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A Father and Son With Mental Retardation, a Characteristic Face, Inv(12), and Insertion Trisomy 12p12.3-p11.2

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A male patient with mental retardation (MR) and mild facial features was shown by high-resolution G-banding to have pericentric inversion of chromosome 12 with an unknown segment inserted into the long arm of the inverted chromosome [46,XY,inv(12)(pter → p11.2::q14.1 → p11.2::?::q14.1 → qter)]. Both the inverted chromosome 12 and clinical manifestations were transmitted to his son. Karyotypes of the propositus' parents were normal. Studies with fluorescence in situ hybridization (FISH) in both the propositus and his son revealed that the extra segment was derived from 12p. Further FISH mapping and the genome-wide copy number detection by GeneChip Mapping 100K Array showed that an 11-Mb segment of 12p between two BAC clones, RP11-22H10 and RP11-977P2, was inserted at one of the reunion points in the long arm of the inv(12) chromosome. Analysis of parent–child transmissions of duplicated alleles using microsatellite markers defined the maternal origin of the chromosomal anomaly in the propositus and suggested a mechanism of its formation through a sister-chromatid rearrangement (SCR), that is, mismatched pairing and unequal crossover between sister chromatids as well as three break rearrangements including a U type rearrangement. Karyotypes of the propositus and his son were thus inv(12)(pter → p11.22::q14.1 → p12.3::q14.1 → qter). This is the first report of "pure" proximal 12p-trisomy including p12.3–p11.22 region. © 2006 Wiley-Liss, Inc.

Key words: inversion; duplication; partial trisomy 12p; mental retardation; FISH; genome-wide copy number detection

INTRODUCTION

Since the initial description of the trisomy 12p syndrome by Uchida and Lin [1973], a total of 39 additional cases have been described [Plaja et al., 1998; Tekin et al., 2001; Zumkeller et al., 2004; Tsai et al., 2005]. Common phenotype constituting the pure trisomy 12p syndrome included increased birth weight, hypotonia, developmental delay, and facial features characterized by a round face with prominent cheeks, prominent forehead, broad nasal bridge, short upturned nose, long philtrum, thin upper lip, broad everted lower lip, and abnormal ears [Tsai et al., 2005].

We encountered a 34-year-old man with mental retardation (MR) and mild facial anomalies who was shown by high-resolution G-banding to have pericentric inversion [46,XY,inv(12)(p11.2q14.1)] with an extra chromosomal material of unknown origin inserted into 12q14. Both the karyotype and phenotype were transmitted to his son. Assuming that the MR and facial features in this family was associated with their chromosome abnormalities, we carried out an investigation, especially focusing on the unknown extra material and inversion breakpoints.

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MATERIALS AND METHODS

Clinical Report

The propositus, a 34-year-old man, was born with full-term delivery to a G1P1, 23-year-old mother with unremarkable pregnancy history. Consanguinity was denied. Birth weight was 3,200 g, length 46 cm, and OFC 39 cm. He sat alone at 9 months, crawled, walked alone, and spoke single words at age 15 months. He was first seen by us because of intellectual disability at age 9 years. Clinical observation at that time showed mental retardation and a characteristic face. GTG-banding showed that his karyotype was inv(12)(p11q14). Despite the advice for prenatal diagnosis, the propositus got married and had a son in August 2003. Both the propositus and his son were interviewed again in November 2004, because the propositus' parents observed that their grandson had almost the same condition as their son. On physical examination, the propositus' height was 165 cm, weight 65 kg, and OFC 58 cm and facial features of broad forehead, short nose, and lax lower lip were found (Fig. 1A). Psychometry showed moderate mental retardation with estimated IQ of 39. EEG suggested neuronal dysfunction in the cerebral cortex. The brainstem evoked potential implicated impairment of the visual pathway bilaterally. CT and MRI were normal. High-resolution GTL-banding showed a 46,XY,inv(12)(p11.2q14.1) karyotype with an extra chromosomal material of unknown origin inserted into the long arm of the inverted chromosome 12. The karyotypes of his parents were normal. Thus, the karyotype is interpreted as 46,XY,inv(12)(pter → p11.2::q14.1 → p11.2::?::q14.1 → qter) de novo (Fig. 1B).

