

Familial translocation with partial trisomy of 13 and 22: evidence that specific regions of chromosomes 13 and 22 are responsible for the phenotype of each trisomy¹

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SUMMARY A newborn infant with clinical and pathological findings typical of trisomy 13 and 22 syndromes had an extra chromosome which was a derivative chromosome from maternal balanced translocation affecting Nos. 13 and 22; 47,XY,+der(22),t(13:22)(q22:q12)Mat. The presence of extra specific euchromatic regions of No. 13(13q22 and/or 13q34) and No. 22 (22q11) seem to be responsible for the trisomy 13 and 22 syndromes.

The development of new banding techniques has led to the identification of various new types of chromosome aberrations, especially those of the duplication-deficiency type of structural abnormality. Consequently syndromes of partial trisomies or monosomies will gradually be delineated by correlation between the chromosomal aberrations and their phenotypic manifestations. It is envisaged that a trisomy syndrome may not be caused by complete trisomy but by duplication of certain specific euchromatic regions of a chromosome. In fact, it has been demonstrated that the presence of an extra region of No. 21 (21q-) is the cause of Down's syndrome (Williams *et al.*, 1975; Poissonnier *et al.*, 1976). We were able to demonstrate in a patient with an extra chromosome consisting of a 22/13 translocation, that the presence of specific regions of chromosomes No. 13 and No. 22 are responsible for the phenotypic manifestations of the trisomy 13 and 22 syndromes.

Case report

The proband (C:072575), a white newborn male infant with multiple congenital anomalies, was born after 43 weeks' gestation, the only child of a 31-year-

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old mother and a 31-year-old father. The pregnancy was complicated in the first trimester by vaginal spotting for which Provera was given. There was a history of difficulty in conceiving and one early spontaneous abortion 13 months before the birth of the proband. The patient's Apgar score was 6 at 1 minute. His birth weight was 3240 g with a head circumference of 32.5 cm and length of 55.5 cm.

The following anomalies were observed: sloping forehead, large fontanelles, widely separated cranial sutures, facial asymmetry, capillary telangiectasis on both eyelids, wide epicanthal folds, anti-mongoloid slanting of eyes, depressed nasal bridge, prominent nose, increased philtral length, macrostomia, midline cleft of hard and soft palate, a natal tooth, micrognathia, bilateral microtia, right preauricular sinus, suboccipital haemangiomas, narrow asymmetric chest, dorsal kyphoscoliosis, widely spaced nipples, single umbilical artery, small scrotum with neither testicle palpable in the sac or in the inguinal canals, small penis, flexion contractures of major joints (elbow, wrist, hip, and knee), finger-like malopposed thumbs, subluxation of the metacarpophalangeal joint of the right thumb, flexion contractures of other fingers, fifth finger overriding fourth finger, hypoplastic nails, six arches on finger tips, distal loop in the hallucal area, and arches on both big toes (Fig. 1).

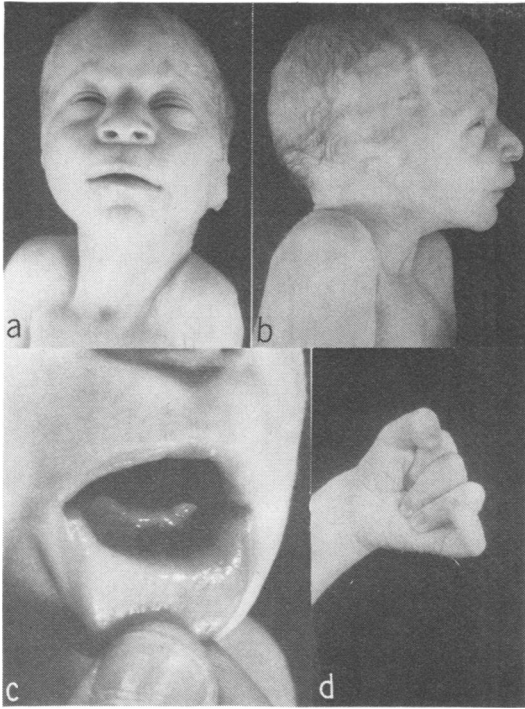


Fig. 1 Gross appearance of patient showing peculiar facies (a, b), natal tooth (c), and hand (d).

