

## Inherited Tandem Duplication of the X Chromosome: Dup(X)(q13.2-q21.2) in a Family

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A 2-year-old boy who was failing to thrive and who had multiple anomalies was found to have a maternally derived tandem duplication of the long arm of the X chromosome: dup(X)(q13.2-q21.2). The karyotyping interpretation was further confirmed by fluorescence in situ hybridization studies in which a double gene dosage of the X-inactivation-specific transcript (gene locus on Xq13.2) and a whole chromosome X painting on the abnormal X were noted. He suffered from hypotonia, gastroesophageal reflux, laryngomalacia, recurrent infections, immunodeficiency (IgG4 deficiency), dysgenesis of the corpus callosum, proximal renal tubular acidosis, and nephrolithiasis. His mother and elder sister also had the same rearrangement, the dup(X), on one of their X chromosomes. However, the mother was in good health, but the sister suffered from nephrolithiasis. The clinical variability in this family with the Xq duplication is reported and discussed. (*Chang Gung Med J* 2004;27:685-90)

**Key words:** X chromosome, Xq duplication, failure to thrive, immunodeficiency, nephrolithiasis.

In males, duplication of a portion of chromosome Xq is always associated with multiple congenital anomalies and developmental delay.<sup>(1-3)</sup> Pertinent physical findings in these children include facial dysmorphism (frontal bossing, short palpebral fissures, epicanthal folds, ptosis, hypertelorism, a flat nasal bridge, simple ears, a high-arched palate, micrognathia, and down-turned corners of the mouth), severe growth and mental retardation, hypoplastic genitalia, and hypotonia.<sup>(1-3)</sup> In the majority, the rearranged X chromosome is inherited from the mother, who carries the anomaly in 1 of her X chromosomes.<sup>(1-5)</sup> Most females recognized as having dup(Xq) are phenotypically apparently normal relatives of phenotypically abnormal males. The phenotypical normalcy has been attributed to selective inactivation of the duplicated X chromosome, and only a few distinctly phenotypically abnormal females with dup(Xq) have been reported.<sup>(6-8)</sup> A fami-

ly with an Xq duplication showing different phenotypes is reported.

### CASE REPORT

This male patient was born at 37 weeks' gestation via a vaginal delivery, to a 30-year-old gravida 2, para 2, healthy woman and had a birth body weight (BW) of 2450 g. The perinatal course was complicated with arrhythmia, delay of initial crying, and cyanosis. The mother had a past history of hyperthyroidism, and his elder sister had nephrolithiasis of unknown cause. After birth, hypotonia, weak crying, and feeding problems such as vomiting, choking, and poor weight gain were noted. Recurrent febrile episodes occurred to him from the age of 4 days, and he was admitted to the hospital many times because of aspiration pneumonia, urinary tract infection, and diarrhea. At 5 months old, metabolic

