

At least nine cases of trisomy 11q23→qter in one generation as a result of familial t(11;13) translocation

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Abstract

Carriers of balanced reciprocal translocations may have a (high) risk for producing liveborn children with an unbalanced karyotype. We report a large family in which a translocation between the long arm of chromosome 11 and the short arm of chromosome 13 is segregating in at least five generations. During the course of our study 15 carriers of the balanced translocation were identified and nine cases of partial trisomy of the long arm of chromosome 11 were detected during pre- and postnatal studies. Several of the patients were thoroughly clinically examined and compared with similar published cases.

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Partial 11q trisomy was recognised as a distinct clinical entity in 1977 and referred to as the duplication 11(q21 to 23→qter) syndrome.¹⁻³ Since then, a number of additional patients have been described with partial trisomy 11q. In many of them, however, this trisomy was accompanied by monosomy of yet another chromosome owing to the presence of an unbalanced translocation.^{4,5} Besides these cases, numerous patients have been reported with double trisomy for the distal part of 11q as well as the proximal part of 22q resulting from 3:1 segregation in the well known t(11;22) translocation.^{6,7}

We present a large family in which a translocation t(11;13)(q23;p13) segregates. The translocation has been inherited in at least five generations and appears to be associated with a very high risk for unbalanced offspring. Since the distal part of the long arm of chromosome 11 is translocated to the tip of the short arm of chromosome 13, an unbalanced karyotype results in either pure monosomy or trisomy 11q without any other additional aneuploidy. This could define more precisely the clinical presentation of these chromosomal imbalances.

Case reports

PATIENT 1

Patient 1 was born in 1969 (V.9, fig 1). This boy was the first child of healthy, unrelated parents (father aged 26 years, mother aged 25

years). Pregnancy and delivery were uneventful. The birth weight was 3620 g. There was marked neonatal hypotonia. At the age of 9 months a dislocation of the right hip was treated conventionally without success. From the age of 5 years tonic-clonic epileptic convulsions occurred that responded well to anti-convulsant drugs. Other medical problems were recurrent upper airway infections and obstipation. The boy lives in a home for the mentally retarded. He is able to walk with support, but there is no speech.

Examination at the age of 25 years showed a severely retarded man with a height of 170 cm (3rd centile) and weight of 62.7 kg (10th centile) (fig 2, table 1). The head circumference was 56.5 cm (50th centile). There was asymmetry of the face, strabismus, and short, upward slanting palpebral fissures. The nose was short with a bulbous tip and a long philtrum. A high arched palate, eversion of the lower lip, and mild micrognathia were noted as well. The penis was small. Several skeletal deformities were seen, such as scoliosis, clinodactyly, and club feet.

Chromosomal analysis at the age of 4 years showed a 13p+ chromosome (partial trisomy 11q) which resulted from a translocation t(11;13)(q23;p13) in his father: 46,XY,der(13)t(11;13)(q23;p13)pat.

He had a younger sister who died at birth from asphyxia. No congenital malformations were seen in this girl and she had a normal karyotype (V.10).

PATIENT 2

Patient 2 was born in 1984 (V.4, fig 1). This boy was the first born child of healthy, unrelated parents (father aged 29 years, mother aged 25 years). He was born by breech presentation at a gestational age of 45 weeks. The birth weight was 3040 g and length was 51 cm. There were neonatal feeding problems because of micrognathia. At the age of 18 months a dislocation of the right hip was corrected surgically. During the second year of life two convulsions were observed. He is now free of convulsions without medication. Recurrent upper airway infections have occurred. The patient was able to sit and walk without support at the age of 11 months and 5 years, respectively. He has no speech, but some non-verbal communication is possible.