The baby did very poorly from the beginning. He was unable to tolerate oral feeding well. A systolic murmur was heard on the fifth day of life. On the ninth day of life he developed seizures and continued to have them until he expired on the eleventh day. Necropsy showed the following additional abnormalities: absence of olfactory bulbs and tracts; micropolygyria of the frontal lobes; atrial-septal defect (ostium II); aberrant origin of the right subclavian artery from the descending aorta; origin of the right vertebral artery distal to left subclavian artery; absence of left umbilical artery; supernumerary adrenal gland at hilus of left kidney; accessory adrenal cortical nodules; intestinal malrotation; enlargement and excessive lobulation of the spleen; accessory spleens; bilateral nephromegaly with nodular renal blastoma and focal cortical and medullary dysplasia (Fig. 2); hydronephrosis and hydroureter; moderate, bilateral, rudimentary uterus, cervix, and vagina with urethral connection; abdominal testes. The death of the patient was attributed to bilateral, acute, diffuse pyelonephritis and *Escherichia coli* septicaemia.

CYTOGENETIC STUDY

The patient's peripheral blood leucocytes were cultured with phytohaemagglutinin and a specimen of

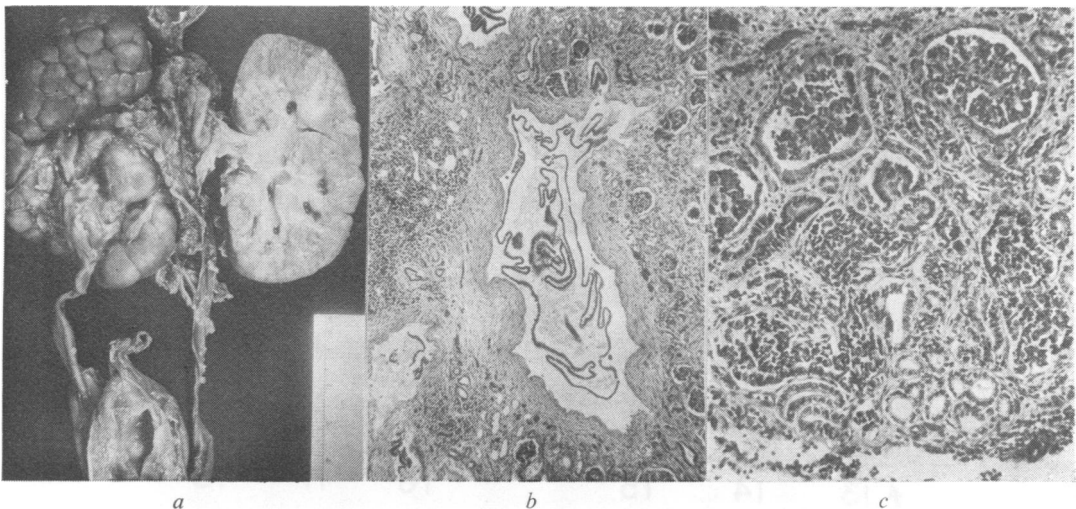


Fig. 2 (a) Gross appearance of kidneys. External surface of enlarged right kidney shows bizarre shape with exaggerated and irregular fetal lobulations and anterior rotation of hilus with extrarenal pelvis and abnormal, elongated extrarenal calyces. Cut surface of left kidney shows scattered minute cysts and occasional pale nodules. Calyces and ureters are dilated. Supernumerary adrenal gland is seen between the two kidneys (rudimentary uterus is hidden behind urinary bladder). (b) Focal renal dysplasia with cystic dilation of collecting tubules and fibrosis, seen here at corticomedullary junction. Developmental changes are complicated by pyelonephritis. (Haematoxylin and eosin $\times 160$.) (c) Renal cortex showing one of many foci of nodular renal blastema in addition to normally developed glomeruli. (Haematoxylin and eosin $\times 430$.)

