Detailed Analysis of Japanese 1q Partial Duplication/Triplication Syndrome

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Search Terms:	trisomy 1q, tetrasomy 1q, congenital, genotype-phenotype correlation, downslanted palpebral fissure, recurrent respiratory tract infection

Detailed Analysis of Japanese 1q Partial Duplication/Triplication Syndrome

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ABSTRACT

Partial 1q trisomy syndrome is a rare disorder, with particularly few cases reported in Japan. Because unbalanced chromosomal translocations often occur with 1q trisomy, it is difficult to determine whether patient symptoms are related to 1q trisomy or other chromosomal abnormalities. The present study evaluated genotype–phenotype correlations of 26 Japanese cases diagnosed with 1q partial trisomy syndrome. DNA microarray was used to investigate the duplication/triplication region of 16 cases. Although there was no overlapping region common to all 26 cases, the 1q41-qter region was frequently involved. One case diagnosed as a pure internal trisomy of chromosome 1q by G-banded karyotype analysis was instead found to be a pure partial tetrasomy by CytoScan HD Array. In four 1q trisomy syndrome cases involving translocation, the translocated partner chromosome could not be detected by DNA microarray analyses despite G-banded karyotype analysis, because there were a limited number of probes available for the partner region. DNA microarray and G-banded karyotyping techniques were therefore shown to be compensatory diagnostic tools that should be used by clinicians who suspect chromosomal abnormalities. It is important to continue recruiting affected patients and observe and monitor their symptoms to reveal genotype–phenotype correlations and to fully understand their prognosis and identify causal regions of symptoms.

Key words: trisomy 1q; tetrasomy 1q; microarray; genotype-phenotype correlation

INTRODUCTION

Partial 1q trisomy syndrome is a rare disorder, with only a few cases reported to date [Balasubramanian et al. 2009; Cocce et al. 2007; Kulikowski et al. 2008; Nowaczyk et al. 2003]. The major symptoms include short stature, multiple minor anomalies, and mental retardation. Unbalanced chromosomal translocation is a common occurrence in patients with 1q trisomy, so it is not always possible to determine whether observed symptoms occur because of the 1q trisomy or other chromosomal abnormalities.

DNA microarray analysis is a powerful diagnostic tool for chromosomal abnormalities that can be used to complement G-banded karyotype analysis, because evaluation of the multiplexed region by this latter technique is sometimes inaccurate.

The present study investigated the clinical signs and symptoms of 26 Japanese patients diagnosed with 1q partial trisomy/tetrasomy syndrome. Microarray analysis was conducted of 16 of these cases to study their duplication/triplication regions. One case was reported previously as the first known survivor of a congenital diaphragmatic hernia with a pure duplication of chromosome 1q [Otake et al. 2009].

MATERIALS AND METHODS

Patients

Twenty-six Japanese patients from 24 families diagnosed by G-banded karyotyping with partial trisomy of the long arm of chromosome 1 were enrolled in this study. One of the patients died at the age of 8 months, and two families each contained two affected brothers. Observed congenital anomalies including developmental delay, hypotonia, and facial anomalies were recorded by the general practitioners of the patients following a questionnaire.

Ethical Approval

This study was approved by the Institutional Review Board Committees of Misakaenosono Mutsumi Developmental, Medical, and Welfare Center. Patients or their parents provided their written informed consent for microarray analysis and the publication of genetic and clinical data after the removal of identifiable information, except one patient (patient ID 15 in Table I) who was acquired an agreement in a document from his parents to be shown his facial photograph in Figure 2.

Molecular Studies

Ten patients whose peripheral blood were available were analyzed by CytoScan HD Array (Affymetrix Santa Clara, CA), six patients had already been analyzed by microarray-based comparative genomic hybridization (array-CGH) at Saitama Children's Medical Center (patient ID 3, 4, 6, and 16 in Table I) and at Tokyo Women's Medical University Institute for Integrated Medical Sciences (patient ID 7 and 14 in Table I), and analysis of the remaining 10 patients was by G-banded karyotyping and fluorescence in situ hybridization (FISH) at their home hospital.

