

Patient Report

Inverted duplication/deletion of the short arm of chromosome 8 in two patients with tetralogy of Fallot

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The relationship between congenital heart defects (CHD) and chromosomal aberration has been well discussed. Payne *et al.* suggested that CHD may often be frequently due to a single-gene defect.¹ It is known that 22q11.2 deletion syndrome is often associated with tetralogy of Fallot (TOF) and aortic arch anomalies.^{2,3} The relationship between CHD and chromosome 8 aberration has also been reported. Deletions in the distal region of chromosome 8p (del8p) are associated with CHD, typically in the form of atrioventricular septal defect.^{4,5} San Luis Valley recombinant chromosome 8 syndrome (SLV Rec8), which is characterized by both deletion of the short arm of chromosome 8 (8p23.1–8pter) and duplication of the long arm of chromosome 8 (8q22.1–8qter), is strongly associated with TOF.^{6–8} Forty-two out of 45 patients with SLV Rec8 exhibited CHD, 17 of them having TOF.⁸ We now report two Japanese patients with TOF who showed a chromosomal abnormality: inverted duplication of the short arm of chromosome 8 (inv dup 8) within deletion of 8p23.1–8pter.

Patient report

Case 1

A Japanese girl aged 2 years and 2 months was the fifth child of healthy parents. At her birth, her father was aged 42 and mother 39. Her eldest brother suffers from mild mental retardation without CHD. She was born at 40 weeks'

gestation after an uncomplicated pregnancy and delivery, and weighed 2776 g. Two days after birth, she was referred to our hospital because of a heart murmur and was diagnosed as having TOF and atrial septal defect. Physical examination revealed hypotonia, prominent forehead, posteriorly angulated ears, broad nose with depressed nasal bridge, wide mouth, high-arched palate, downward slanting eyes (Fig. 1a), and cyanosis in the lips and nail beds. She showed unilateral sensorineural hearing loss. Computed tomography of the brain showed agenesis of the corpus callosum and brain atrophy.

A modified Blalock–Taussig shunt operation was carried out when she was 9 months. Her psychomotor retardation was severe. She could hold up her head at the age of 1 year and 10 months and has not been able to roll over. At 2 years of age, her weight was 8.6 kg (–2.0 SD) and height was 83.2 cm (–0.6 SD).

Case 2

Case 2 involved an 11-year-old Japanese boy, born as the third child after 37 weeks' gestation to a 34-year-old mother and a 36-year-old father. His birthweight was 2163 g. His parents and two brothers were all healthy. He was diagnosed as having TOF and an abnormality of chromosome 8 at 9 months of age. He was admitted to our hospital for a modified Blalock–Taussig shunt operation at 11 years, when his height was 117 cm (–3.9 SD) and weight was 24 kg (–1.7 SD). His dysmorphic features resembled those of case 1: hypotonia; prominent forehead; posteriorly angulated ears; broad nose with depressed nasal bridge; wide mouth; high-arched palate; and downward slanting eyes (Fig. 1b), but he did not show hearing loss. He presently shows evidence of severe motor delay with mental retardation. He can stand only with support and is unable to raise himself from the prone position. Magnetic resonance imaging revealed agenesis of the corpus callosum.

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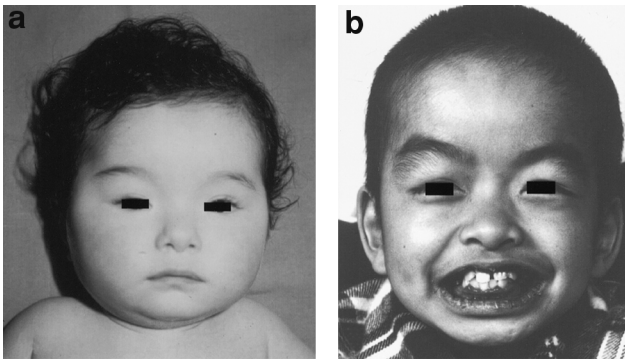


Fig. 1 (a) Case 1, (b) case 2.

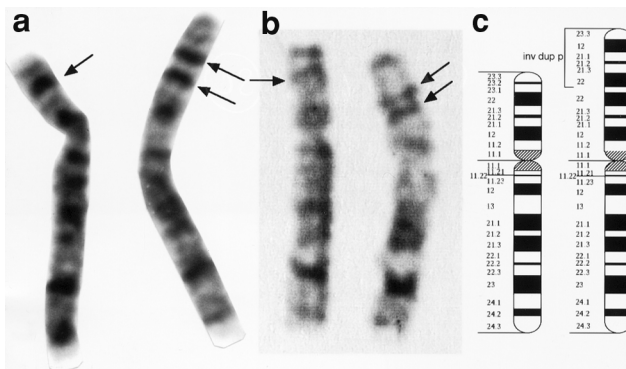


Fig. 2 Chromosomal study and ideogram of chromosome 8. Inverted duplication of the short arm segment 8p12–8p23.1 and deletion of the region 8p23.1–8pter is shown. Break points are 8p12 and 8p23.1 (arrow sign). Karyotype of this patient is der(8)(qter→p23.1:p23.1→p12:). (a) Case 1, (b) case 2, (c) ideogram of chromosome 8.

Cytogenetic analysis

A chromosomal study of high-resolution banding technique of case 1 revealed the presence of the chromosomal aberration on the short arm of chromosome 8 with the breakpoints of 8p12 and 8p23.1 (Fig. 2a). Case 2 showed the same chromosomal aberration (Fig. 2b); inverted duplication of a short arm segment 8p12–8p23.1 and deletion of a region 8pter–8p23.1 (Fig. 2c).