The propositus' son was born after a full-term delivery to a 25-year-old G1P1 mother with an unremarkable pregnancy history. Consanguinity was denied. Apgar scores were 6–7 at 1 min because of his mild hypoxia due to a circular umbilical cord around his neck and 10 at 5 min. Birth weight was 4,400 g, length 48 cm, and OFC 40 cm. He raised his head at age 3 months, sat alone at 8 months, said single words, and walked alone at 13 months. He had a patent anterior fontanel. He resembled the father in facial appearance (Fig. 1A). Psychometry at age 15 months using Bayley Infantile Intelligence Development Scale showed that, Intelligence Developmental Index was equivalent to age 11 months and Motor Developmental Index equivalent to 13 months. Asymmetric infantile sleeping EEG demonstrated dysfunction of the cerebral cortex. CT and MRI were normal. High-resolution GTL-banding showed a 46,XY,inv(12)(pter → p11.2::q14.1 → p11.2::?::q14.1 → qter)pat karyotype (Fig. 1B). Karyotype of his mother was normal.

Fluorescence In Situ Hybridization (FISH) Analysis

Clones were obtained from the RPCI-11 BAC libraries and BAC DNA was isolated using an Automatic Plasmid Isolation System (PI-100, Kurabo Industries, Osaka, Japan). FISH using BAC DNA as a probe was performed on metaphase chromosomes of the propositus and his son. BAC clones mapped to 12p12-p11 and 12q14 were selected using the UCSC genome browser database (http://genome.ucsc.edu) and the contig map covering 12p12-p11 [Sugawara et al., 2003]. FISH analysis was as described previously [Shimokawa et al., 2004].

Genome-Wide Copy Number Detection

DNA from the propositus and his son was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Maxi Kit (Qiagen GmbH, Hilden, Germany). DNA labeling, hybridization, washing, and staining for the GeneChip Mapping 100K Array™ (Affymetrix, Inc., Santa Clara, CA) were performed according to the standard Single Primer GeneChip Mapping Assay protocol (Affymetrix).

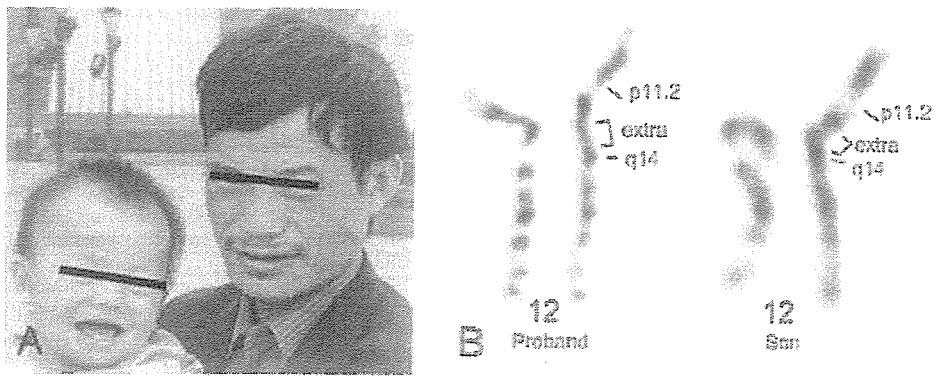

FIG. 1. A: Facial appearance of the propositus at age 33 years and his son at age 15 months. Note the broad forehead, short nose, and lax lower lip. B: GTG-banded partial karyotype, showing inv(12)(p11.2q14.1) with an extra material inside the inversion.

Detection was performed with an Affymetrix Fluidics Station 400 and the GeneChip Scanner 3,000 with high-resolution scanning patch. The signal intensity data from the GeneChip Operating software were analyzed by GeneChip DNA Analysis Software (GDAS 2.0). Individual SNP copy numbers and chromosomal regions with gain or loss were evaluated with the Affymetrix GeneChip Chromosome Copy Number Tool. Copy numbers higher than 2.5 were plotted for each chromosome separately with green bars, copy numbers lower than 2.5 are represented by red bars.