In CytoScan HD Array, 250 ng DNA was processed according to the manufacturer's instructions (Affymetrix) and the genotype was called using the chromosome analysis suite (ChAS) 2.1 provided by Affymetrix. For 1q partial tetrasomy confirmation, FISH was performed using two bacterial artificial chromosome clones as probes: RP11-qq48E24 (red) mapped on 1q:223,027.951-223,195.957, and PR11-224O19 (green) on 1q: 218,465,977-218,651,767. The detailed FISH protocol was previously described [Shimokawa et al. 2004].

RESULTS

A total of 16 1q trisomy/tetrasomy patients were analyzed by DNA microarray: six by array CGH (ID 4–7, 14, 16 in Table I), and ten by CytoScan HD Array (ID 1-3, 8–13, 15 in Table I). The multiplicated chromosomal regions are illustrated in Figure 1. Although no overlapping region was common to all 26 cases, the 1q41-qter region was frequently involved (Fig. I). The largest duplication was of 94 Mb at 1q21.3-q44 (chr1:154,425,885-ter) (ID13 in Table I), and the smallest was of 3.7 Mb at 1q43-q44 (chr1:242,772,255-ter) (ID14 in Table I).

The second smallest multiplexed region included about 7 Mb (ID 15 in Table I), and G-banded karyotype analysis suggested that it was an internal 1q trisomy located at 46,XY,dup(1)(q32.1q42.1) (Fig. 2B). However, CytoScan HD Array analysis showed that it was instead present as four copies. This pure partial tetrasomy is the first known report of partial triplication of the long arm of chromosome 1, and was confirmed by FISH analysis (Fig. 2C, 2D). The affected individual demonstrated more symptoms than other patients with trisomy (Table II).

We also identified two patients showing mosaic ring 1q trisomy, with mosaic ratios of normal cells to trisomy cells of 7:23 (ID 25) and 5:25 (ID 26).

In four cases of 1q trisomy with translocation shown by G-banded karyotype analysis, the translocated partner chromosome could not be detected by DNA microarray. In two of these cases (ID 5 and 8, Table I), distal regions of 1q were translocated to the short arm of chromosome 15, known as the acrocentric chromosome. In the other two cases (ID 10 and 11, two brothers), the 1q distal region was translocated to the telomere of the short arm of chromosome 19 that might have few probes to detect the deletion.

Twelve of the cases examined by DNA microarray had a partial 1q duplication that occurred because of an unbalanced translocation with another chromosome, so it was difficult to explain these symptoms as phenotypes of pure 1q trisomy syndrome. However, other unbalanced translocations involved the short arm of a telochromosome or the terminal region of another

chromosome, and such cases may be more similar to those of pure trisomy in terms of phenotype.

The birth weight of affected patients tended to be low, with eight cases below the 3rd percentile. After birth, major facial features included a prominent forehead (n=13), downslanted palpebral fissures (n=11), microganthia (n=19), and ear anomalies (n=20). Mild cardiac defects were common, such as atrial septal defects, ventricular septal defects, and mild aortic regurgitation. Recurrent respiratory tract infections, and anomalies of the central nervous and urogenital systems (mainly inguinal hernias and cryptorchidism) were also often observed. These symptoms are summarized in Table II. Phenotype–genotype correlations suggested that the number of symptoms increased as the duplicated region became larger, and these tendencies were more obvious for cardiac, respiratory, and urological symptoms. On the other hand, facial features were observed regardless of the duplication size. Developmental delay was observed in all cases, but there was no obvious relationship between the severity of developmental delay and the size of the duplicated region.

DISCUSSION

In the present study, 26 cases of 1q partial trisomy syndrome including two families with two brothers and one previously reported case [Otake et al. 2009] were identified following a questionnaire survey by Japanese pediatric geneticists. Sixteen cases underwent DNA microarray analysis to investigate the relationship between their symptoms and the duplication region. Mental retardation was observed in all cases regardless of duplication size, although the number of other symptoms tended to increase as the duplication region became larger. The major symptoms of 1q multiplication syndrome were shown to be a prominent forehead, downslanted

palpebral fissures, micrognathia, ear anomalies, mild cardiac anomalies, recurrent respiratory tract infections, and mild urogenital disease such as inguinal hernias or cryptorchidism.