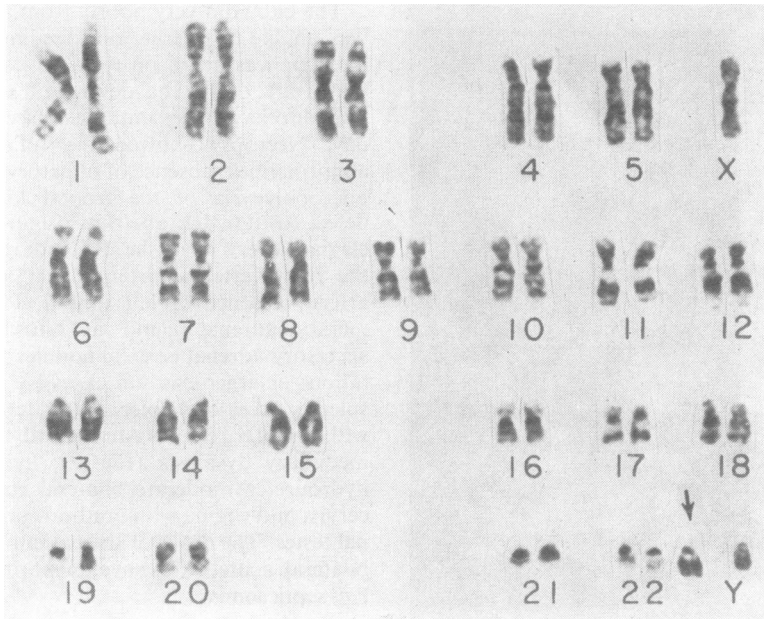


Fig. 3 G-banding karyotype of patient showing extra chromosome (arrow); 47,XY,+der(22),t(13:22)(q22:q12)mat.

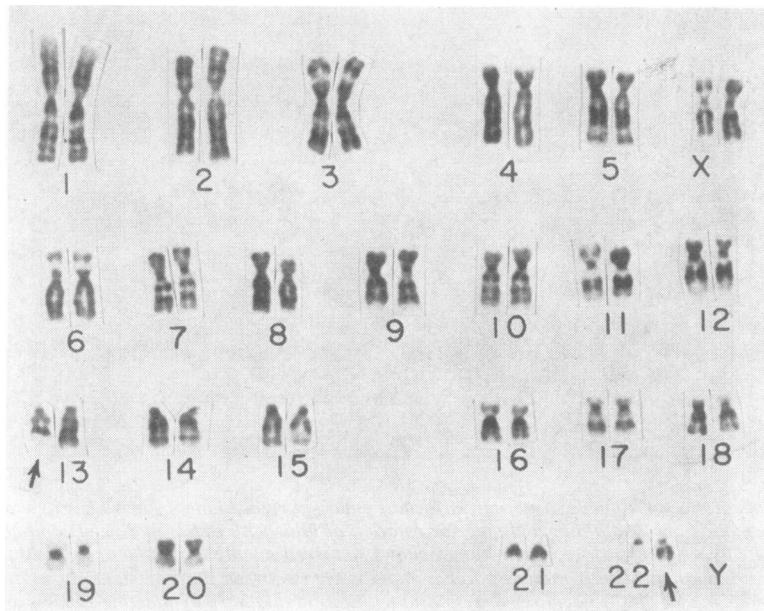


Fig. 4 G-banding karyotype of mother showing balanced reciprocal translocation of Nos. 13 and 22 chromosomes; 46,XX,t(12:22)(q22:q12).

