Patient Report

A case of "Mirror" duplication of chromosome 21 with complete phenotype of Down syndrome

Introduction

The "mirror" (reverse tandem) duplication of chromosome 21 is a rare chromosomal aberration. Several cases have been described previously[1,2]; however, only a few of them demonstrated chromosome breakpoints in detail by using the cytogenetic and/or molecular techniques.[2] The "Down syndrome critical region" (DSCR) is a chromosome 21 segment containing genes responsible for many features of Down syndrome (DS), and is located on 21q22.2 to q22.3.[3,4]

We here report a patient with "mirror" duplication of chromosome 21, whose karyotype is 46,XX, psu idic(21)(q22.3). Clinically, she is completely compatible with DS and does not have any finding caused by monosomy for 21q22.3 region.

Case report

The patient, a 2-year-old Japanese girl, is the second among two children of non-consanguineous healthy parents. Her mother and father were 34 and 39 years old at the time of her birth, respectively. She was born at 38 weeks of gestation with

weight of 3,132 g (mean) and length of 49.0 cm (mean). Pregnancy and delivery were uneventful. She had hyperbilirubinemia at the age of 3 days, and was given phototherapy for 3 days. Because of heart murmur and her facial expression suggestive of DS, she was referred to our hospital at the age of 5 days. Since she fulfilled more than 13 of 25 items in Jackson's checklist (Table 1),[5] she was clinically diagnosed as DS. Cardio-echogram examination revealed that she had tetralogy of Fallot (TOF), small atrial septal defect, and pulmonary infundibular and valvular stenosis. She has been taking diuretics since 22 months of age. When examined at 2 years of age, her weight was 11.45 kg (+0.2 SD) and height 79.9 cm (-1.4 SD), and her total developmental quotient was 60. She was not complicated with Bethlem myopathy and infectious susceptibility. Data from her ordinary biochemical investigations and thyroid hormone examinations were within normal range.

Cytogenetic analysis

Chromosome analysis of cultured peripheral blood lymphocytes of the patient revealed the karyotype as 46,XX,psu idic(21)(q22.3). To validate trisomic/monosomic regions of the abnormal chromosome 21 precisely, we performed FISH using 12 BAC clones which were mapped to 21q22.2-q22.3 region (according to Human GenomeBrowser May 2004 version : http://genome.ucsc.edu/cgi-bin/hgGateway?db=hg11) (Table 2, Fig.2). FISH analysis

clearly revealed that the breakpoint of inverted duplication of the psu idic(21) chromosome was mapped between RP11-867D1 and RP11-323F14. And duplicated and deleted regions were 44.4-Mb and 2.1-Mb in extent, respectively.

Discussion

Patients with "mirror" duplication of the chromosome 21 have been infrequently reported. Either a reciprocal translocation or an exchange between the arms of the chromosome or sister chromatids has been postulated to cause such "mirror" duplication.[2] Unfortunately, chromosome breakpoints were determined in detailed in only a few cases among them. Pangalos et al.[2] reported three patients with "mirror" duplication who had the breakpoints at 21q22.3, as in our patient. However, more detailed analysis revealed that chromosome breakpoints were variable among those including our patient (Table 2, Fig.2).

Our patient as well as Patient B described by Pangalos et al. had TOF. Barlow et al. reported association of the region around PFKL gene on 21q22.3 with TOF.[9] Although the detailed information is not available, similarity of chromosomal organization between the two patients (Table 2 and Fig.2) may confirm the report by Barlow et al.

In addition to our patient, all three patients reported by Pangalos et al. were phenotypically DS, and monosomy of distal 21q22.3, ranging from the telomere to PFKL, apparently had no significant effect on the expression of DS phenotype.