Our study also identified the first known partial 1q tetrasomy case using CytoScan HD Array, from an initial diagnosis of internal trisomy by G-banded karyotyping. In four of the 1q trisomy syndrome cases with translocations (ID 5, 8, 10, and 11 in Table I), translocated partner chromosomes could not be detected by DNA microarray analyses despite G-banded karyotype analysis. In all cases, this could be explained by difficulties in identifying suitable probes for detection. In two cases (ID 5 and 8), 1q had been translocated to the short arm of chromosome 15 known as the acrocentric chromosome [Carter 2007]. This chromosomal region carries ribosomal RNA genes which lack a microarray probe, so it was not possible to detect the change in multiplication number. In the other two cases (ID 10 and 11, two brothers), 1q had been translocated to the telomere of the short arm of chromosome 19, that also has few microarray probes.

Two ring chromosome 1 cases were found in the 10 cases analyzed only by G-banded karyotype analysis. Almost all previous ring chromosome 1 cases have exhibited trisomy mosaicism [Kosztolanyi et al. 2011; Wray et al. 2007]. Only one case with a non-mosaic ring chromosome 1 has been reported, and the supernumerary chromosome of this case was revealed to be a segment of 1q12q21.3 including at least 6 Mb of long arm euchromatin [Barbi et al. 2005]. This suggests that it is difficult for a ring chromosome case with a large part of chromosome 1 to survive except as a mosaicism.

Few adult cases of 1q trisomy syndrome have been reported previously [Barros-Nunez et al. 1989; Fryns et al. 1980; Lukusa et al. 1998; Van Buggenhout et al. 1998], so the prognosis is poorly understood. Moreover, because the eldest case of the present study is only 21 years old, adult onset symptoms have yet to be revealed and the course of symptoms is incomplete.

Susceptibility to respiratory tract infections is common in previous 1q multiplication syndrome cases[Balasubramanian et al. 2009; Barros-Nunez et al. 1989]. In our study some cases required frequent hospitalizations and a home oxygen therapy (HOT), but they often appeared to improve with age to be able to stop HOT and the frequency of hospitalization was decreased. Similarly, although psychomotor developmental delay is often severe in infancy, our patient with 1q tetrasomy, 5 years old boy indicated developmental delay, but started walking at 1 year, 9 months old and recently began to speak sentences haltingly. Therefore, to fully understand the prognosis of these patients, we must continue to observe their symptoms, particularly those of the older cases with 1q multiplication.

The 1q41-qter of chromosome 1 was the most frequently involved region in our study, even though it contains no known characteristic features such as low-copy number repeats. Although the partner chromosomes were various, there were a number of symptoms common to translocated and pure trisomy/tetrasomy cases such as anomalies of the eyes, ears, nose, and mouth, and recurrent respiratory tract infections. However, unbalanced translocations involving different chromosomes sometimes modified symptoms such as ptosis, scoliosis, and hand/foot malformations. Therefore, we propose that when clinicians encounter a patient with such symptoms, they should suspect 1q multiplication syndrome and undertake molecular analysis using G-banded karyotyping and DNA microarray. Caution must be exercised when interpreting such analyses, however, because abnormalities in G-banded karyotyping do not always indicate genome imbalances and *vice versa*. Additionally, because it can be difficult to quantify precise copy numbers by G-banding alone, clinicians suspecting chromosomal abnormalities should also consider using DNA microarray as a compensatory diagnostic tool.

In conclusion, we report 26 Japanese 1q trisomy/tetrasomy syndrome patients. Sixteen cases were examined by microarray analysis, providing useful information about the relationship between symptoms and duplication regions.

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Figure Legends

FIG. 1 Schematic of the multiplexed regions of the 26 cases with partial 1q trisomy/tetrasomy syndrome. Blue bars represent males, and red bars represent females. The cases are divided into those with translocations, those with pure multiplications, and those for whom DNA microarray was not performed. Striped bars represent 'mosaic' cases. The asterisk indicates the tetrasomy case.

FIG. 2 A 1q partial tetrasomy case. (A) Facial features. Prominent forehead, triangle face, downslanted palpebral fissures, widely spaced eyes, low set and deformed ears, thin upper lip, and microganthia/retrognathia were existed. (B) G-band karyotype analysis showing the diagnosis of 1q partial trisomy (arrows). (C) Dual color FISH of a metaphase cell. The multiple copies cannot be clearly seen because the region is very narrow. (D) Dual color FISH of an interphase cell. Three copies of one chromosome can be seen, each with three probes. The other chromosome of the pair is normal.