Short Tandem Repeat Polymorphism (STRP) Analysis

Short tandem repeat polymorphism (STRP) analysis was performed on DNA from the propositus, his son, and the propositus' parents using 12 microsatellite markers that are located around the duplication region, according to Généthon Genetic Map [Dib et al., 1996]. PCR was performed at 95°C for 12 min, then for 10 cycles at 95°C for 30 sec, 52°C for 30 sec, and 72°C for 40 sec, finally for 25 cycles at 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec in a 20 μl reaction volume containing 50–100 ng genomic DNA, 1 U AmpliTaq Gold polymerase (Applied Biosystems, Foster City, CA), 500 nM primers, 1.5 mM $MgCl_2$, 200 μM dNTP, and 1× PCR buffer. PCR products were electrophoresed on the ABI Prism 3100 Genetic Analyzer (Applied Biosystems) and analyzed with software, GeneScan Analysis v.3.7, and Genotyper v.3.7 (Applied Biosystems).

RESULTS

FISH Analysis of the Inversion Breakpoints and the Extra Chromosome Material

A series of clones that are mapped to 12p12.1-11.22 (Fig. 2A) all hybridized to the short arm of normal chromosome 12 and to the both short and long arms of the inv(12) chromosome. In addition, three signals for these clones were shown in interphase nuclei (data not shown). These findings indicated that the extra material inserted into the inv(12) was derived from a 12p12.1-p11.22 segment.

BAC clone RP11-977P2 showed a common signal at the normal 12p and the long arm of the inv(12), but the signal on the inv(12) was 10-fold less intense (Fig. 2B), the finding implicating that the 12p breakpoint (the proximal boundary of the duplicated segment) of the inv(12) was covered by this clone. RP11-22H10 and RP11-606D9 showed a common signal on the short arms of both the normal 12 and the inv(12), and a 10-fold less intense signal at the long arm of the inv(12) than the common signals. It is most likely that a boundary of the duplicated segment was located within a 29-kb region between nucleotide position (nt) 17695757 and nt 17725491 according to the sequences of RP11-679C18 and RP11-22H10. Therefore, the inv(12) chromosome was confirmed to have a 12p12.3-p11.22 duplication spanning about 11 Mb from nt 17695757 to nt 28878898. FISH with double-color probes, RP11-977P2 and RP11-768G10, confirmed an inverted insertion of the segment into the 12q14.1 breakpoint (Fig. 2B). Three BAC-contig clones telomeric to RP11-1149N16 assigned the 12q breakpoint within RP11-41H6, which showed a common signal at 12q in both normal and inv(12) chromosomes as well as a faint signal at 12p of the inv(12) (Fig. 2C).

Increased Copy Number of a 12p Segment

Using the Affymetrix GeneChip, we detected the increased copy number of a 12p segment in the propositus and his son. Figure 3 shows a detailed plot of the copy number for individual SNP loci along chromosome 12p from the two patients. Based on the estimated copy numbers, SNP loci at 12p11.22 (*Hin*dIII: SNP_A-1662961 and SNP_A1719060) and at 12p12.3 (*Xba*I: SNP_A-1716707 and SNP_A-1757551) have 2.5- to 3.5-fold amplification (data not shown) concurrently in the propositus and his son, the results being consistent with the mapping profile by the FISH study.

Parental Origin and Mechanism of Formation of the 12p Duplication

As the propositus' parents had normal karyotypes, aberrant chromosome 12 of the propositus was the de novo type. Parent–child allele transmissions were analyzed with 12 microsatellite markers located within the duplicated region. Six markers were informative to trace the allele transmissions, and clearly defined the aberration of maternal origin (Table I). In view of the results of the FISH and GeneChip Analyses, both the propositus and his son should have three copies of alleles at each polymorphic site in the duplicated region. However, since there were no polymorphic sites showing three distinct alleles, one of the two alleles detected at each site in the two patients must be duplicated. In addition, such alleles deduced to be involved in the duplication commonly in the two patients were all derived from the propositus' mother (Table I). These findings were well interpreted to be a result of sister-chromatid rearrangement (SCR).

