Hum. Genet. 56, 21–51 (1980)

Human Genetics

Original Investigations

The 11q;22q Translocation: A European Collaborative Analysis of 43 Cases

M. Fraccaro[1], J. Lindsten[2], C. E. Ford[3], and L. Iselius[2]

A. Antonelli[4], P. Aula[5], A. Aurias[6], A. D. Bain[7], M. Bartsch-Sandhoff[8], F. Bernardi[9], E. Boyd[10], L. F. Buchanan[11], A. H. Cameron[12], A. de la Chapelle[13], G. Ciuffa[14], C. Cuoco[15], B. Dutrillaux[6], G. Dutton[16], M. A. Ferguson-Smith[10], D. Francesconi[1], J. P. M. Geraedts[3], G. Gimelli[15], J. Gueguen[6], E. Gärsner[17], A. Hagemeijer[18], F. J. Hansen[19], P. E. Hollings[20], T. W. J. Hustinx[21], A. Kaakinen[22], J. J. P. van de Kamp[23], H. von Koskull[24], J. Lejeune[6], R. H. Lindenbaum[25], H. R. McCreanor[20], M. Mikkelsen[26], F. Mitelman[27], B. Nicoletti[4], I. Nilsby[28], A. Nilsson[29], B. Noel[30], E. Padovani[9], F. Pasquali[1], J. de Pater[31], C. Pedersen[32], F. Petersen[26], E. B. Robson[33], J. Rotman[6], M. Ryynänen[34], E. Sachs[18], J. Salat[6], R. H. Smythe[20], I. Stabell[32], I. Šubrt[35], P. Vampirelli[36], G. Wessner[37], L. Zergollern[38], and O. Zuffardi[1]

[1] Department of General Biology and Medical Genetics, University of Pavia, Pavia, Italy
[2] Department of Clinical Genetics, Karolinska Hospital, Stockholm, Sweden
[3] Department of Human Genetics, University of Leiden, Leiden, The Netherlands
[4] Cytogenetics Center, Institute of General Biology II, University of Rome, Rome, Italy
[5] Department of Paediatrics, University Hospital, Helsinki, Finland
[6] Institut de Progénèse, University of Paris, Paris, France
[7] Department of Pathology, Royal Hospital for Sick Children, Edinburgh, Great Britain
[8] Department of Human Genetics, University Hospital, Essen, Germany
[9] Genetics Center, Central Hospital Borgo Roma, Verona, Italy
[10] Medical Genetics Department, Royal Hospital for Sick Children, Glasgow, Great Britain
[11] New Plymouth, New Zealand
[12] Department of Pathology, The Children's Hospital, Birmingham, Great Britain
[13] Department of Medical Genetics, University of Helsinki, Helsinki, Finland
[14] Neonatal Pathology Division, S. Giovanni Hospital, Rome, Italy
[15] Laboratory II, Gaslini Institute, Genova, Italy
[16] Department of Psychiatry, County Hospital, Hereford, Great Britain
[17] Department of Pediatrics, Central Hospital, Växjö, Sweden
[18] Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands
[19] Department of Pediatrics, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[20] Cytogenetics Laboratory, Wellington, New Zealand
[21] Department of Human Genetics, Catholic University, Nijmegen, The Netherlands
[22] Central Hospital, Tampere, Finland
[23] Department of Pediatrics, University of Leiden, Leiden, The Netherlands
[24] Laboratory of Prenatal Genetics, Helsinki University Hospital, Helsinki, Finland
[25] Department of Medical Genetics, Oxford, Great Britain
[26] The John F. Kennedy Institute, Department of Medical Genetics, Glostrup, Denmark
[27] Department of Clinical Genetics, University Hospital, Lund, Sweden
[28] Department of Pediatrics, Central Hospital, Karlskrona, Sweden
[29] Department of Pediatrics, S:t Görans Hospital, Stockholm, Sweden
[30] Cytogenetics Laboratory, Central Hospital, Chambéry, France
[31] de Ederhorst, Ede, The Netherlands
[32] University Institute of Clinical Genetics, Department of Pediatrics, Institute of Pathology, The University Hospital, Odense, Denmark
[33] The Galton Laboratory, University College, London, Great Britain
[34] Department of Gynecology and Obstetrics, Kuopio University Central Hospital, Kuopio, Finland
[35] Institute for the Care of Mother and Child, Prague, Czechoslovakia
[36] A.I.A.S. Centre, Piacenza, Italy
[37] Department of Pediatrics, Central Hospital, Kristianstad, Sweden
[38] Human Genetics Center, Djecja Klinika Rebro, Zagreb, Yugoslavia