Examination at the age of 10 years showed a moderately to severely retarded boy with a

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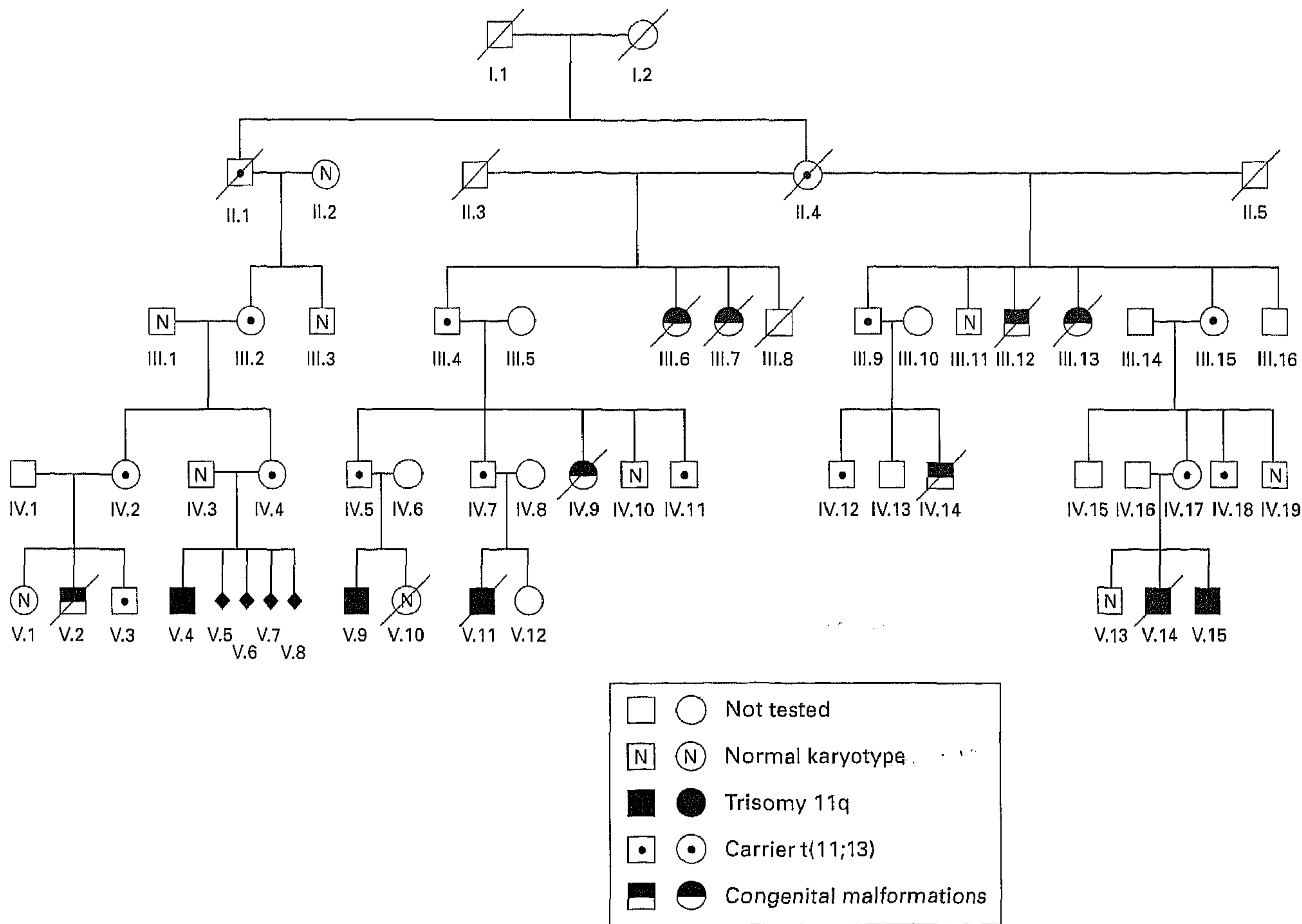


Figure 1 Part of the pedigree in which the translocation $t(11;13)$ is segregating.

height of 138 cm (25th centile) and weight of 33 kg (50th centile) (fig 2, table 1). The head circumference was 55 cm (75th centile). There was asymmetry of the face, telecanthus, and upward slanting palpebral fissures. The nose was short with a full tip and a long philtrum. A high arched, narrow palate and micrognathia were seen. There were undescended testicles and a micropenis.