Table I. Results of the microarray and G-banded karyotyping

Patient ID	Chromosomal region	Locus min	Locus max	Size (Mb)	Partner chromosome	Additional information	Array platform
With translocation							
1	1q42.13q44 x3	228,715,922	Telomere	20.5	3p		CytoScan HD
2	1q42.11q44 x3	224,105,294	Telomere	25.1	10q		CytoScan HD
3	1q41q44 x3	222,850,184	Telomere	26.4	3p	brothers	aCGH
4	1q41q44 x3	222,850,184	Telomere	26.4	3p		aCGH
5	1q41q44 x3	222,484,842	Telomere	26.8	15p		CytoScan HD
6	1q41q44 x3	220,743,362	Telomere	28.5	4q		aCGH
7	1q41q44 x3	217,145,425	Telomere	32.1	4q		aCGH
8	1q41q44 x3	216,695,471	Telomere	32.6	15p		CytoScan HD
9	1q32.3q44 x3	213,082,506	Telomere	36.2	17p		CytoScan HD
10	1q32.2q44 x3	208,088,170	Telomere	41.2	19p	brothers	CytoScan HD
11	1q32.2q44 x3	208,081,639	Telomere	41.2	19p		CytoScan HD
12	1q25.2q44 x3	178,804,354	Telomere	70.4	Xq		CytoScan HD
13	1q21.3q44 x3	154,425,885	Telomere	94.8	Xq		CytoScan HD
Pure' trisomy/tetrasomy							
14	1q43q44 x3	242,772,255	Telomere	3.7	-	4q trisomy	aCGH
15	1q41q42.12 x4	217,681,385	224,643,997	7.0	-	tetrasomy	CytoScan HD
16	1q32.1q41x3	206,571,280	223,308,139	16.7	-		aCGH
Without microarray							
17	1q43q44 x3				6q		-
18	1q42.3q44 x3				14q		-
19	1q42.1q44 x3				-		-
20	1q42.1q44 x3				14q		-
21	1q41q44 x3				21q		-
22	1q41q44 x3				-		-
23	1q21q31 x3 (mosaic, 9:21)				-		-
24	1q12q23 x3				-	died at 8 months	-
25	ring (mosaic, 7:23)				-		-
26	ring (mosaic, 5:25)				-		-

