Duplication of segment 1p21 following paternal insertional translocation, ins(6;1)(q25;p13.3p22.1)

Algirdas Utkus, Irina Sorokina, Vaidutis Kucinskas, Benno Röthlisberger, Damina Balmer, Lukrecija Brecevic, Albert Schinzel

Abstract

A moderately mentally retarded 3 year old boy showed minor anomalies including a prominent forehead and flat occiput, exophthalmos, large and prominent ears, high arched palate, umbilical hernia, sacral dimple, and irregular position of the toes. Cardiac sonography disclosed a chorda running through the left ventricle. Cytogenetic investigation of the family showed a balanced insertional translocation of segment 1p13→p22 into distal 6q in the father which had led, through unbalanced segregation, to duplication of 1p13.3→p22.1 in the proband. Familial duplication of such a small interstitial segment of 1p has not been reported previously, and the paucity of abnormal physical findings in the proband compared to previous patients with a similar aberration is remarkable.

(*J Med Genet* 1999;**36**:73–76)

Keywords: chromosome duplication 1p; dual colour FISH; unbalanced insertional translocation

Human Genetics Center, University of Vilnius, Santariskiu 2, LT-2021 Vilnius, Lithuania
A Utkus
I Sorokina
V Kucinskas

Institute of Medical Genetics, University of Zurich, Rämistrasse 74, CH-8001 Zurich, Switzerland
B Röthlisberger
D Balmer
L Brecevic
A Schinzel

Correspondence to:
Professor Schinzel.

Received 23 January 1998
Revised version accepted for publication 4 June 1998

Balanced insertional translocations leading to unbalanced offspring are rare in humans; they are the most frequent underlying cause of familial duplications of interstitial segments. Thus, such familial duplications are rare as well and their clinical pictures are mostly not well defined. Only a few cases with interstitial duplication of the short arm of chromosome 1 have been reported, among which there are only two instances of unbalanced familial insertional translocations leading to interstitial duplications, both of the segment 1p21→p31.[1 2]

We report clinical, cytogenetic, and molecular findings of another patient with interstitial duplication of a segment of 1p13.3→p22.1 resulting from unbalanced segregation of a paternal insertional translocation between chromosomes 1 and 6 as shown by GTG banding and fluorescence in situ hybridisation (FISH).

Case report

The proband, a boy, was the product of the fourth pregnancy of a healthy, 34 year old mother and her 34 year old partner. A paternal aunt was reported to have had cleft palate and died at 7 months of unknown causes (birth measurements unknown). The pedigree is otherwise unremarkable with respect to spontaneous abortions, stillbirths, malformations, and mental handicap. The first pregnancy resulted in a stillbirth at 38 weeks; birth weight was 2650 g. This male stillbirth reportedly did not have externally visible malformations, but no necropsy was performed. The second pregnancy resulted, at 41 weeks, in the birth of a normal and healthy boy weighing 3950 g and measuring 53 cm in length. The third pregnancy resulted in early spontaneous abortion.

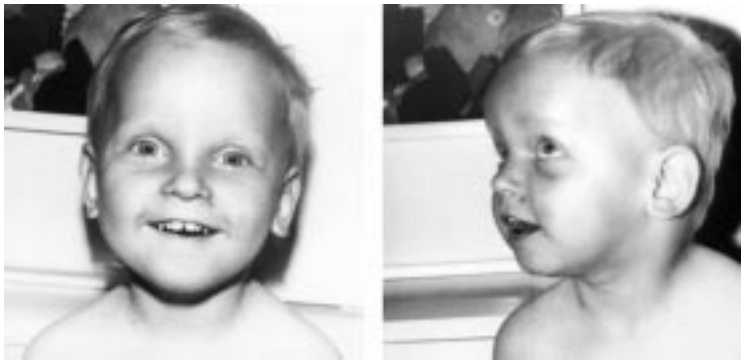

Figure 1 Head of the proband at 3 years of age. Note prominent and wide forehead and mild hypertelorism.