Offprint requests to: J. Lindsten

0340-6717/80/0056/0021/$ 06.20

Summary. Translocation between the long arms of chromosomes 11 and 22 is usually detected in offspring with an unbalanced karyotype following a 3 : 1 disjunction resulting in "partial trisomy." Since by the end of 1976 it was suspected that this translocation might be more frequent than one would deduce from published reports, it was decided to call for a collaborative effort in Europe to collect unpublished cases. In response, 42 cases were collected in Europe, and one case from New Zealand was added. The following countries were represented with the number of cases indicated in parentheses: Czechoslovakia (2), Denmark (4), Finland (3), France (6), Germany (1), Italy (5), The Netherlands (9), Sweden (6), United Kingdom (4), Yugoslavia (2). The wide geographical distribution indicates a multifocal origin of the translocation. Among the unpublished cases, 31 were ascertained as unbalanced carriers [47,XX or XY,+der(22),t(11;22)] and 12 as balanced balanced carriers [46,XX and XY,t(11;22)]. Among the published cases, 10 were ascertained in unbalanced and 3 in balanced carriers. The breakpoints of the translocations indicated by the contributors varied, the most frequently reported being 11q23;22q11 (25 cases), followed by q25;q13 (10 cases). While the first one seems more likely, it was not possible to decide whether the breakpoints were the same in all cases.

All 32 probands with unbalanced karyotypes had inherited the translocation, 31 from the mother and only 1 from the father. This ratio became 43 : 1 when the published cases were added. A segregation analysis revealed that in families ascertained through probands with unbalanced karyotypes there was a ratio of carriers to normal (all karyotyped) 54 : 55, not a significant difference. The formal maximum (minimum) recurrence risk for this unbalanced translocation was calculated to be 5.6% (2.7%). When the ascertainment was through a balanced proband, the maximum risk was 2.7%. The risk was calculated as 5.7% for female and 4.3% for male carriers. The mean family size was 1.67 for the offspring of female carriers and 0.78 for the offspring of male carriers. This significant difference suggests that heterozygosity for the translocation reduces fertility in males. Indeed, several of the probands with balanced karyotypes were ascertained because of sub- or infertility. Only 2 de novo translocations were found among the 59 probands, and both, were among the 12 cases ascertained as balanced carriers. The source, quality, and quantity of the clinical data for the subjects with unbalanced karyotypes were variable, and no definite conclusions were possible about phenotypes. The following signs were recorded in 10 or more of the 45 cases: low birth weight, delayed psychomotor development, hypotonia, microcephaly, craniofacial asymmetry, malformed ears with pits and tags, cleft palate, micro-/retrognathia, large beaked nose, strabismus, congenital heart disease, cryptorchidism, and congenital dislocation of the hip joints. Many signs were similar to those considered typical of trisomy 11q, and the phenotype coincided almost completely with the presumptive phenotype of complete trisomy 22. No cases with coloboma was recorded, while other signs of the "cat-eye" syndrome were found in several probands. This might indicate that individuals with the cat-eye syndrome and carriers of the unbalanced 11/22 translocation have the same segment of 22 in triplicate plus or minus another chromosome segment.

Introduction

By the end of 1976 it started to become apparent that reciprocal translocations between the long arms of chromosomes 11 and 22 were more frequent than one would deduce from published reports. It soon became obvious that most balanced carriers of this translocation were ascertained through offspring with unbalanced karyotypes and apparent "partial trisomy 22" due to a 3 : 1 disjunction. The balanced 11;22 translocation may be difficult to detect because the involved segments are small, and we think that nobody should feel inferior for having missed it. In fact, several authors of this paper went through such an experience.