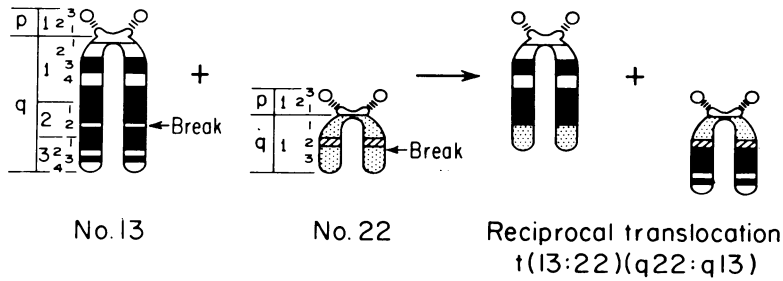


Fig. 5 Diagram showing exact breakage and rearrangement points on No. 13 and No. 22 chromosomes; $t(13:22)(13qter \rightarrow 13q22::22q12 \rightarrow 22pter)$.

skin was taken for fibroblast culture. All 50 peripheral leucocytes and 50 fibroblasts examined showed a modal number of 47 chromosomes with an extra acrocentric chromosome of a size between the D and G group chromosomes. To identify this abnormal karyotype we used both quinacrine fluorescent staining (Breg, 1972) and a trypsin-Giemsa banding technique (Hirschhorn *et al.*, 1973). With both Q and G banding techniques this extra chromosome was identified as a translocation chromosome consisting of the short arm, centromere, and the proximal half of the long arm of No. 22 and the distal one-third of the long arm of No. 13 (Fig. 3). Chromosome analysis of the patient's phenotypically normal mother showed a balanced translocation affecting a No. 13 and a No. 22 chromosome (Fig. 4). The banded karyotype of the mother allowed us to confirm the exact breakage and rearrangement points on the No. 13 and No. 22 chromosomes, $t(13:22)(13qter \rightarrow 13q22::22q12 \rightarrow 22pter)$ (Paris Conference, 1971) (Fig. 5). The patient therefore was trisomic for the distal third of the long arm of chromosome 13 and the short arm and the proximal half of the long arm of chromosome No. 22.

Discussion

The trisomy 13 syndrome was not generally recognized until its chromosomal aetiology was discovered by Patau *et al.* in 1960. Smith (1964), Warkany *et al.* (1966), and Taylor (1968) reviewed the clinical and necropsy findings of trisomy 13 and concluded that despite the variability in the expression of the trisomy 13 syndrome from case to case the total pattern of anomalies is specific enough for clinical recognition. Trisomy 22 was suspected as a syndrome by Uchida *et al.* (1968) and recognized as a clinical entity by Hsu *et al.* (1971). With banding studies Punnett *et al.* (1973) confirmed three cases of trisomy 22 in a study of four non-mongoloid children with an extra G-group chromosome. Recently the

Table Clinical and pathological findings of patient compared with the findings of trisomy 13 and 22

Abnormalities in the patient	Trisomy 13	Trisomy 22
Absence of olfactory bulbs and tracts	+	-
Micropolygyria of frontal lobes	+	-
Microcephaly	+	+
Wide cranial sutures and fontanelles	+	-
Epicanthal folds	+	+
Bilateral microtia	+	-
Preauricular sinus	-	+
Cleft palate	+	+
Micrognathia	+	+
Capillary haemangiomas	+	-
Flexion deformities of major joints	+	+
Flexion deformities of fingers	+	+
Malopposed and finger-like thumb	-	+
Cryptorchism	+	+
Absence of left umbilical artery	+	-
Atrial septal defect (ostium II)	+	+
Bilateral nephromegaly	+	-
Intestinal malrotation	+	-
Supernumerary adrenal gland, adrenal cytomegaly	+	-

syndrome has been well delineated by Alfi *et al.* (1975) and Penchaszadeh and Coco (1975).