DISCUSSION

Using FISH with genomic clones and an Affymetrix genome-wide copy number detection system, we have identified in the patient and his son an 11-Mb duplication of a 12p12.3-p11.2 segment inserted into the 12q breakpoint of inv(12)(p11.22q14.1). To our

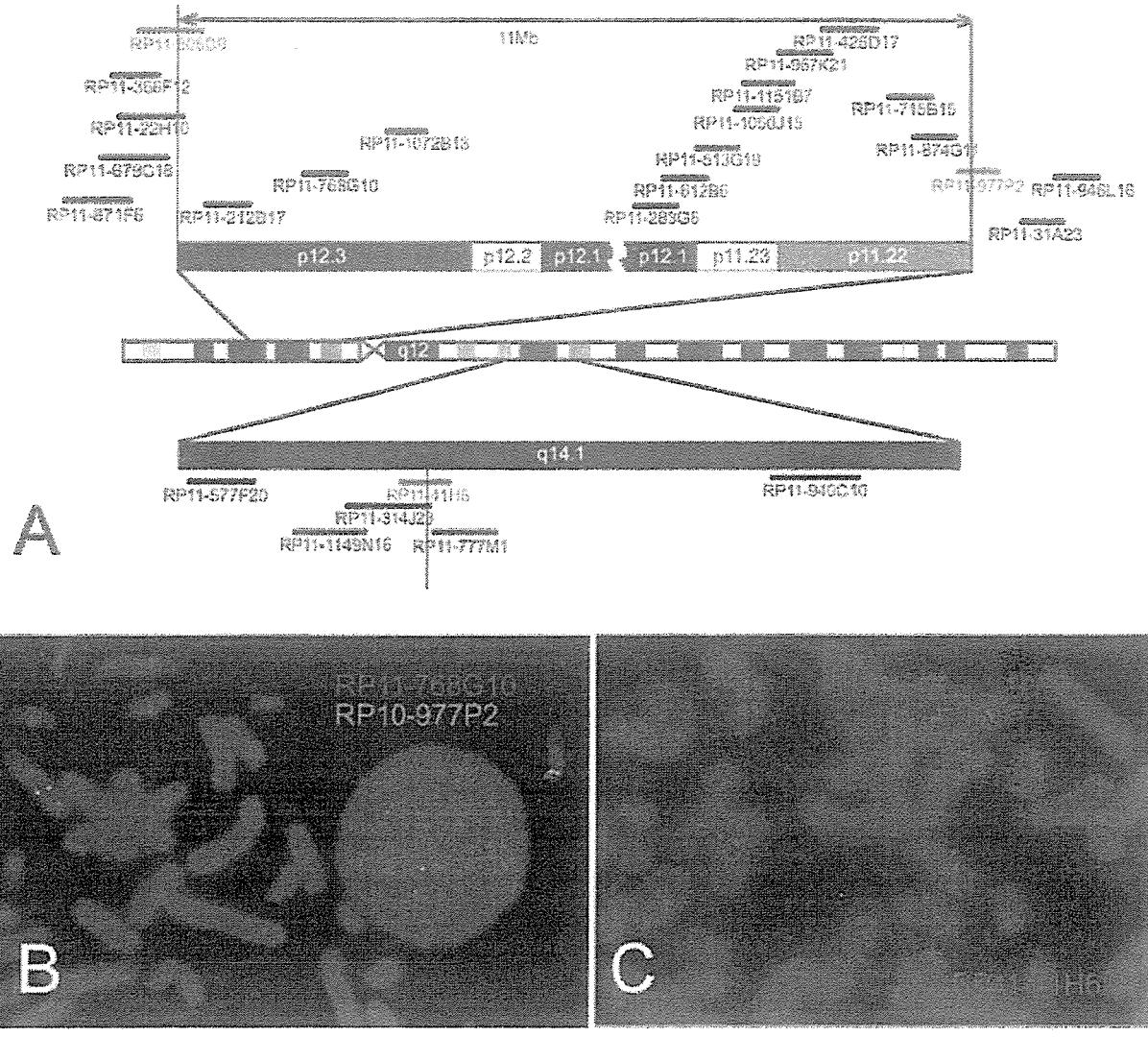

FIG. 2. **A**: Ideogram showing three breakpoints and the extent of a duplicated segment of chromosome 12 seen in the propositus and his son, and a series of BAC clones mapped to 12p12.1-11.22, 12p12.3, 12p11.22, and 12q14.1. Bar at the bottom represents an 11-Mb duplication of 12p. **B**: Two-color FISH analysis with BAC clones RP11-768G10 (red) and RP11-977P2 (green) as probes, showing a signal order of red-green-green-red from the telomere to the centromere in the derivative chromosome 12. The finding indicates that a portion of the short arm of chromosome 12 is inserted into its long arm, together with a pericentric inversion. **C**: FISH analysis of the propositus using a BAC clone (RP11-41H6), showing signals in both the normal 12p and the long arm of the inv(12) chromosome 12 in addition to a faint signal on its short arm. The finding indicates that the 12q breakpoint of the inverted chromosome lies within the clone.

knowledge, this is the first reported "pure" proximal trisomy 12p. With microsatellite analysis, we also defined the mechanism of formation of the duplication and inversion in the propositus to be of maternal origin, that is, SCR due to mismatched pairing and unequal crossover between sister chromatids, as well as three break rearrangements including a U type rearrangement [Van Dyke, 1988] (Fig. 4A).