Fluorescence *in situ* hybridization, undertaken with a chromosome 8 painting probe (Oncor, Gaithersburg, USA), yielded consistent fluorescent staining along the entire length of both the normal and abnormal chromosomes 8 of both patients. Cohybridization was carried out using a telomeric (mapped to 8p23.1-pter, Oncor) and chromosome 8 α -satellite probes (Oncor) on the metaphase plates from both patients. No signal for the telomeric region was detected at

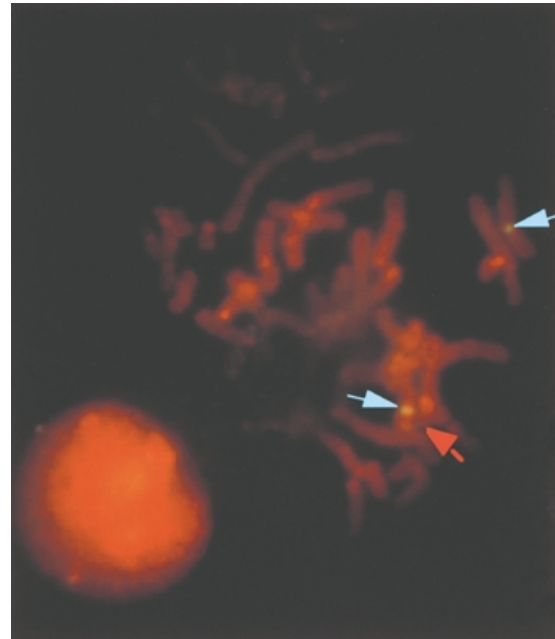


Fig. 3 Fluorescence *in situ* hybridization on chromosomes of case 2 using a telomeric 8p probe and a chromosome 8 α -satellite probe. Normal chromosome 8 shows two signals, one at a centromeric region (blue arrow) and the other at a telomeric region of the short arm (red arrow), whereas abnormal chromosome 8 shows only a centromeric signal.

the short arm end of the abnormal chromosome 8, although hybridization signals were present at both the centromeric and telomeric regions of the normal chromosome 8 (Fig. 3). Therefore, karyotypes of the two cases were der(8)(qter→p23.1::p23.1→p12:), indicating an inverted duplication of the short arm segment 8p12–8p23.1 and a deletion of the region 8pter–8p23.1.

The parents of case 1 had normal karyotypes (data not shown). We could not obtain informed consent for the chromosomal study of the eldest brother of case 1 or the parents of case 2.

Discussion

We reported two Japanese patients with inv dup 8p associated with TOF. The patients had the same chromosome band: der(8)(qter→p23.1::p23.1→p12:). The dysmorphic features of the two patients were similar to those of previous reported cases. At least 50 cases of inv dup 8p have been reported, including 11 patients with CHD. However, there have been no cases of TOF. In patients with inv dup 8p, different break points and regions of duplication have been detected. Dill *et al.* detected chromosomal deletion in a patient with inv

dup 8p with the use of a DNA probe.⁹ More recently, Guo *et al.* suggested that with inv dup 8p, most cases involve a telomeric deletion.¹⁰ At least 27 cases of inv dup 8p that showed deletion of the short arm of chromosome 8 have been described. Among 11 patients who showed similar deletions to our patients, only one had CHD. The CHD in this patient was not TOF, but atrial and ventricular septal defect.¹⁰ Furthermore, it has been reported that del8p is associated with CHD.^{4,5} The characteristic CHD with a del8p is atrio-ventricular septal defect, but not TOF.

A relationship between chromosomal abnormalities and TOF has been reported; 22q11.2 deletion syndrome is often associated with TOF and arch anomalies.^{1,2,11} San Luis Valley recombinant chromosome 8 syndrome, showing a deletion of 8p23.1–8pter and duplication of 8q22.1–8qter, is also associated with TOF.^{6–8} The dysmorphic features of our patients were not similar to those of 22q11.2 deletion syndrome, and our patients did not show thymic hypoplasia, cleft palate, or hypocalcemia. It is known that 22q11.2 deletion syndrome is associated with abnormalities of the aortic arch.¹¹ However, our patients did not exhibit these anomalies. Chromosomal analysis of SLV Rec8 revealed an unbalanced recombinant chromosome 8, designated rec(8)dup(8q)inv(8)(p23q22). Therefore, SLV Rec8 involves both deletion of 8p23.1–8pter and duplication of 8q22.1–8qter. Gelb *et al.* showed that 42 out of 45 cases with SLV Rec8 had CHD, and 17 out of the 42 had TOF, and suggested that chromosome 8 abnormalities are associated with TOF.⁸ However, del8p is associated with CHD, but not TOF.^{4,5} Devriendt *et al.* suggested that the gene responsible for the CHD in del 8p is centromeric from the SLV Rec8 break point.⁴ Alternatively, Gelb *et al.* suggested that CHD in SLV Rec8 may result from the combined effect of the 8q duplication/8p deletion.⁸ Our patients are the first cases of inv dup 8p in Japan to be reported. Furthermore, there are no reports of inv dup 8p with TOF to be reported. Inv dup 8p with TOF may differ according to race.

The region of the deletion in our patients seems identical to those observed in SLV Rec 8. These findings suggest that deletion of 8pter–8p23.1 is causally related to TOF.

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