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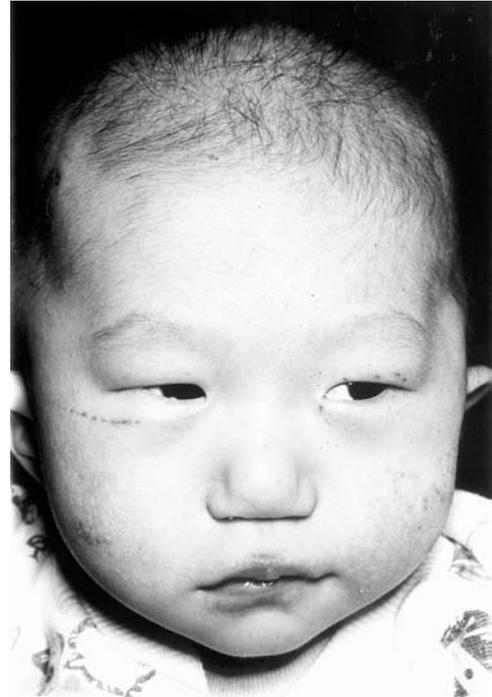
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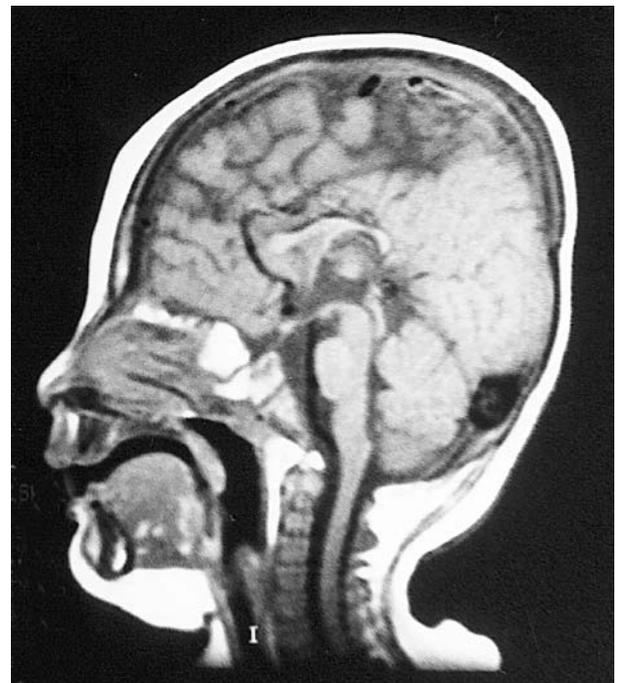
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acidosis developed, and proximal renal tubular acidosis was diagnosed; this was treated with bicarbonate salt. Hypoparathyroidism and nephrolithiasis were noted at 6 months, when the intact parathyroid hormone was below 15.9 (normal, > 35.3) pg/mL, vitamin 1,25 (OH)<sub>2</sub>D was 15.15 (normal, 16.4-42.4) pg/ml, and the 24-h urine calcium (Ca) excretion was 8.01 mg/kg/24 h with a Ca/Cr ratio of 0.859 (normal, < 0.2). At 7 months old, Nissen fundoplication was performed owing to ineffective medication for the severe gastroesophageal reflux with esophageal stenosis. A herniorrhaphy was performed at 9 months for a bilateral inguinal hernia. Aseptic meningitis occurred at 11 months. Because of persistent poor feeding and malnutrition, a Hickman/Port-A catheter was inserted for parenteral nutrition at 16 months.

For recurrent infections such as chronic diarrhea, otitis media, sinusitis, and pneumonia, the blood immunoglobulin (Ig) levels were checked and revealed an IgG of 373 mg/dl, IgA of 28 mg/dl, IgM of 47 mg/dl, and IgE of 68 mg/dl. Among the subclasses of IgG, the level of IgG4 was 0 mg/dl. Therefore, immunodeficiency with IgG4 subclass deficiency was diagnosed, and intravenous immunoglobulin (IVIG) was regularly provided from the age of 15 months. At the age of 2 years, his BW was 7.1 kg, height was 72 cm, and head circumference was 40.2 cm (all below the 3rd percentile). His motor developmental milestone occurred at around 8 months old. Physical examination showed frontal bossing, short palpebral fissures, epicanthal folds, ptosis, hypertelorism, a flat nasal bridge, simple ears, a high-arched palate, micrognathia, down-turned corners of the mouth, a short neck (Fig. 1), pectus excavatum, short fingers and toes, hypoplastic genitalia with microtestes (with a volume of < 1 ml), and generalized hypotonia. A hemogram showed mild anemia (hemoglobin of 9.4 g/dl). The liver and renal functions were normal. Electroencephalography showed diffuse cortical dysfunction. Magnetic resonance imaging (MRI) study of the brain done at 1 year disclosed dysgenesis of the corpus callosum, delayed myelination, and ventriculomegaly. Follow-up MRI at 2 years showed corpus callosum dysgenesis with absence of the rostrum (Fig. 2). Muscle biopsy showed negative findings. An intestinal villi biopsy revealed chronic inflammation with lymphoplasmal cell infiltration, and congestion in the