Chromosomal analysis at the age of 6 months showed the same trisomy 11q as was present in patient 1.

The parents of this patient had four other pregnancies and all four were terminated because prenatal karyotyping showed trisomy 11q. Pathological examination after the first termination showed a male growth retarded fetus of 19 weeks gestational age with micrognathia, low set ears, and a ventricular septal defect.

PATIENT 3

Patient 3 was born in 1985 (V.15, fig 1). This boy was the third child born to healthy, unrelated parents (father aged 28 years, mother aged 25 years). Pregnancy and delivery were uneventful. The birth weight was 3350 g. There was a Pierre-Robin malformation, atrial septal defect, and neonatal hypotonia. He had bilateral Perthes disease at the age of 9 years. During infancy two febrile convulsions were observed. Recurrent upper airway infections

occurred. The boy was able to sit and walk without support at the age of 10 months and 6 years, respectively. His speech was limited to a few words but well developed non-verbal communication was present.

Examination at the age of 9 years showed a moderately retarded child with a height of 130 cm (10th centile) and weight of 30 kg (50th centile) (fig 2, table 1). The head circumference was 56 cm (90th centile). There was asymmetry of the face, a short nose, and a long philtrum. A high and narrow palate, micrognathia, and low set ears were observed. There was an inguinal hernia and a micropenis.

Chromosomal analysis two weeks after birth showed trisomy 11q.

The first born child of this family was healthy and had a normal karyotype.

PATIENT 4

Patient 4, a brother of patient 3 and the second child of this family (V.14, fig 1), died at the age of 6 months because of a heart defect complicated by a severe infection. This boy was born after a normal pregnancy, with a birth weight of 3500 g. Besides the congenital heart defect, a Pierre-Robin sequence, anal atresia, and micropenis were present. Marked hypotonia was noted as well. Photographs of this boy showed a striking resemblance to patient 3.