In 1977 M. Fraccaro and J. Lindsten after consulting with some colleagues, chiefly Margareta Mikkelsen and M. A. Ferguson-Smith, decided to initiate a cooperative study to collect as many unpublished cases of the translocation as possible in order to enable us to analyze its segregation pattern. For this purpose a letter was circulated in Europe, and a total of 43 unpublished families were collected. The published cases were also analyzed but only those cases are included which were either reported as 11;22 translocations or revised as such by the authors themselves. Although in some cases the published photographs could show the unrecognized 11;22 balanced translocation, it was decided to avoid the dubious practice of identifying chromosomes in published photographs. Thus, a total of 44 probands from 43 families were collected for analysis. This large amount of material of heterogeneous origin and completeness was evaluated by M. F. and J. L. using the numerous suggestions made by the contributing authors. However the coordinators wish to stress that omissions and mistakes in the compilation are likely to be their own fault.

Materials and Methods

The unpublished cases were divided into two groups: those ascertained as unbalanced carriers (group A) and those ascer-

Table 1. Basic information on probands (and their parents) ascertained as unbalanced carriers. Breakpoints of the translocation are those indicated by the authors

Case no.	Sex	Date of birth			Age at last examination	Living or dead	Birth weight (g)	Parental age at birth		Parent carrier	Breakpoints 11;22
		yr	mo	d				Mo	Fa		
1	M	77	05	17	10 m	d	3080	21	22	Mo	q23;q13
2	M	76	08	08	18 m	l	3060	33	34	Mo	q23;q13
3	M	70	01	28	6 y	l	2800	24	28	Mo	q23;q11
4	M	77	02	03	30 min	d	1790	18	21	Mo	q23;q11
5	F	71	09	22	7 y	l	2760	30	35	Mo	q25;q12
6	M	77	11	04	5 m	l	2930	37	40	Mo	q25;q12
7	F	71	07	21	5¼ y	l	3965	33	35	Mo	q25;q13
8	F	57	—	—	20 y	l	2450	33	35	Mo	q25;q13
9	M	72	04	15	2½ y	l	1750	22	28	Mo	q25;q13
10	M	56	08	18	7 y	l	2200	44	47	Mo	q25;q12
11	F	73	06	22	5 y	l	2600	25	25	Mo	q25;q12
12	F	73	01	22	5 y	l	3010	23	25	Mo	q23;q11
13	M	60	03	06	19 y	l	2090	26	28	Mo	q23;q12
14	F	75	05	18	9 m	l	2320	26	29	Mo	q23;q11 or q24;q12
15	M	77	04	05	4½ h	d	3110	30	29	Mo	q25;q13
16	F	70	08	31	8½ y	d	2265	27	31	Mo	q25;q13
17	M	74	08	02	5 y 3 m	l	3200	23	31	Fa	q25;q13
18	M	—			1 h	d	2500	32	33	Mo	q25;q13
19	M	79	—	—	5½ m	l	3380	28	33	Mo	q24;q12
20	M	78	—	—	3 m	l	2950	34	—	Mo	q24;q12
21	F	77	07	22	7 m	l	2790	42	43	Mo	q23;q11
22	M	77	—	—	2 y	d	2950	21	25	Mo	q23;q11
23	M	62	01	12	17 y	l	2700	44	—	Mo	q25;q13
24	F	67	—	—	11 y	l	3000	27	33	Mo	q23;q11
	F	76	—	—	2½ y	l	3000	36	42	Mo	q23;q11
25	F	74	09	02	3½ y	l	2450	17	20	Mo	q23.1;q11.1
26	F	76	08	04	9 m	l	3130	36	42	Mo	q23.1;q11.1
27	M	78	06	02	5 m	l	3200	21	19	Mo	q23.1;q11.1
28	M	77	03	04	2 y	d	2900	25	27	Mo	q25;q13
29	M	70	06	03	9 y	l	3130	29	35	Mo	q25;q13
30	M	67	09	08	8 y	l	2200	40	—	Mo	q23;q11
31	M	76	02	08	2 y	l	2820	29	29	Mo	q23;q11