**Fig. 1** The patient at 1 year old.

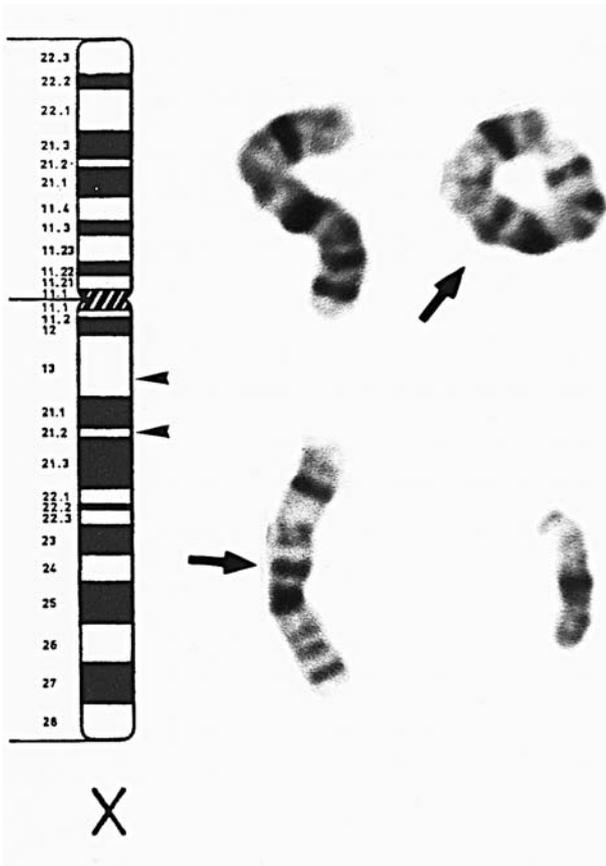


**Fig. 2** Magnetic resonance imaging study of the brain disclosing corpus callosum dysgenesis with the absence of the rostrum.

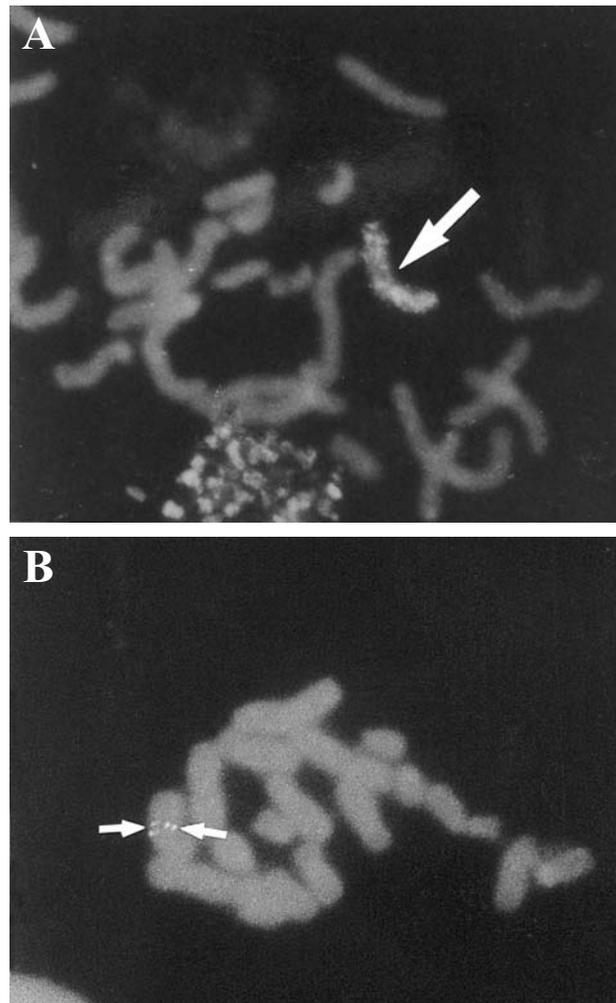
laminae propriae. An endoscopic examination was negative. A Tc99m scan showed a mildly prolonged gastric emptying time. Thus a percutaneous endoscopic gastrostomy was performed at 2 years.

Metabolic and endocrinological investigations demonstrated normal thyroid function, low growth hormone (GH) and IGF-I levels with GH of 5.45 ng/ml (> 6.5 ng/ml at 22:00) and IGF-I of < 10 ng/ml. The urine organic acid profile was normal. The follow-up Ig levels after long-term IVIG therapy were 848, 57, and 85 mg/dl for IgG, IgA, and IgM, respectively. His elder sister, who was also short, was also found to have hypercalciuria complicated with nephrolithiasis. Chromosome analysis of the

patient showed 46, Y, dup(X)(q13.2-q21.2), while the mother and elder sister revealed 46, X, dup(X)(q13.2-q21.2)(Fig. 3). The nature of the rearranged segment was confirmed by utilizing high-resolution G banding and fluorescence in situ hybridization (FISH) studies. FISH with an X-chromosome painting probe verified the X-chromosome origin of the entire duplication (Fig. 4A), and with a single-copy XIST probe mapping to Xq13.2, revealed double signals in the duplicated X chromosome (Fig. 4B).