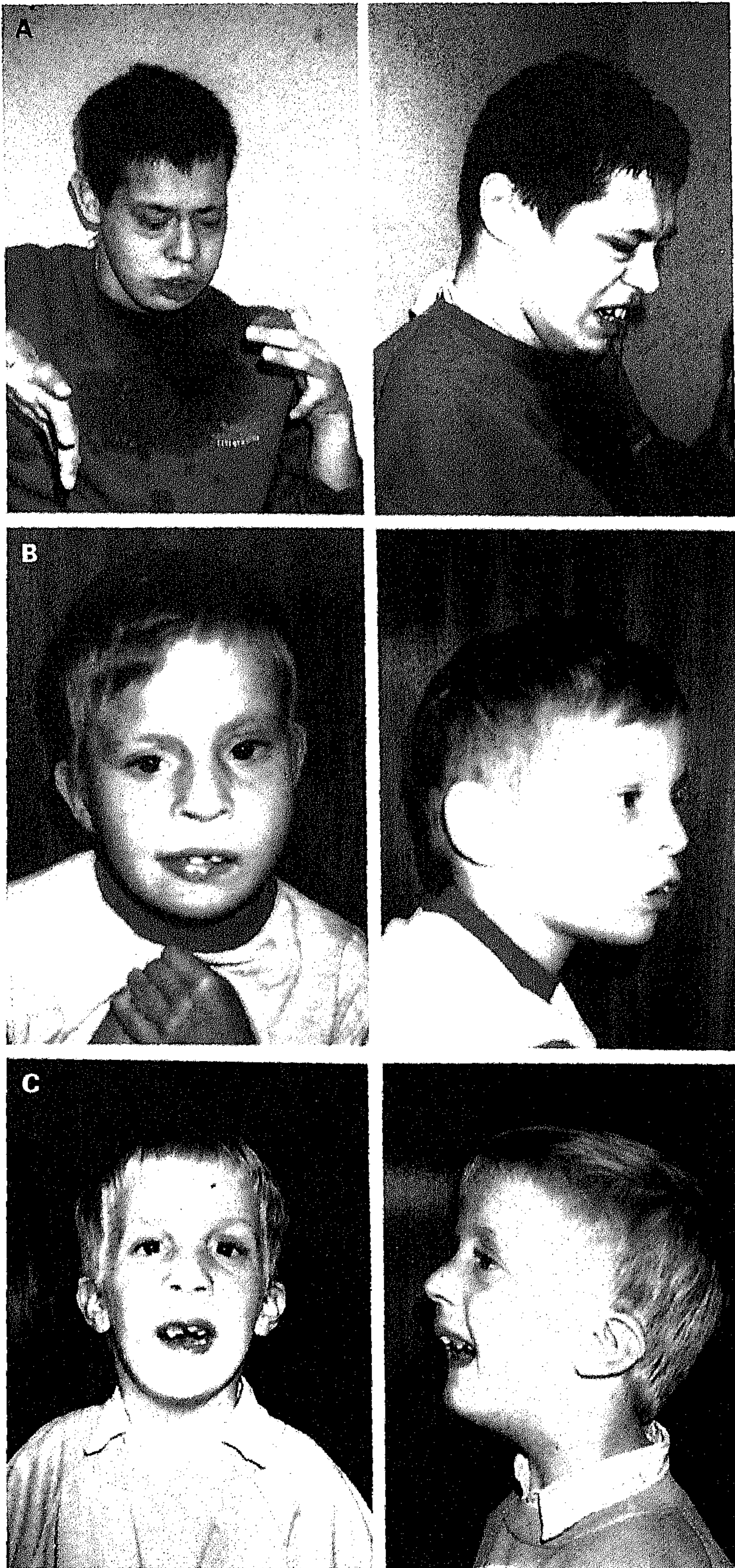


Figure 2 Facial features of patients 1 (A), 2 (B), and 3 (C).

Postmortem chromosomal investigation of cultured fibroblasts showed the same chromosomal aberration as was found in his brother.

PATIENT 5

Patient 5, a first cousin of patient 1, was born in 1974 and died at the age of 10 months

because of respiratory problems (V.11, fig 1). This boy was the first child born to healthy, unrelated parents (father aged 26 years, mother aged 23 years). Severe micrognathia and psychomotor retardation were noted in this boy. Necropsy showed an atrial septal defect with aortic coarctation and bilateral dysplasia of the hips.

Chromosomal analysis showed trisomy 11q.

PATIENT 6

Patient 6, a maternal aunt of patients 1 and 4, was born in 1949 and died at the age of 23 years (IV.9, fig 1). The cause of death is not known. She was mentally retarded, unable to sit, and had short stature. Photographs of this girl showed a phenotype that markedly differed from the phenotypes of the patients described above. There was no micrognathia, nor a bulbous nose, but striking hypertelorism with a flat, broad nasal bridge was present.

Chromosomal analysis was not performed.

Materials and methods

In the majority of patients and other family members cytogenetic investigations were performed on cultured peripheral lymphocytes. The only exceptions were cases V.5 to V.8 (fig 1), who were examined prenatally on chorionic villi or cultured amniotic cells, and case V.14 who was studied on cultured fibroblasts after the child had died. Chromosome slides were made according to routine procedures and cytogenetic analyses were performed on GTG banded metaphases. In one patient and one carrier several slides were NOR stained to see whether the 13p+ chromosome had retained the satellite stalks with the nucleolar organiser region (NOR).