Several mechanisms were possible to explain the clinical manifestations of mental retardation and facial features in our patients, for example, a functional imbalance of chromosome such as a dose effect of the duplication of 12p or disruption of gene(s) at the inversion breakpoints. However, according to information from the NCBI and the UCSC database, we did not find any known gene or refseq at the two breakpoint regions. Furthermore, disruption of gene(s) at either breakpoint was unlikely, because such a gene can be compensated by its intact copy on the duplicated chromosome.

Using the GeneChip Mapping 10K SNP Array, Rauch et al. [2004] concluded that the deduction of reliable cut off levels for array peaks allowed rapid molecular karyotyping with high sensitivity and specificity. Employing the GeneChip Mapping 100K SNP Array with a much denser SNP distribution that allows at least 0.5-Mb resolution, we successfully determined the extent of duplicated segment in our family and reproduced the results of FISH analysis.

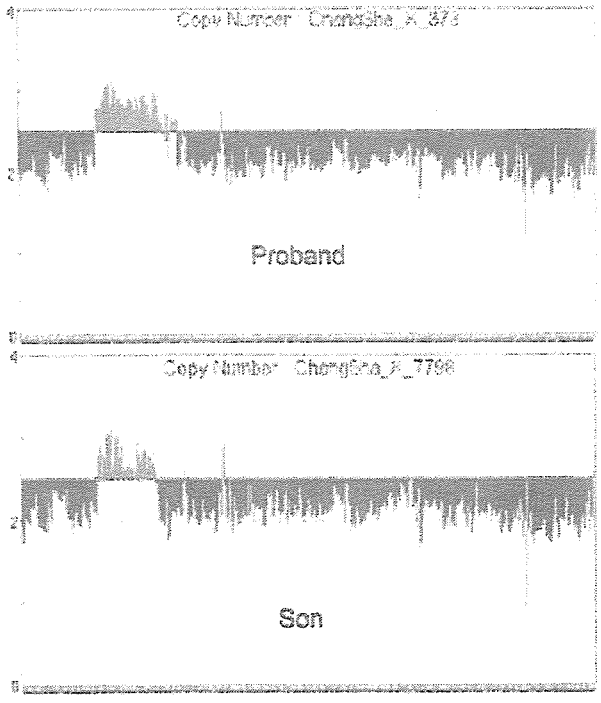

FIG. 3. Plots of the copy number for individual SNP loci along chromosome 12p in the propositus and his son by GeneChip Mapping 100K Array, showing a 2.5- to 3.5-fold amplification in both the two patients. Copy numbers >2.5 are plotted in green, and those <2.5 are represented in red.