**Fig. 3** Partial karyotypes of the mother (upper) and the son (lower) by G-banding showing the q13.2-q21.2 duplication. The duplicated X chromosome is indicated (arrows). The duplicated segment is marked by arrowheads in the ideogram.



**Fig. 4** FISH studies with probes for (A) the painting chromosome X and (B) the XIST region. Arrows indicate the duplicated X chromosome and the double XIST signals, respectively.

## DISCUSSION

Duplication of a segment of the long arm of chromosome X is a rare event. The findings reported in most cases are severe growth and mental retardation, hypoplastic genitalia including undescended testis, and hypotonia.<sup>(1-5)</sup> Feeding difficulties are also frequently seen in infancy. Endocrine dysfunction (i.e., GH deficiency and hypothyroidism) appears both centrally and peripherally.<sup>(4,5)</sup> In the present case, the duplicated segment consisting of Xq13.2-q21.2 has expanded the clinical spectrum of the Xq duplication syndrome, including proximal renal tubular acidosis, immunodeficiency with IgG4 deficiency, agenesis of the corpus callosum, and nephrolithiasis.

Normally in humans, 1 X chromosome is inactivated in female somatic cells during early embryonic development, in order to maintain a balanced genetic constitution of genes expressed from the X chromosome between males and females (Lyon's hypothesis). If the cell's active X chromosome contains a duplication, the 2 copies of the genes are both abnormally expressed. The phenotype of the proband is considered to be the consequence of a functional disomy, Xq13.2-q21.2. This doubling of gene products can result in birth defects, learning problems, and mental retardation. The duplicated X chromosome, random X inactivation pattern, and the FISH study indicated that the abnormal X chromosome was the basis of the patient's phenotype. These abnormalities can also be explained by expression of recessive genes on the active X chromosomes, or by an imprinting effect.<sup>(7)</sup> The different phenotypes in the carrier mother and elder sister may be explained by different patterns of X-inactivation.<sup>(7-9)</sup>

Yokoyama et al. reported on a boy with severe growth retardation and mental retardation who was found to have a maternally derived tandem dup(X)(q13.3-q21.2).<sup>(4)</sup> Growth hormone deficiency with empty sella syndrome may explain the growth failure of these patients.<sup>(4,5)</sup> Comparison of the phenotypes of patients with a direct duplication of part of Xq reveals the existence of structural determinants within the Xq13-q21 region, determinants of ovarian function within q22 to q27, and the X inactivation center within or proximal to band Xq13.3.<sup>(6)</sup>

Tandem repeats of chromosome material can arise as inverted or as direct duplications. These find-

ings show that the inversion duplication is the result of a postzygotic error in the proband's mother.<sup>(5,10,11)</sup> Such duplications of the X chromosome are instructive regarding X-linked genetic determinants of phenotypes.<sup>(6)</sup>

In conclusion, 3 cases in a family were identified as having the Xq duplication by using an X chromosome-specific painting probe and a unique sequence probe for XIST. Duplication of segments of Xq in the male patient was associated with major developmental and mental impairments. However, the different phenotypes in the 2 female cases are considered to be resulted from selective inactivation.<sup>(12)</sup>

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## 一 家族之遺傳性X染色體長臂重覆複製：Dup(X)(q13.2-q21.2)

侯家瑋

一名2歲有生長不良及多重畸形的男孩被發現帶有源於母親的X染色體長臂重覆複製。螢光原位雜交法發現XIST（基座位於Xq13.2）之雙倍劑量及經由全X染色體探針之分析証實病人之核型：dup(X)(q13.2-q21.2)。病童罹患的疾病包括低張力、胃食道逆流、喉頭軟化症、重覆感染、近端腎小管酸中毒、免疫球蛋白G4缺乏症、胼胝體發育不良及高尿鈣症合併腎結石。這些症狀都是尚未報告的。其母及姊有相同核型，但是母親身體健康無異狀但姊姊有腎結石及高尿鈣症。本文將報告且討論此帶有複製Xq家庭成員之臨床變異。（長庚醫誌 2004;27:685-90)

**關鍵字：**X染色體，X染色體長臂重覆複製，生長不良，免疫缺乏症，腎結石。

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