

A Case of an Interstitial Tandem Direct Duplication of Long Arm of Chromosome 4: 46, XY, dup (4) (q25q31.3) de novo

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ABSTRACT

We report a 4 2/12-year-old Japanese boy with a de novo direct tandem dup (4) (q25q31.3). The major clinical picture includes postnatal growth and psychomotor retardation, thick eyelashes, a cleft lip, and large and prominent helix and antitragus. He did not have any hearing deficit. His eyegrounds were normal. There was no organ malformations including brain, kidney, liver, pancreas, gallbladder, urinary bladder, stomach, and heart. Routine hematological tests, blood chemistry including thyroid hormones, and urinalysis including urinary screening tests for congenital metabolic disorders showed normal results. He showed an electroencephalographic abnormality which could have resulted from mild aseptic meningitis at 2 months. Our case supports the idea that the association of thumb and renal deformities in duplication 4q syndrome is related to the region 4q22-q23 as many researchers have already pointed out.

Key words: *Interstitial duplication 4q, Trisomy 4q25q31.3*

The association of thumb and renal deformities has been noted as a characteristic clinical manifestation in 4q syndrome. A recent comparative analysis of cases of 4q interstitial duplication has shown that segment 4q22-q23 is responsible for the association¹⁷⁾.

Partial trisomy 4q usually results from a parental translocation while de novo interstitial duplication is less frequent among trisomy 4q patients¹⁶⁾; only nine cases have been reported including our case^{5-8,11,13,15,17)}. We describe a 4 2/12-year-old Japanese boy with an interstitial tandem duplication of the long arm of chromosome 4 (q25→q31.3), and compare the clinical picture and duplicating regions with those of eight other cases. De novo duplications such as our case might be useful in studying genotype-phenotype correlations to delineate a precise aneuploidy syndrome.

CASE REPORT

Patient S.H., a Japanese boy born on Jan 17, 1993, was the first child of a nonconsanguineous

marriage. The mother was 28 years old and the father 29 when he was born. The pregnancy was complicated by a threatened abortion at 2 months of pregnancy. The mother was otherwise healthy and did not take any alcohol or medications during pregnancy. The boy was born at 37 weeks by a vaginal delivery from a vertex position without complications, and with birth weight 2,500 g (6th percentile), length 48.0 cm (18th percentile), and head circumference 31.5 cm (7th percentile). His perinatal history was uneventful. The development of his body weight and height had been around 10th percentile of the standard since birth. However, his psychomotor development was not delayed: social smile started at 3 months, head control at 3 months, sitting at 7 months, standing at 10 months, and walking at 16 months. He had a mild aseptic meningitis at 2 months but completely recovered. He also experienced varicella at 3 months and exanthema subitum at 10 months. The physical examination at his first visit to our clinic at 1 4/12 years old showed a 8.7 kg of body weight (7th percentile)

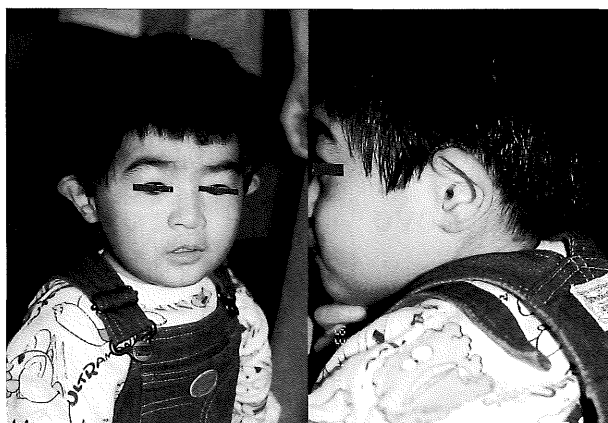


Fig. 1. Frontal and left side view of the patient.



Fig. 2. Electroencephalogram of the patient.

and 75.1 cm of height (7th percentile), thick eyelashes, large and prominent helix and antitragus, a cleft lip operated on at 4 months, and a peg shaped deformity in the right lower central incisor (Fig. 1). No other malformations including cryptorchidism were found. The muscle tone was normal.

Magnetic resonance imaging of the brain showed no abnormality of the architecture. Abdominal and cardiac ultrasonographic examination showed no organic malformations including kidney, liver, pancreas, gallbladder, urinary bladder, stomach, and heart. Audiometry (conditioned orientation reflex) showed no hearing deficit. An electroencephalogram showed focal



Fig. 3. Partial karyotype showing GTG banding of chromosome 4 and dup (4) (q25q31.3). The left side chromosome is normal control. The right side chromosome is dup (4) (q25q31.3) of the patient. The segment between arrows is the duplicated segment.

spikes in the left central and right occipital areas although he had not experienced clinical seizures (Fig. 2). Fundusoscopic examination showed normal eyegrounds. A routine hematological test, blood chemistry including thyroid hormones, and urinalysis including screening tests for congenital metabolic disorders showed normal results. Chromosome analysis with G banding technique showed a karyotype of 46, XY, dup (4) (q25q31.3) (Fig. 3). The karyotypes of the parents were normal. The evaluation of physical and mental development by Enjoji's development test (revised edition) showed his developmental quotient as 79, indicating a moderate retardation.