aCGH, microarray-based comparative genomic hybridization

Table II-1. Clinical features in patients with our partial trisomy 1q

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at participation (years)	6m	5	4	2	1	2	17	14	19	1	3	3	1
Partner chromosome	3p	15p	10q	3p	3p	4q	4q	15p	17p	19p	19p	Xq	Xq
Low birth weight	-	-	+	-	-	-	NA	+	-	NA	-	+	+
Large Head circumstance at birth	+	+	-	+	+	+	NA	NA	+	NA	NA	-	+
Mental retardation	+	+	++	NA	++	++	+++	+++	++++	NA	+	++	NA
Head, face													
Macrocephaly	-	-	-	-	-	-	+	-	+	+	+	+	-
Wide fontanelles	+	-	-	-	-	+	-	-	-	+	-	-	-
Prominent forehead	+	+	-	+	+	+	-	+	-	+	+	+	-
Triangular face	-	-	+	-	-	-	-	+	-	+	+	+	-
Downslanted palpebral fissures	-	-	-	-	-	-	+	+	+	+	+	-	-
Widely spaced eyes	-	+	-	+	+	+	+	-	+	-	-	-	+
Low-set ear	+	+	+	-	+	-	-	+	+	+	+	+	-
Deformed ear	+	-	-	+	+	+	-	-	+	+	+	+	-
Depressed nasal bridge	+	-	-	+	+	-	-	+	-	+	+	+	-
Low nasal tip	-	-	-	+	+	+	-	-	-	+	+	+	-
Long philtrum	+	-	-	-	-	+	-	-	+	+	+	+	-
High palate	+	+	-	-	-	-	+	-	+	+	+	+	-
Thin upper lip	+	-	-	+	+	-	-	-	+	+	+	-	-
Micrognathia/Retrognathia	+/+	-/-	+/-	+/+	+/+	+/+	+/-	+/+	-/+	+/+	+/+	+/+	+/-
Short neck	-	-	-	+	+	+	-	+	-	+	+	+	-
Hirsutism	-	-	-	+	+	+	+	-	+	-	-	-	-
Cardiovascular system	-	-	-	-	-	MR	VSD	-	AS, PS	ASD	ASD	ASD	ASD (severe)
Central nervous system													
Ventriculomegaly	-	-	+	+	-	-	-	+	-	+	+	+	-
Hydrocephalus	-	-	-	-	-	-	-	-	-	-	-	+	+
Cerebellar hypoplasia	-	-	-	-	-	-	-	+	-	-	-	-	+
Others	-	-	-	hypoplasia of cerebral parenchyma and corpus callosum	-	-	corpus callosum hypoplasia	-	-	cerebral parenchyma hypoplasia	hypoplasia of optic nerves	-	-
Respiratory system													
Laryngomalacia	+	-	+	+	-	+	-	-	-	±	±	-	+
Recurrent respiratory tract infection	-	-	+	+	-	-	-	+	+	+	+	+	-
Chest hypoplasia	-	-	-	-	-	+	-	-	-	-	-	-	+
Gastrointestinal system	-	-	-	-	-	-	-	-	+	-	-	+	-
Urogenital system	+	-	-	-	-	+	-	+	-	+	+	+	+
Skeleton													
Axial	-	-	-	-	-	-	scoliosis	-	scoliosis	-	-	-	-
Fingers	short finger	polydactyly	-	hypoplastic nail	-	slender finger	slender finger	hypoplastic nail	-	polydactyly	-	-	-
Toes	-	-	-	-	-	-	-	talipes valgus	-	-	-	-	-
Overlapping toes	-	-	+	+	-	+	-	+	-	-	+	-	+

+; present, -; absent, NA; not available, (+; mild, ++; moderate, +++; severe, ++++; most severe in the 'Mental retardation' raw), ASD; atrial septal defect, VSD; ventricular septal defect, MR; mitral regurgitation, TR; tricuspid regurgitation, AS; aortic valve stenosis, PS; pulmonary stenosis, TOF; tetralogy of Fallot,