As well as these studies, in one healthy carrier of the translocation fluorescent in situ hybridisation (FISH) was performed with chromosome specific paints of chromosomes 11 and 13 (pBS11 and pBS13, respectively), to rule out any additional abnormalities. FISH studies were performed as described elsewhere.²³

Results

Exactly the same unbalanced karyotype (46, XY,13p+) was independently discovered after two probands were cytogenetically investigated because they presented at birth with multiple congenital abnormalities (cases V.9 and V.15). Chromosome studies of the parents showed a translocation $t(11;13)(q23;p13)$ (fig 3) in the father and mother. NOR staining clearly showed that the 13p+ chromosome had retained the nucleolus organiser region (fig 3), while FISH studies confirmed that a piece of chromosome 11 was present at the top of the aberrant chromosome 13 without any additional aberrations (results not shown). Subsequent family studies showed a relatively large pedigree which connects both sibships (part of the pedigree is presented in fig 1). Besides the two index patients, we identified another two

Table 1 Comparison of clinical features between patients with pure trisomy 11q and those with additional chromosomal anomalies

	+ Deletion of another chromosome	Resulting from t(11;22)	Pure trisomy 11q	Present patients t(11;13)
<i>General</i>				
Gestational age (wk)	32-47	32-42	33-40	39-45
Low birth weight	7/17 0/4	3/8	0/2	
Short stature	14/16	7/8	2/2	0/3
Mental retardation	14/14	5/5	2/2	4/4
Neonatal hypotonia	6/15	0/6	1/1	4/4
Hypertonia	8/16	5/7	0/1	2/3
<i>Skull</i>				
Microcephaly	12/17	4/8	2/2	0/3
<i>Eyes</i>				
Epicanthus	5/16	1/8	1/2	0/3
Hypertelorism	4/16	3/8	0/2	0/3
Slanted palpebral fissures	5/16	5/8	1/2	3/3
<i>Nose</i>				
Short nose/long philtrum	14/16	6/8	2/2	4/4
<i>Mouth</i>				
High arched palate	8/13	0/1	1/1	3/3
Cleft palate	3/10	6/8	0/2	2/4
Retracted lower lip	10/16	6/8	2/2	2/3
Microretrognathia	16/17	6/8	2/2	5/5
<i>Ears</i>				
Low set	13/16	5/8	2/2	2/3
Dysplastic	9/16	5/8	0/2	1/3
<i>Thorax</i>				
Short neck	8/16	2/8	1/2	0/3
Laterally displaced nipples	4/14	2/7	0/1	1/3
Congenital heart defect	13/16	6/7	1/2	3/5
Hernia (inguinal/umbilical)	3/16	2/8	1/2	1/3
Micropenis	4/8	4/4	2/2	4/4
<i>Skeletal deformities</i>				
Dislocation of the hip	6/16	2/7	0/2	3/4
Club feet	2/17	1/8	0/2	1/3
Clavicular defect	4/12	0/2	0/2	0/3

References 1, 3-5, 8-22.