DISCUSSION

Interstitial duplication of a chromosome occurs by either of two mechanisms: an insertion from the homologous chromosome or unequal sister chromatid exchange or crossing over in meiosis or mitosis¹⁴. Comparing the clinical pictures in our case and other cases of de novo partial duplication 4q, growth and psychomotor retardation, low-set and/or malformed ears, and a high nasal bridge are found to be prominent features as shown in Table 1. Furthermore, Zollino M. et al¹⁷ delineated an association of thumb and renal deformi-

ties in specific cases which include 4q22-q23 in the duplication segment. The case presented in our paper supports their idea. Navarro E.G. et al¹¹⁾ reported a case of de novo dup (4) (q21q28) which had low-set thumbs but lacked renal anomalies. There are two more cases of duplication 4q which have a duplication segment of q25-qter¹⁰⁾ or q31-qter¹²⁾; both lack the duplication of 4q22-q23 segment and possess both thumb and renal deformities (Table 2). Since these two cases have other chromosomal anomalies—one has partial trisomy 9p and the other monosomy 5p—these anomalies together with partial trisomy 4q may affect the thumb and renal deformities.

Polycystic kidney disease 2 (PKD2) gene has recently been localized on chromosome 4q21-23⁹⁾. PKD has an autosomal dominant inheritance and causes bilateral renal and liver cysts as a major

ties (Table 2). Since these two cases have other chromosomal anomalies—one has partial trisomy 9p and the other monosomy 5p—these anomalies together with partial trisomy 4q may affect the thumb and renal deformities.

Table 1. Clinical manifestations in de novo interstitial duplication 4q.

manifestation	Present Case	Halal F. ⁷⁾	Jeziorowska A. ⁸⁾	Fryns J.P. ⁶⁾	Vogel W. ¹⁵⁾	Dutrillaux B. ⁵⁾	Taylor K.M. ¹³⁾	Zollino M. ¹⁷⁾	Navarro E.G. ¹¹⁾
duplicated segment	q25-q31.3	q23-q27	q21.3-q31.3	q25-q31	q22-q34	q22-q34	q26-q35	q13-q22	q21-q28
age (yr)/sex	4 2/12/M	2 1/4/F	3/M	6 1/2/F	6/F	2 1/4/F	6 1/2/M	15 1/2/F	2 3/4/F
growth retardation	+	+	+	+	+	+	+	+	+
psychomotor retardation	+	+	+	+	+	+	+	+	+
microcephaly	—	+	+	—	—	+	+	—	—
epicanthic folds	—	+	+	—	+	+		—	+
strabismus	—	+	+	—	—	—		—	
high nasal bridge	—	—	+	+	+	+	+	—	+
cleft lip	+	—	—	—	—	—	—	—	—
retromicrognathia	—	—	+	—	+	+		+	+
low-set and/or malformed ears	+	—	+	+	+	+	+	—	+
sacral dimple	—	+	—	—	—	+		—	
scoliosis	—	—	+	+	—	—	+	—	
congenital heart defect	—	+	—	—	—	—	—	—	—
hypoplastic thumb	—	—	+	—	+	+	—	—	+
syndactyly	—	—	—	—	+	—	—	+	
renal hypoplasia	—	—	+	—	+	+		—	—
epilepsy	—	—	—	+	—	+	+	—	+

Table 2. Thumb and renal deformities in partial duplication 4q syndrome.

Duplicated segment	Thumb deformities	Renal deformities	Reference
[group 1]			
q21.3-q31.3	absence/malformation	bil. dilated ureters	Jeziorowska A. ⁸⁾
q22-q34	left aplasia	left renal hypoplasia	Vogel W. ¹⁵⁾
q22-q34	bil. digitalized thumb	left renal hypoplasia	Dutrillaux B. ⁵⁾
q21-qter	bifid right thumb	bil. renal hypoplasia	Biederman B. ¹⁾
q12 or 22-qter	digital thumbs	dilatation of ureter	Cervenka J. ²⁾
q21-q28	low-set thumbs		Navarro E.G. ¹¹⁾
[group 2]			
q25-qter	proximally inserted thumbs	horseshoe kidney	Narahara K. ¹⁰⁾
q31-qter	overlapping fingers	horseshoe kidney	Oka S. ¹²⁾

Group 1 includes the patients with de novo 4q trisomy including q22-23 segment and with thumb and/or renal deformities. Group 2 includes the patients with 4q trisomy other than q22-23 segment and with both thumb and renal deformities.

manifestation⁴). It is interesting to know whether the mutation of PKD2 gene occurred in partial duplication 4q syndrome with kidney anomalies because PKD patients lack congenital somatic malformations such as those listed in Table 1.

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