Table II-2. Clinical features in patients with our partial trisomy 1q

Patient ID	14	15	16	17	18	19	20	21	22	23	24	25	26
Age at participation (years)	21	5	15	17	2	7	2	10	8	7m	8m*	10	12
Partner chromosome				6q	14q		14q	21q					
Low birth weight	+	-	+	-	-	+	-	NA	+	-	+	-	NA
Large Head circumstance at birth	-	-	-	+	+	NA	+	NA	-	NA	-	-	NA
Mental retardation	++	+	++	+++	+	+	+	NA	+++	+++	NA	NA	NA
Head, face													
Macrocephaly	-	-	-	-	+	+	+	-	-	+	-	-	-
Wide fontanelles	-	+	-	-	-	-	+	-	-	+	-	-	-
Prominent forehead	-	+	-	-	-	+	+	-	-	+	-	-	-
Triangular face	-	+	-	+	-	-	+	-	-	-	-	-	-
Downslanted palpebral fissures	+	+	+	+	-	-	+	-	-	+	-	-	-
Widely spaced eyes	+	+	-	+	-	-	-	-	-	-	-	-	-
Low-set ear	+	+	-	+	+	+	+	-	-	+	-	-	-
Deformed ear	-	+	+	+	-	+	-	-	-	+	-	-	-
Depressed nasal bridge	-	-	+	-	-	+	-	+	-	+	-	-	-
Low nasal tip	-	-	+	-	-	-	-	-	-	-	-	-	-
Long philtrum	-	-	+	+	-	+	-	+	-	+	-	+	-
High palate	+	+	-	+	-	-	+	+	-	+	-	-	-
Thin upper lip	-	-	+	-	-	+	-	-	-	-	-	-	-
Micrognathia/Retrognathia	+/-	+/-	+/+	+/-	-/-	-/+	+/-	+/+	-/-	+/+	-/-	+/-	-/-
Short neck	-	-	-	-	-	+	-	+	-	+	-	-	-
Hirsutism	-	-	-	-	-	+	-	+	-	+	-	-	-
Cardiovascular system	-	TR	ASD	-	-	ASD	-	-	-	-	TOF	VSD	VSD
Central nervous system													
Ventriculomegaly	-	+	-	-	-	-	+	-	+	-	-	-	-
Hydrocephalus	-	-	-	+	-	-	-	+	-	-	-	-	-
Cerebellar hypoplasia	-	-	-	-	-	-	-	+	-	+	-	-	-
Others	-	hypoplasia of optic nerves and brainstem, retinochoroidal atrophy	-	-	-	-	-	-	-	corpus callosum hypoplasia	hypoplasia of optic nerves, retinochoroidal atrophy	-	-
Respiratory system													
Laryngomalacia	-	+	-	-	+	+	+	+	-	+	-	+	-
Recurrent respiratory tract infection	-	-	-	-	+	+	+	+	-	+	-	-	-
Others	-	-	flat larynx, lung hypoplasia	-	-	-	-	flat larynx	-	-	-	-	-
Gastrointestinal system	+	-	-	-	+	-	-	-	-	+	-	+	+
Urogenital system	+	-	+	-	-	+	-	+	+	+	-	-	-
Skeleton													
Axial	-	-	-	scoliosis	-	scoliosis	-	scoliosis	-	-	-	scoliosis	-
Fingers	-	polydactyly	-	slender finger	polydactyly	polydactyly	polydactyly, syndactyly	-	-	slender finger, comptodactyly	short finger	-	-
Toes	-	talipes varus	-	-	-	flat foot	-	talipes valgus, hypersensitive planta	-	flat foot	-	talipes varus	talipes varus
Overlapping toes	-	+	+	+	+	-	+	-	-	+	-	-	-

+; present, -; absent, NA; not available, (+; mild, ++; moderate, +++; severe, ++++; most severe in the 'Mental retardation' raw), ASD; atrial septal defect, VSD; ventricular septal defect, MR; mitral regurgitation, TR; tricuspid regurgitation, AS; aortic valve stenosis, PS; pulmonary stenosis, TOF; tetralogy of Fallot, *age of death.