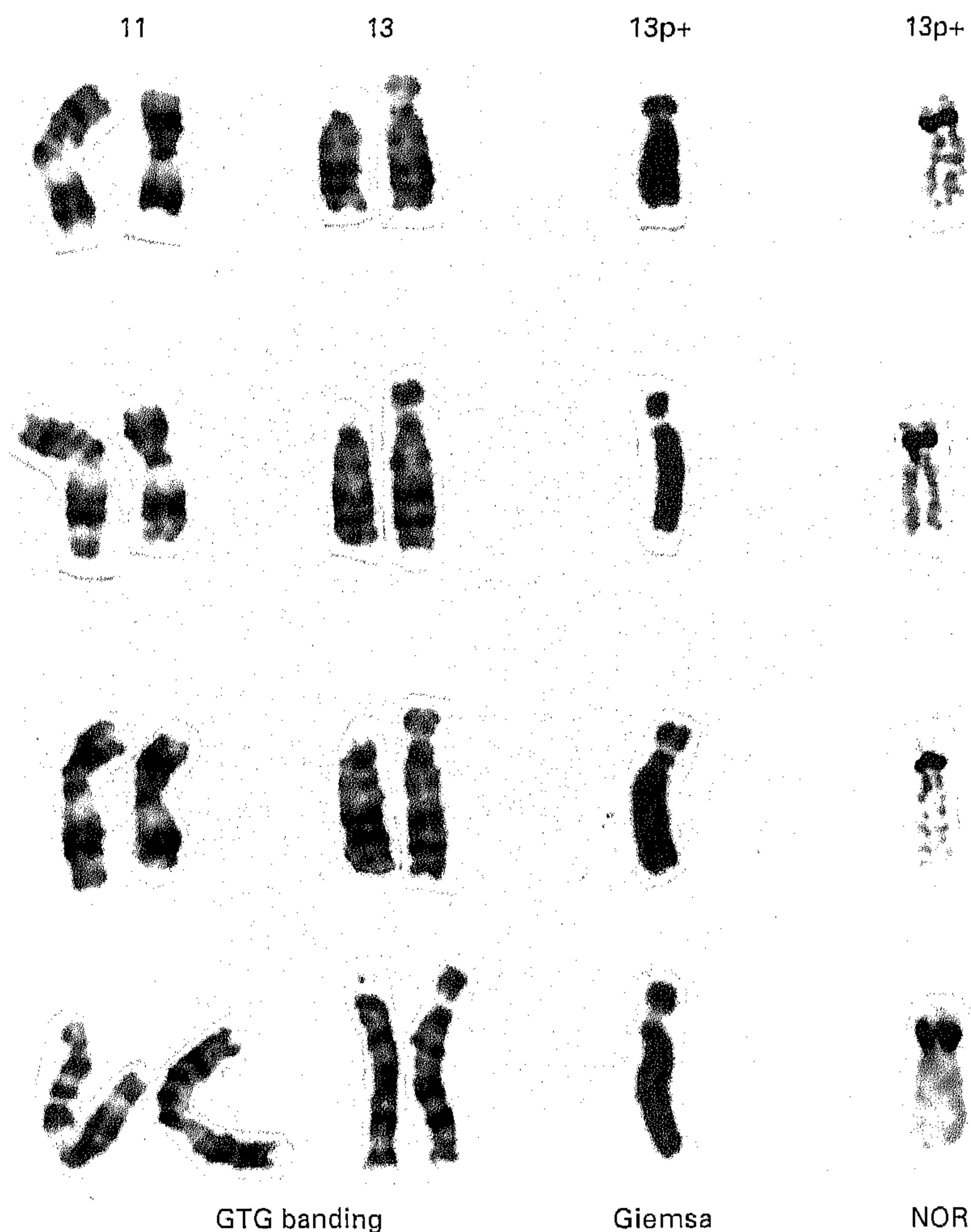


Figure 3 Appearance of the translocation chromosomes after GTG banding in a normal healthy carrier. The normal chromosomes 11 and 13 are on the left and the translocation chromosomes on the right. The aberrant chromosome 13 is shown after conventional Giemsa staining and after staining of the nucleolar organizer region (NOR).

patients with partial trisomy 11q (V.4 and V.11). From a fifth patient (V.14), initial chromosome studies on cultured fibroblasts had been interpreted as a normal 46,XY male karyotype with a variant 13p+. After discovering the translocation t(11;13) in his mother, the chromosomes of V.14 were re-evaluated and partial trisomy 11q was found.

Since carriers of this translocation have a high risk of producing unbalanced offspring, prenatal diagnosis was offered to them. So far, four prenatal investigations have been performed on pregnancies of one female carrier (IV.4) and all four fetuses showed partial trisomy 11q because of the presence of the 13p+ chromosome (V.5 to V.8). In all cases the parents requested termination of the pregnancy.

Besides the five liveborn children with an unbalanced karyotype, another seven children in this family were born with multiple congenital anomalies of unknown cause. One of them was stillborn (V.2) and a second child lived only a couple of hours (IV.14), while others survived for 6 months up to 3 years (III.6, 7, and 12). Only two of the patients survived longer and reached ages of 13 (III.13) and 23 years (IV.9), respectively. Unfortunately, cytogenetic studies were not performed and hardly any clinical data were available from these patients, except for some pictures of case IV.9 (patient 6). Thus, we are not able to compare them with the other patients.

Apart from the patients and the people with a normal karyotype, we could identify 15 carriers of the translocation in this family, either directly from chromosome studies or indirectly from the pedigree (fig 1).