Based on analysis of genotype-phenotype correlation of our case, the region from RP11-323F14 to RP11-135B17 does not appear to play an important role for the phenotype of DS. Monosomy in our patient involved three genes, ITGB2 (CD18), COL6A1, and COL6A2 (Fig.2). Leukocyte adhesion deficiency and Bethlem myopathy are caused by the mutations of ITGB2 gene and COL6A1/COL6A2 gene, respectively;[7,8] however, both gene products, working as a hetero-dimer, would not take any influence of monosomic state on the protein structures. Therefore, it is no wonder that our patient lacks any symptom suggestive of infectious susceptibility or myopathy. Likewise, our patient lacked any other phenotypic feature suggestive of monosomy 21q22.3, such as large ears, high nasal bridge, or retromicrognathia that were described in other reports.[10]

As discussed above, “mirror” duplication of chromosome 21 can provide us an opportunity to precisely determine phenotype-genotype correlation. Further accumulation of those cases and detailed cytogenetic and molecular analyses are warranted.

References

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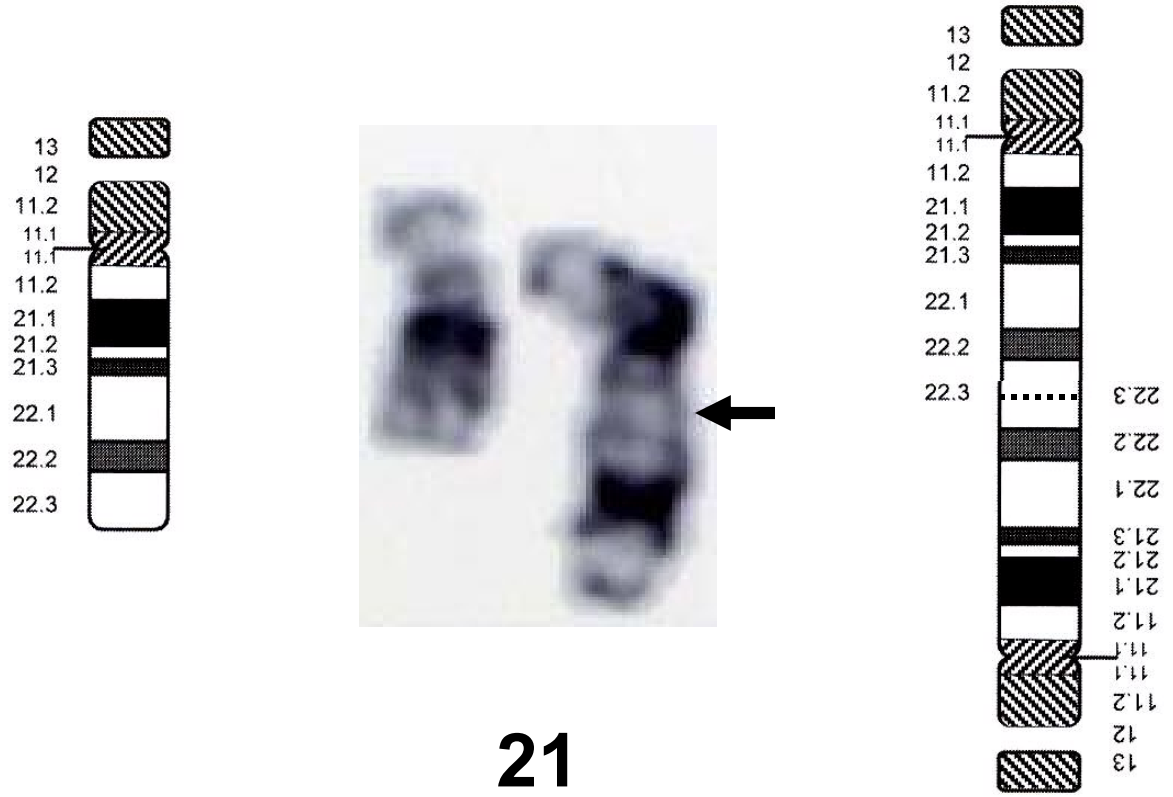

