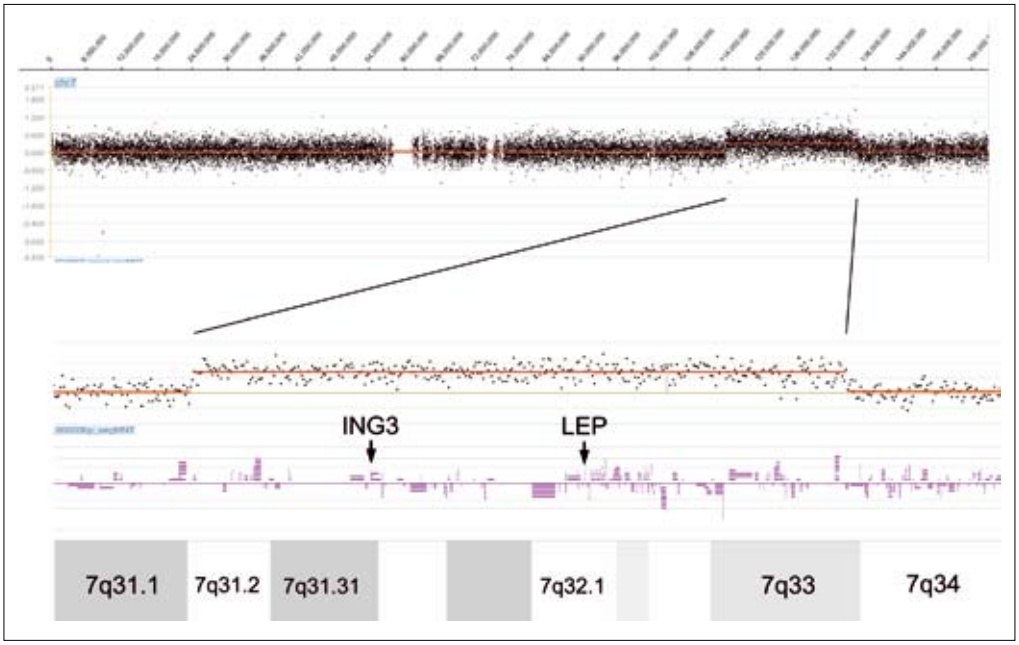

Figure 3: High-resolution array-based comparative genomic hybridization (aCGH) shows a duplication of 7q31.2→q33 encompassing a region from 114,330,000 bp to 136,590,000 bp in the proband.

DISCUSSION

Patients with dup(7)(q31→qter), dup(7)(q31.2→qter) or dup(7)(q31.3→qter) have been reported to be associated with variable non-specific abnormalities and the common findings of developmental delay, hypertelorism, macrocephaly, frontal bossing, a short neck and low-set ears (1-6, 8, 12, 14-15, 17-19, 22-24). Pure interstitial duplication of 7q with the proximal breakpoint at 7q31 is very uncommon. To our knowledge, only one case has been reported (25). Zelante *et al*. (25) reported an interstitial *de novo* tandem duplication of chromosome 7q (7q31.1→q35) in an 18-month-old boy with mild facial dysmorphism, moderate intellectual disability, speech delay, low birth weight, short stature, scaphocephaly, frontal bossing, epicanthic folds, a depressed nasal bridge, a small nose, mild convergent strabismus on the right eye, low-set ears and micrognathia. Our case represents the shortest duplicated interval of pure interstitial duplication of 7q involving 7q31 reported so far. Our case shared the common phenotype of partial 7q duplication and the findings of low birth weight, strabismus, speech delay and short stature as described by Zelante *et al*. (25). Our case had gene dosage increase of *ING3* at 7q31.31 and *LEP* at 7q32.1

and the phenotype of growth restriction and short stature. ING3 (inhibitor of growth 3) (OMIM 607493) belongs to ING tumor suppressor proteins that are critical regulators of chromatin acetylation required for genome expression and perpetuation (9). Decreased expression of *ING3* has been associated with cancer (13). LEP (leptin) (OB) (OMIM 164160), a hormone secreted by adipocytes, acts on the hypothalamus to regulate appetite, neuroendocrine function and bone remodeling, and to inhibit food intake and bone formation (7, 9, 21). Congenital leptin deficiency is associated with severe early-onset obesity in human (16). Lipodystrophic mice with leptin deficiency have high bone mass and an advanced bone age (11). Leptin has both antiosteogenic and anorexigenic functions (11). The consequence of over-expression of *ING3* and *LEP* is unclear at present. We speculate that the gene dosage increase effect of *ING3* and *LEP* may be partially responsible for the phenotype of growth restriction and short stature in this patient.

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