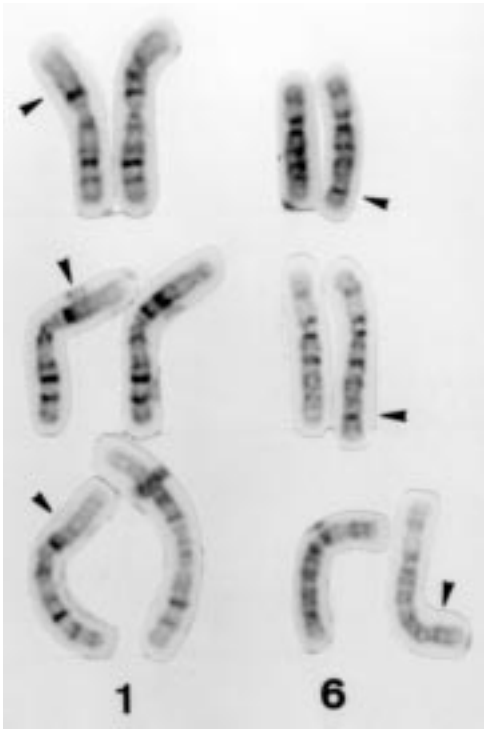

Figure 2 Chromosomes 1 and 6 from GTG banded metaphases of the proband's father. Arrows point to the segment 1p21 missing on chromosome 1 (left) but inserted into the long arm of chromosome 6 (right).

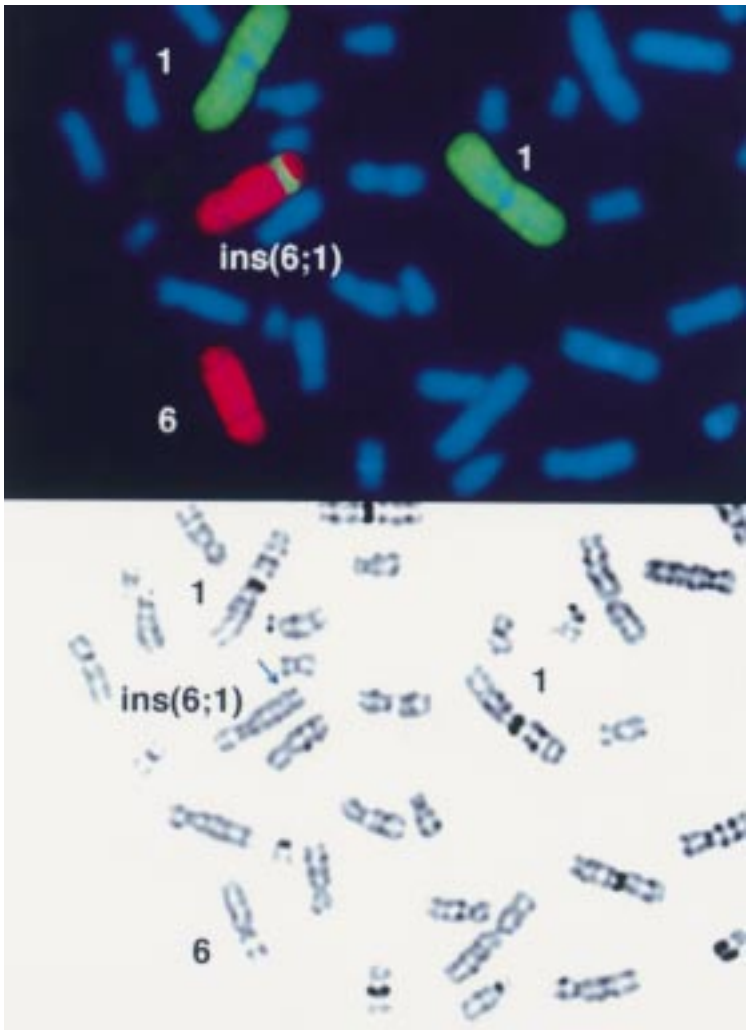

Figure 3 Dual colour FISH of a metaphase of the proband (top) with GTG banded control (bottom). Chromosome 1 is painted in green, chromosome 6 in red. Note the insertion of a segment of chromosome 1 into distal 6q.