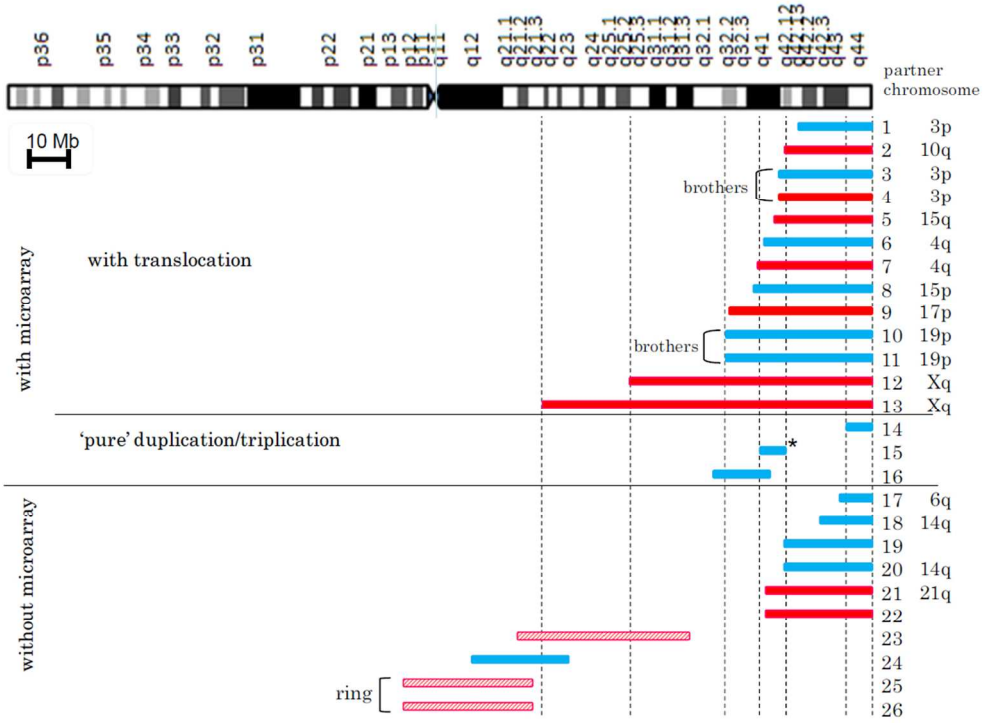

FIG. 1 Schematic of the multiplexed regions of the 26 cases with partial 1q trisomy/tetrasomy syndrome. Blue bars represent males, and red bars represent females. The cases are divided into those with translocations, those with pure multiplications, and those for whom DNA microarray was not performed. Striped bars represent 'mosaic' cases. The asterisk indicates the tetrasomy case.
414x305mm (72 x 72 DPI)

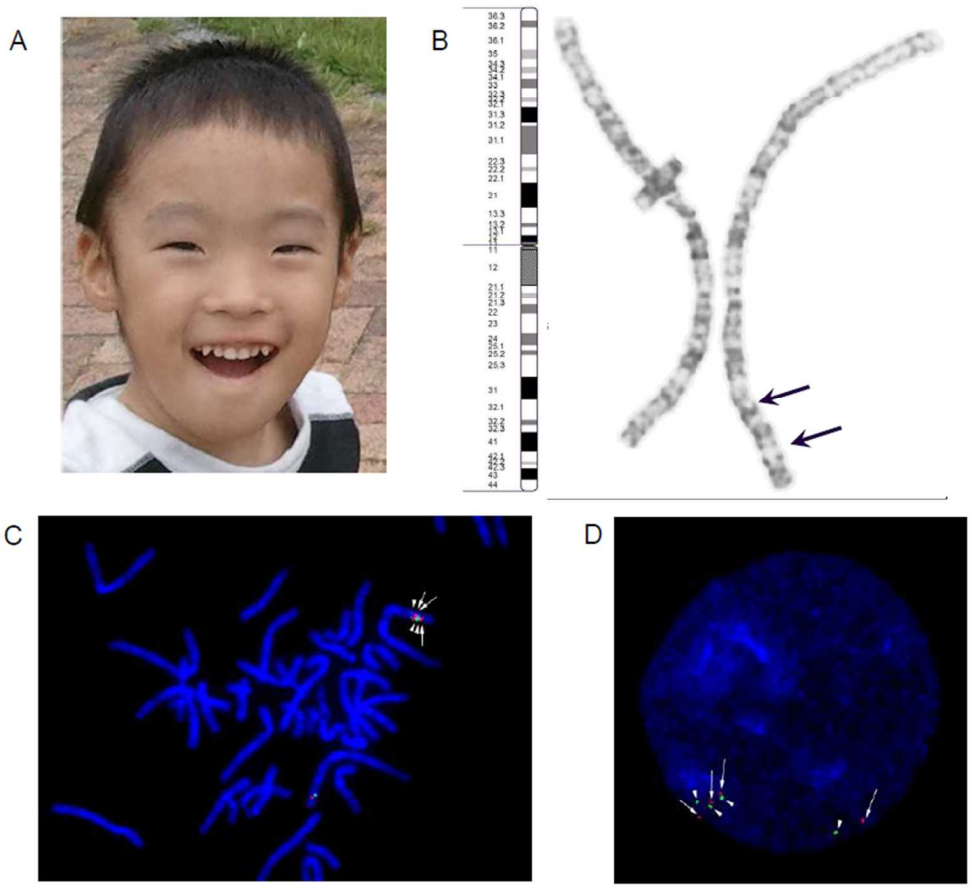

FIG. 2 A 1q partial tetrasomy case. (A) Facial features. Prominent forehead, triangle face, downslanted palpebral fissures, widely spaced eyes, low set and deformed ears, thin upper lip, and microganthia/retrognathia were existed. (B) G-band karyotype analysis showing the diagnosis of 1q partial trisomy (arrows). (C) Dual color FISH of a metaphase cell. The multiple copies cannot be clearly seen because the region is very narrow. (D) Dual color FISH of an interphase cell. Three copies of one chromosome can be seen, each with three probes. The other chromosome of the pair is normal.
301x271mm (72 x 72 DPI)