The clinical and pathological findings of our case were compared to the findings of trisomy 13 and 22, and our patient presented most of the major phenotypic features of both trisomies (Table). Phenotypic features suggestive of trisomy 13 included absence of the olfactory bulbs and tracts, micropolygyria of frontal lobes, wide cranial sutures and fontanelles, epicanthal folds, bilateral microtia, capillary haemangiomas, cardiovascular anomalies including absence of one umbilical artery, genitourinary tract and gastrointestinal tract anomalies. Features suggestive of trisomy 22 were typical facial appearance, preauricular sinus, finger-like malopposed thumbs, and deformed lower extremities (Alfi *et al.*, 1975; Penchaszadeh and Coco, 1975). The features common to both trisomic syndromes were microcephaly, prominent beaked nose, micrognathia, cleft palate, and atrial septal defect.

It may be noted that though renal anomalies are a common feature of trisomy 13 nodular renal blastema are not a distinctive feature of this chromosomal aberration. However, these have been reported in subjects with trisomy 18 (Bove *et al.*, 1969).

A few instances of partial trisomy of the distal portion of the long arm of 13 have been described. Hoehn and Wolf (1971) reported a 13q+ chromosome in a patient with characteristics of trisomy 13 syndrome. Autoradiographic study of this 13q+ chromosome showed a possible duplication of the distal third of the long arm. Fryns and Eggermont (1974) described a child with some of the clinical features of trisomy 13 due to a de-novo translocation of the distal two-thirds of the long arm of chromosome No. 13 to the long arm of chromosome No. 6 resulting in trisomy of the distal portion of chromosome No. 13. Recently Escobar *et al.* (1975) reported one case of partial trisomy for the distal one-third of chromosome 13 and reviewed four other cases. They suggested a new syndrome for this type of trisomy. However, three out of four previously reported cases were not studied with the banding technique, thus the extra chromosomal material was not clearly identified. Moreover, one cannot be certain whether absence of a few major features of trisomy 13 is due to partial trisomy or a variation of the phenotypic expression of trisomy 13 itself.

Our patient manifested most of the major features of trisomy 13 except for the ocular anomaly and polydactyly. Among three cases of complete trisomy 13 ascertained by prenatal diagnosis (Butler *et al.*, 1973; Lawrence *et al.*, 1974; H. J. Kim, L. Y. F. Hsu, and K. Hirschhorn, unpublished information) ocular abnormalities were found in only one and polydactyly in one other case. However, scalp defect and/or absence of olfactory bulbs or tracts were found in all three cases. Prenatal diagnosis of trisomy 13 may eventually provide a better assessment of the range of phenotypic manifestations of this trisomy without biased postnatal ascertainment. A review of necropsy findings of trisomy 13 by Warkany *et al.* (1966) showed that arrhinencephaly was the most common CNS malformation (25/32). Thus far, from either postnatal or prenatal diagnosis, it seems that scalp defect or arrhinencephaly, or both, are characteristic of trisomy 13 syndrome. One of the cases of trisomy 22 reported by Punnett *et al.* (1973) showed rather typical features of trisomy 22, though the extra chromosome contained only the proximal half of the long arm of No. 22. Therefore the findings of the previously reported cases of partial trisomy 13 and 22 as well as our case indicate that the presence of an extra proximal half of the long arm of No. 22 is responsible for trisomy 22 syndrome and the presence of an extra distal one-third of the long arm of No. 13

is responsible for the clinical features of trisomy 13.

Recently Williams *et al.* (1975) reported familial Down's syndrome due to t(10:21) and showed evidence that the Down phenotype is related to trisomy of the distal segment but not the proximal segment of 21q. In general, heterochromatin is thought to be located primarily in those chromosome regions which stain densely by G-banding while euchromatic regions stain lightly or not at all. It has also been inferred that euchromatin is genetically active whereas constitutive heterochromatin does not contain structural genes coding for proteins (Comings, 1972). Therefore we propose that presence of duplicated euchromatic regions of No. 22 (22q11) and No. 13 (13q22 and/or 13q34) are responsible for the trisomy 22 and 13 syndromes.

These specific euchromatic regions probably contain gene(s) which are responsible for various degrees of developmental retardation and malformation associated with the trisomy syndromes. Such gene(s) when present in triple dose may cause a regulatory imbalance in cellular differentiation at critical times of embryogenesis.

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