Discussion

Trisomy of the distal part of the long arm of chromosome 11 is a very well known chromosomal syndrome.^{1,3,4} However, most patients have with this trisomy yet another trisomy or monosomy, which might influence the clinical outcome. Therefore, we compared the clinical findings in our patients, with pure trisomy 11q, with those previously published (table 1). It appeared that a number of dysmorphisms and malformations are very typical of trisomy 11q since they can be observed in almost all patients independent of the presence of other abnormalities. There are also a number of aberrations that are found only in patients with a specific translocation and might thus be the result of another chromosomal imbalance (table 1). Apart from the mental retardation which is found in all patients, typical dysmorphisms and malformations that are present in patients with trisomy 11q, including our patients, are slanted palpebral fissures, a short nose with a long philtrum, a high arched or cleft palate, microretrognathia with retracted lower lip, low set ears, a congenital heart defect, micropenis, and dislocation of the hips. A Pierre-Robin sequence is also quite a common complication. Clinical findings that are more often present in patients with an accompanying deletion or trisomy of another chromosome

include intrauterine growth retardation, epicanthus, hypertelorism, dysplastic ears, and a short neck.

As yet, it remains unclear whether the translocation segregating in this family is a true reciprocal one, as there are three other options. (1) The translocation is reciprocal with the distal part of 11q located on the short arm of chromosome 13 and the telomeres of 13p present on the der(11q). (2) It is a one way translocation from 11q to 13p, while new telomeres have been synthesised or added by telomere capture at the remaining 11q-. That such mechanisms exist has been reported earlier.²⁴⁻²⁶ (3) There is an insertion of the distal part of 11q excluding the telomeres into the short arm of 13p just below the telomeres.

Subtelomeric specific DNA sequences used as probes for FISH could discriminate between these options and such studies are currently in progress. However, which of these options reflects the real situation is merely an academic question since it probably does not change the risk for carriers of this translocation having unbalanced offspring.

In the last generation of this family, we were able to study 13 meioses and nine times an unbalanced karyotype was found with in every case the same 13p+ chromosome resulting in a partial trisomy 11q. Five of these were detected in liveborn malformed children while the other four presented during prenatal diagnoses. This implies that carriers of the translocation t(11;13) have a very high risk, in the order of at least 20%, for having liveborn offspring with an aberrant karyotype.²⁷⁻²⁸ Taken all together, the fact that there is no history of an increased number of spontaneous abortions in this family implies that trisomy as well as monosomy 11q23→qter is likely to be compatible with life.

It seems odd that the nine unbalanced cases we encountered all showed partial trisomy 11q, whereas not a single case of partial monosomy 11q was detected, the more so because numerous case reports indicate that monosomy 11q23→qter or Jacobsen syndrome is compatible with life as well.²⁹⁻³³ However, there have been seven other patients in this family who could not be studied and it is feasible that some of them did carry monosomy of 11q, for instance patient 6. Nevertheless, it would be interesting to perform meiotic studies in a carrier of this translocation, to find out whether there is some kind of selection during meiosis in favour of the 13p+ chromosome, as has been shown to exist for other translocations.

VARIATION OR ABERRATION

Carriers of translocations of relatively small chromosomal pieces onto a short arm of an acrocentric chromosome may have a very high risk of having unbalanced offspring.²⁷⁻²⁸ This is because of a 2:2 adjacent I segregation which preferentially occurs during meiosis I in this type of translocation. Subsequently, the result is partial monosomy or trisomy of the translocated segment. It is, therefore, of great importance to recognise the presence of such an (unbalanced) translocation to initiate the

search for carriers and to offer the possibility of prenatal diagnosis. In the present family, the 13p+ chromosome was detected the first time in a patient, but initially misinterpreted as a chromosomal variant, a polymorphism without any clinical consequences. As a result, the parents were not investigated and a second patient was born. Thus, a large short arm on acrocentric chromosomes warrants further studies in all cases to rule out a translocation, especially if it is seen in a patient with mental retardation or congenital anomalies or both.

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