On the basis of a classification for trisomy 12p proposed by Stengel-Rutkowski et al. [1981] and later by Allen et al. [1996], a total of 23 patients (including two cases we described) with "pure" trisomy 12p, either as the result of a duplication or an unbalanced translocation with the short arm of an acrocentric chromosome, have been known (Table II). Twelve of them were classified as partial trisomy 12p, and five were trisomy for terminal 12p (Fig. 4B). Because most of these previously reported cases of trisomy 12p had not undergone detailed phenotypic evaluations with consistent criteria, we subdivided cases of "pure" trisomy 12p into four groups, that is, A, B, C and D, according to the extent of 12p-duplicated region involved (Table II). Accordingly, some refinements in karyotype–phenotype correlation of trisomy 12p could be made. Accessory nipples and

TABLE I. Parent–Child Transmissions of Polymorphic Alleles in the Duplicated Region of the Propositus and His Son

	Father	Mother	Propositus	Spouse	Son
D12S1669	C/C	B/D	C/D	A/B	B/D
D12S1650	A/D	B/C	A/B	B/C	B/C
D12S1688	A/D	B/B	A/B	A/C	A/B
D12S1591	A/B	D/E	A/D	C/E	C/D
D12S1617	C/E	A/B	A/E	D/F	A/D
D12S1640	B/C	A/A	A/C	C/C	A/C

Alleles informative are underlined.

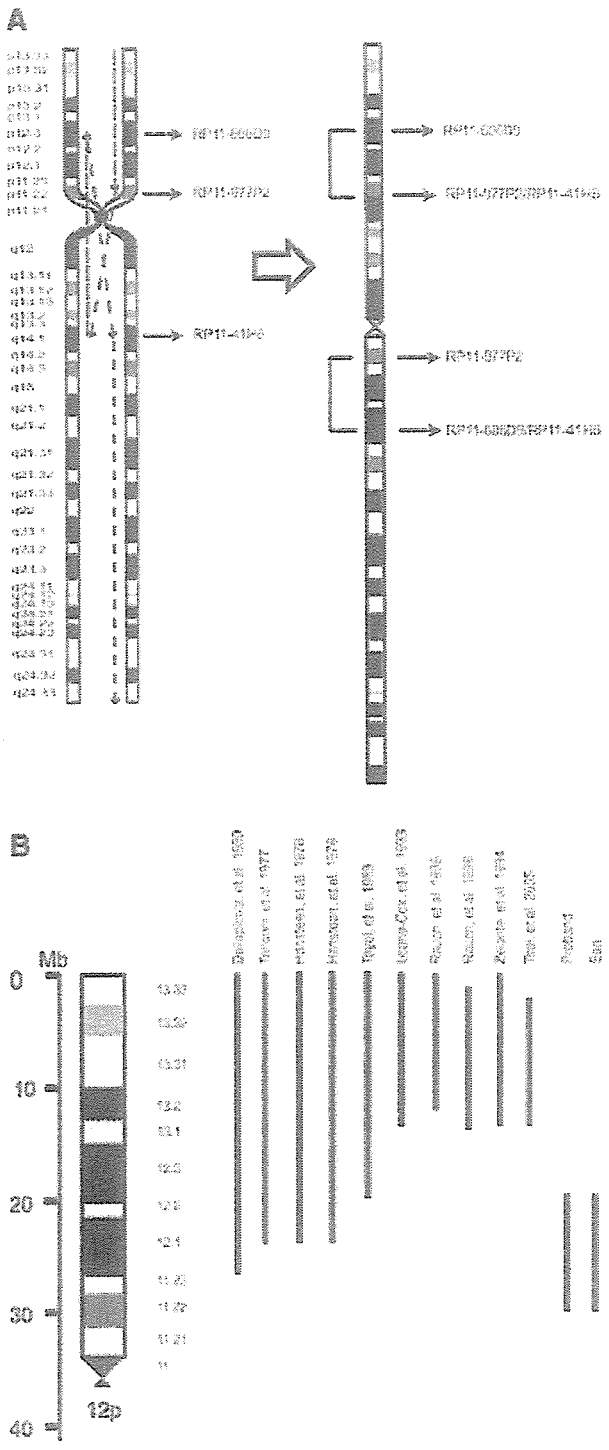

FIG. 4. **A**: A possible mechanism of formation of the 12p duplication and pericentric inversion 12 of the propositus, depicting mismatched pairing and unequal crossover between sister chromatids, as well as three break rearrangements (solid, hollow, and shade squares, respectively) including a U type rearrangement. **B**: Extent of duplication in previous and present cases.