Figure 1

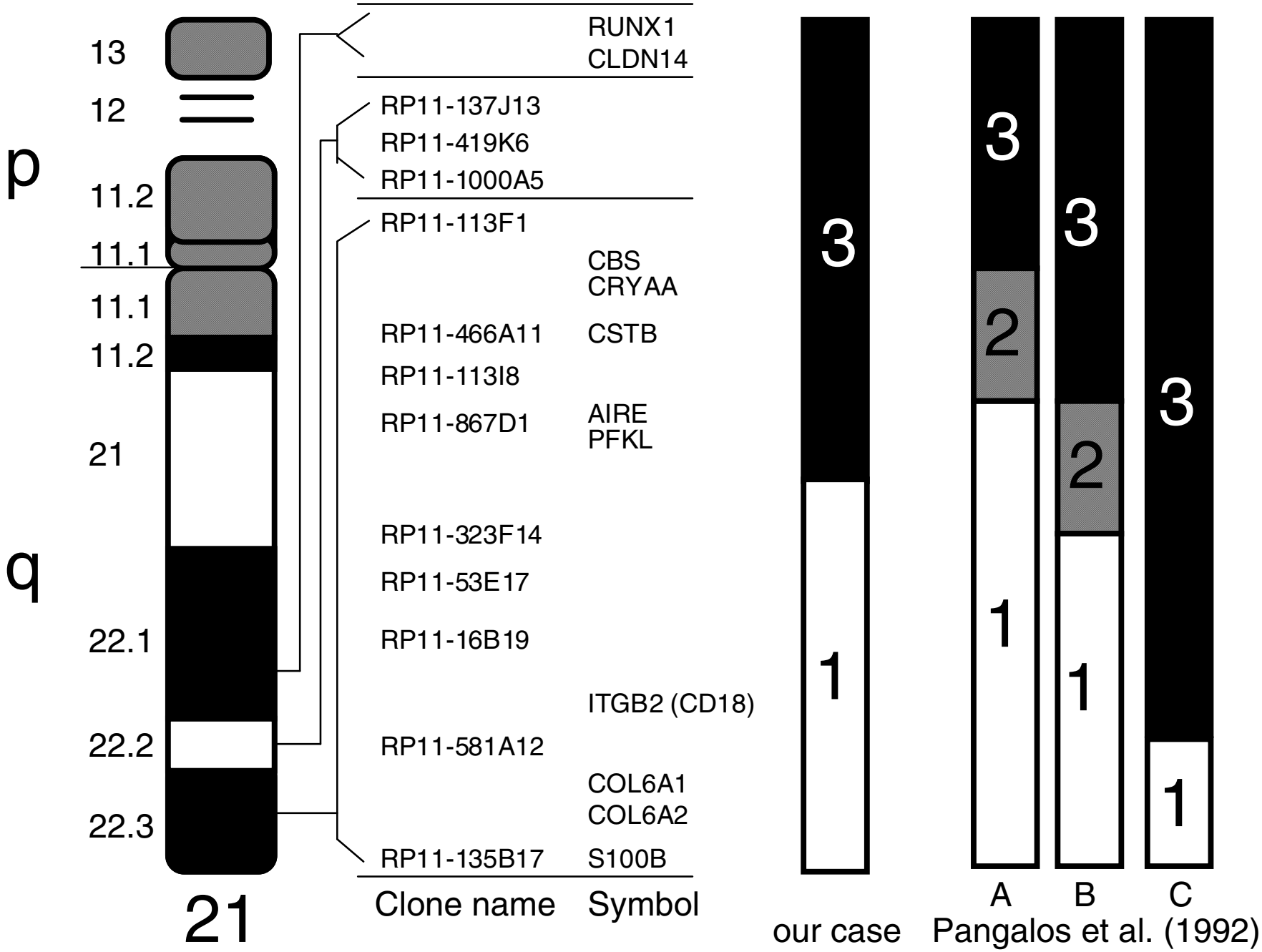
13
12
p
11.2
11.1
11.1
11.2
21
q
22.1
22.2
22.3
21
RUNX1
CLDN14
RP11-137J13
RP11-419K6
RP11-1000A5
RP11-113F1
CBS
CRYAA
RP11-466A11
CSTB
RP11-113I8
RP11-867D1
AIRE
PFKL
RP11-323F14
RP11-53E17
RP11-16B19
ITGB2 (CD18)
RP11-581A12
COL6A1
COL6A2
RP11-135B17
S100B
Clone name
Symbol
3
1
3
2
1
3
2
1
3
1
A
B
C
our case
Pangalos et al. (1992)

Figure 2

Table 1 Jackson's checklist of cases presented in this report and by Pangalos et al.