The proband was born at 38 weeks of a normal pregnancy. Birth weight was 2680 g (10th centile), length was 51 cm (50th-90th centile), and occipitofrontal head circumference (OFC) was 37 cm (>>90th centile). Apart from a relatively large head, nothing abnormal was noted at birth or during the early postnatal period. There were no major problems with feeding and growth was normal. However, delayed motor development was noticed in early infancy; he sat at 9 months and walked independently at 17 months of age.

Clinical examination at 3 years of age (fig 1) showed length 93 cm (10th centile), weight 10.5 kg (<3rd centile), OFC 47 cm (<3rd centile), inner canthal distance 3.0 cm (80th centile), left ear length 6.2 cm (97th centile), left hand length 10.5 cm (25th centile), and left foot length 14.5 cm (25th centile). Dysmorphic features included a broad and prominent forehead with high frontal hairline, flat occiput, one occipital hair whorl in the midline, mild exophthalmos and hypertelorism, horizontal palpebral fissures, small lower incisors with diastema, narrow and high palate, large and prominent, but not misshapen ears, a small umbilical hernia, hypoplastic nipples, normal male genitalia, sacral dimple, normal hands, flat arches of the feet, and irregular position of toes with tibial deviation of the second toes.

Muscle tone was decreased and gait was peculiar with outward rotation of the feet. During the examination, he was constantly moving around and, according to the mother, this is his normal behaviour. There was no speech.

Echocardiography showed an extra chorda running through the left ventricle. Ultrasonographic examinations of the heart, liver, kidneys, pancreas, and spleen showed normal results.

Skull radiographs at 3 years 3 months showed nothing abnormal and radiographs of the hands and feet disclosed osteopenia and retarded bone age (carpal 6 months, phalangeal 18 months in the hands, tarsal 24 months at a chronological age of 3 years 3 months). Apart from mild brachymesophalangism of the little fingers with clinodactyly, no structural anomalies were visible.

CYTOGENETIC INVESTIGATIONS

GTG banded metaphases from lymphocyte chromosome cultures of the proband showed an abnormal chromosome 6 with insertion of a segment into the distal long arm. Maternal chromosomes were normal.

The father's karyotype showed a balanced insertional translocation of an intermediate segment from 1p into 6q (fig 2). Chromosome painting with libraries of chromosome 1 (biotinylated, green) and chromosome 6 (digoxigenised, red)[3] confirmed the unbalanced insertional translocation (fig 3) and a balanced insertion without any evidence of reciprocity, that is, insertion of a segment from chromosome 6 into chromosome 1, in the father. The same balanced insertion was present in the paternal grandmother, while the older brother of the proband had normal chromosomes. The karyotype of the father is 46,XY,ins(6;1)(q25;p13.3p22.1)mat and that of the proband is 46,XY,der(6),ins(6;1)(q25;p13.3p22.1)pat. A cell line from the proband is available.

MOLECULAR INVESTIGATIONS

The following microsatellite markers were used for PRC reactions in the proband and his parents: AMY2B mapping to 1p21; D1S221 and D1S236 mapping to 1p13-p21; D1S2779 mapping to 1p22; D1S424 mapping to 1p21-p31. The reactions were carried out under standard conditions (annealing temperature 56-60°C, 35 cycles). None of the markers was informative for paternal heterozygosity and distinct maternal and paternal alleles. For two markers (D1S2779 and D1S424) one allele was more intense, and both results were compatible with transmission of both paternal alleles to the patient. In addition, paternal uniparental disomy 1 could be excluded by clear biparental inheritance of alleles of markers D1S236, D1S2779, and D1S207 (at 1p32-p33).