TABLE II. Comparison of Clinical Manifestations Among Different Groups of Trisomy 12p

	Reported cases [References]			
	A: Complete trisomy 12p for 12pter-p11.1	B: Terminal trisomy for 12pter-p13.1	C: Distal trisomy for 12pter-p12.1	D: Proximal trisomy for 12p12.3-p11.22
	[1–11]	[12–16]	[17–21]	Present cases
	11 cases	5 cases	5 cases	Propositus son
Birthweight	Normal or increase	Normal or increase	Normal or increase	Normal or increase
Turricephaly	+	−	+	−
Round face and/or prominent cheek	+	+	+	−
High forehead	+	−	+	+
Flat face	+	−	+	+
Epicanthic fold	+	+	+	−
Broad eyebrow	+	−	+	−
Broad nasal bridge	+	+	+	+
Short nose	+	+	+	+
Anteverted nostril	+	+	+	−
Large philtrum	+	+	+	−
Thin upper vermilion	+	+	+	+
Broad everted lower lip	+	+	+	+
Ear anomaly	+	+	+	−
Short neck	+	+	+	−
Polydactyly	+	−	−	−
Accessory nipple	+	−	−	−
Foot deformity	+	−	+	−
Hypotonia	+	+	+	−
Development delay	+	+	+	+
Speech	+	−	+	+
Mental retardation	+++	+	++	+

1, Armendares et al. [1975]; 2, Suerinck et al. [1978]; 3, Parslow et al. [1979]; 4, Parslow et al. [1979]; 5, Stengel-Rutkowski et al. [1981]; 6, Ray et al. [1985]; 7, Pfeiffer et al. [1992]; 8, Rauch et al. [1996]; 9, Allen et al. [1996]; 10, Tekin et al. [2001]; 11, Zumkeller et al. [2004]; 12, Leana-Cox et al. [1993]; 13, Rauch et al. [1996]; 14, Rauch et al. [1996]; 15, Zelante et al. [1994]; 16, Tsai et al. [2005]; 17, Dallapiccola et al. [1980]; 18, Tenconi et al. [1978]; 19, Hansteen et al. [1978]; 20, Hansteen et al. [1978]; 21, Tayel et al. [1989].

polydactyly of toes were only present in a subset of group A patients, suggesting that a segment responsible for these features is confined to the region centromeric to 12p11.22. Likewise, the region important for broad eyebrows and foot deformities may be mapped to a 5-Mb, 12p13.1-p12.3 segment, because they were present in groups A and C patients but not in groups B and D patients. Epicanthal folds, ear anomalies, short neck, and round face/prominent cheeks were observed in groups A, B, and C patients, not in group D patients, suggesting that these features may be associated with a segment telomeric to 12p12.3. Rauch et al. [1996] and Tsai et al. [2005] suggested that terminal 12p (12p13.3-p13.1) might contain a critical region for the facial features of trisomy 12p syndrome and that proximal 12p might contribute more to major structural features. However, the result of analysis based on our classification was inconsistent with their data. The distinct facial features of "pure" trisomy 12p were found in all cases of the four groups, even though mild in group D and no major structural features in group D.

In conclusion, we have reported hitherto undescribed, proximal (12p12.3-p11.2) trisomy associated with inv(12)(p11.2q14.1) in the father and his son. Since conventional cytogenetics only provide a 5–10 Mb resolution and therefore may overlook invisible chromosomal changes, higher resolution molecular cytogenetics, and genome-wide copy number detection techniques should be introduced to make a more accurate and reliable diagnosis of such chromosomal aberrations.

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