	Our case	Pangalos et al.(1992) A	B	C
Brachycephaly	+	+	+	+
Oblique eye fissure	+	+	+	+
Epicanthic eye fold	+	+	+	+
Blepharitis, conjunctivitis	+	ND	ND	ND
Brushfield spots – (iris color)	–		–	–
Nystagmus	+	–	–	–
Flat nasal bridge	+	+	+	+
Mouth permanently open	–	–	–	–
Abnormal teeth	ND	–	ND	–
Protruding tongue (macroglossia)	+	–	+	–
Furrowed tongue	+		ND	+
High-arched palate	+	+	–	+
Narrow palate	+	+	–	+
Folded ear (right, left)	–/–	–/–	–/+	–/–
Short neck	+	+	+	+
Loose skin of neck	–	ND	–	ND
Short and broad hands	+	+	+	+
Short fifth finger (right, left)	+/+	+/+	–/–	–/–
Incurved fifth finger (right, left)	–/–	+/+	–/–	–/–
Transverse palmar crease (right, left)	–/–	–/–	–/–	–/+
Gap between first and second toes (right, left)	–/–	+/+	+/+	+/+
Congenital heart defect	+(TOF)	–	+(TOF)	+(VSD)
Heart murmur	+	–	+	+
Joint hyperflexibility	–	–	–	+
Muscular hypotonia	+	+	+	+
Total	16	12	12	15

ND: not done. TOF: tetralogy of Fallot. VSD: ventricular septal defect.
Particularly important signs are underlined.

Table 2 Results of cytogenetic- and molecular analyses of idic(21)(q22.3) chromosome of the patients including present case and three cases reported by Pangalos et al.

Chr band	BAC clone name	Gene Symbol	Genomic Location		Copy Number			
			start	end	Present Case	Pangalos et al. A	B	C
21q22.12		*RUNX1*	35081968	35182857				
21q22.13		*CLDN14*	36754790	36760595				
21q22.2	RP11-137J13		39627180	39780344	3			
21q22.2	RP11-419K6		40647060	40865029	3			
21q22.2	RP11-1000A5		41000852	41204567	3			
21q22.3		478D2 (*D21S42*)				3	3	3
21q22.3	RP11-113F1		42507241	42689355	3			
21q22.3		*CBS*	43346371	43369493				
21q22.3		*CRYAA*	43462209	43465982		2	3	3
21q22.3		*CSTB*	44018259	44020687				
21q22.3	RP11-466A11		44000835	44208698	3			
21q22.3	RP11-113I8		44158888	44352211	3			
21q22.3	RP11-867D1		44478890	44695209	3			
21q22.3		*AIRE*	44530190	44542528				
21q22.3		*PFKL*	44544357	44571683		1	2	3
21q22.3	RP11-323F14		44822749	45022308	1			
21q22.3	RP11-53E17		44865246	45041136	1			
21q22.3	RP11-16B19		44958870	45143207	1			
21q22.3		*ITGB2 (CD18)*	45130313	45165232		1	1	3
21q22.3	RP11-581A12		45395635	45584697	1			
21q22.3		*COL6A1*	46226090	46249391		1	1	1
21q22.3		*COL6A2*	46342469	46374147				
21q22.3	RP11-135B17		46756339	46932616	1			
21q22.3		*S100B*	46842958	46849424		1	1	1

Figure legends

Fig.1 Chromosome analysis by G-banding method of our case; 46, XX, psu idic (21)(q22.3) .

Fig.2 Cytogenic and molecular analyses of chromosome 21q of cases presented in this report or by Pangalos et al. Numbers in columns at right side indicate copy numbers.