Table 1 Clinical findings in reported patients with duplications of chromosome 1 including at least parts of segments 1p21

Finding	*1**	*2**	*3**	*4**	*This report*
Age at examination (y/mth)	5/6	30/1	0/1	0/10	3/0
Short stature	+	−	+	+	−
Low birth weight	−	+	+	+	−
Microcephaly	?	+	+	+	+
Sloping forehead	−	−	?	+	−
Prominent forehead	−	−	−	?	+
Arched eyebrows	−	+	−	−	−
Long eyelashes	−	−	−	+	−
Blepharophimosis	−	+	?	−	−
Hypertelorism	+	+	+	+	+
Epicanthic folds	+	−	−	?	−
Strabismus	−	−	O	+	−
Upward slanting palpebral fissures	−	+	−	−	−
Midface hypoplasia	+	+	−	−	−
Round face	+	−	−	−	+
Small nose with anteverted nares	−	−	−	+	−
Long philtrum	−	−	−	+	−
High palate	?	?	?	?	+
Cleft palate	−	+	+	−	+
Small mandible	−	+	+	+	−
Simple/dysplastic ears	−	+	+	−	−
Large ears	?	?	−	+	+
Low set ears	−	−	+	+	+
Preauricular fistulas	b	−	−	−	−
VSD	+	−	−	−	−
Other cardiac anomalies	−	−	−	−	+
Sacral dimple	+	+	?	?	+
Spina bifida occulta	+	−	−	−	−
Inguinal hernia	−	−	O	+	−
Cryptorchidism	F	F	F	+	−
Small hands, brachydactyly	+	?	+	?	+
Clinodactyly of 5th fingers	?	+	?	+	+
Dysplastic nails	−	−	?	−	−
Single palmar creases	−	−	−	−	−
Syndactyly 4/5 toes	+	−	−	−	−
Duplicated segment of 1p	p31-p21	p31-p21	p31-p11	p32-p21.2	p22.1-p13.3

*Reference nos.
F = female.
b = bilateral.
O = feature not yet evaluable.
? = unknown/no information.

Discussion

There are only two published reports of 1p segments overlapping with the segment duplicated in our proband and derived from a familial insertion, both of which are larger segments. Schürmann *et al*[1] described a 5½ year old male patient with an unbalanced maternal insertion involving three chromosomes (1, 5, 15) leading to duplication of (1)(p21→p31). Hoechstetter *et al*[2] reported a 30 year old female with an unbalanced segregation of a maternal insertion of a segment of 1p into 13q, leading to duplication of (1)(p21→p31.1). Furthermore, Dhellemes *et al*[4] reported a girl with a de novo presumed inverted duplication of (1)(p11→p31) and Mohammed *et al*[5] presented a 10 month old male with a de novo presumed direct duplication of (1)(p21.2→p32). In neither of these two cases was FISH performed to confirm that the duplicated segment was from chromosome 1. A comparison of the clinical findings in these four patients with those in the proband of this report is shown in table 1. Findings in common with at least one of the four other patients are confined to such non-specific features as microcephaly, hypertelorism, round face, small mandible, large and low set ears, sacral dimple, and small hands and fingers with clinodactyly of the little fingers. Our patient is more mildly affected with respect to growth retardation and phenotypic abnormalities than any of the other patients with overlapping duplicated segments, which can be explained by duplication of a smaller segment than in all the other cases. Surprisingly, however, the patient of Schürmann *et al*[1] at 6 years of age was of normal intelligence while our proband with duplication of a shorter segment of 1p at 3 years of age is clearly retarded in motor and mental development.

Duplication of (1)(p21→p31) was reported in a healthy mother and her healthy 3 month old son; the duplicated segment was inserted into the middle of 1p and was negative with C banding. FISH with a chromosome 1 library stained the entire der(1) chromosome, thus providing evidence that the additional segment is from chromosome 1.[6] As this family is so unusual with respect to its (normal) phenotype, it would be highly desirable to restudy one of the two chromosomally aberrant members by dissection of the duplicated segment and reverse painting through hybridisation to normal karyotypes in order either to confirm the authors' interpretation or to indicate another origin of the additional segment. Owing to the lack of an abnormal phenotype, these two probands were not included in table 1.

The authors are grateful to the parents of the proband for their cooperation. The work was supported by the Swiss National Foundation, grant No 32.37798.93.

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