tained as balanced carriers (group B). The cases found in the literature (group C) were also divided by ascertainment into Ca and Cb, respectively. For each of the families a pedigree was obtained, which was reduced to the informative parts and redrawn to a common standard by the coordinators. Each of the contributing author(s) provided either complete or partial karyotypes of the translocation obtained by one or more of the available banding techniques. The breakpoints (and the eventual alternatives) entered in the various tables below are always those indicated by the contributing authors. In all the case reports, parents, sibs, and relatives of the probands are to be considered clinically normal if not stated otherwise. All the individuals with unbalanced karyotypes had 47,XX or XY,+der(22),t(11;22) karyotype with the breakpoints as entered in Table 1. All the balanced carriers had a 46,XX or XY,t(11;22) karyotype with the breakpoints entered in Table 2. Any additional chromosome abnormalities are indicated on the pedigrees and mentioned in the case reports.

The countries of origin of the probands are indicated in the case reports. The cities name are those in which the main contributors reside. The following countries are represented, with the number of cases indicated in parentheses: Czechoslovakia (2), Denmark (4), Finland (3), France (6), Germany (1), Italy (5), The Netherlands (9), New Zealand (1), Sweden (6), United Kingdom (4), Yugoslavia (2).

Case Reports

Group A
(Ascertained Through Probands with Unbalanced Karyotypes)

Case number, date of birth, age at last examination, birth weight, parental ages at birth, parental carrier, and breakpoints of the translocation are given in Table 1.

Table 2. Probands ascertained as balanced carriers

Case no.	Sex	Date of birth			Date and modality of ascertainment	Translocation received from	Reproductive performance[a]				Breakpoints 11;22
		yr	mo	d							
32	M	49	01	28	1977; three spontaneous abortions	Father	A	A	A	BCF	q23;q11
33	F	47	04	25	1978; investigated because of a familial pericentric inversion of chromosome 2	Father?	—				q23;q11
34	M	24	08	20	1975; infertility	—	—				q24;q11
35	F	54	11	03	1979; two spontaneous abortions plus a stillborn daughter	Mother	A	USF	A		—;—
36	F	35	04	06	1976; prenatal diagnosis because of advanced age	Father	A	NM	A	BCM	q23;q13
37	F	40	06	12	1975; previous malformed children	De novo	USF	NF	USM	NF	q2;q1
38	M	58	08	15	1978; hypogonadism	De novo	—				q2;q1
39	F	41	05	17	1976; repeated spontaneous abortions	Mother	A	A	A		q24;q12
40	M	52	09	25	1977; infertility	—	—				q23.1;q11
41	M	39	—	—	1971; infertility	—	A				q23.1;q11
42	M	48	07	19	1978; infertility	Father?	—				q23.1;q11
43	F	70	04	12	1977; mental retardation, cardiac murmur	Mother	—				q23;q11

[a] A, spontaneous abortion; BC, balanced carrier; N, normal karyotype; S, stillborn and/or malformed; U, karyotype unknown; F, female; M, male; —, no reproduction

Family 1, Stockholm, Sweden. The propositus (Fig. 1b) was referred because of multiple malformations. Normal pregnancy, and delivery at 42 weeks. At birth: length 50 cm, atresia of the left auditory meatus, two preauricular tags and a pit on the right, cleft palate, micrognathia, and left-sided torticollis. On X-ray asymmetrical facial bones (the left temporal bone being smaller than the right); hemivertebrae in the upper part of the cervical spine; normal heart and lungs except for some small areas of atelectasis; normal stomach, duodenum, and jejunum. Normal intravenous pyelography.

Increased concentration of IgM (0.7 g/l) but normal concentration of serum IgG and IgA. The bilirubin concentration was increased (163 μmol/l, 142 μmol/l conjugated). Normal serum electrophoresis with normal concentration of α-1-antitrypsin. Virus isolation negative as were serological tests for syphilis, toxoplasmosis, HB Ag, and anti-HB Ag. Audiological examination was normal on the right side. Ophthalmological investigation normal.

Exploratory laparotomy at 7 weeks showed absence of the gall bladder and extrahepatic biliary ducts. Several enlarged lymph glands were found in the hilar region of the liver. Microscopic examination of a liver biopsy showed stasis of the biliary ducts with infiltration of granulocytes, lymphocytes, and plasma cells. At 4 months he showed jaundice and hepatosplenomegaly. His psychomotor development was normal except for poor head control.

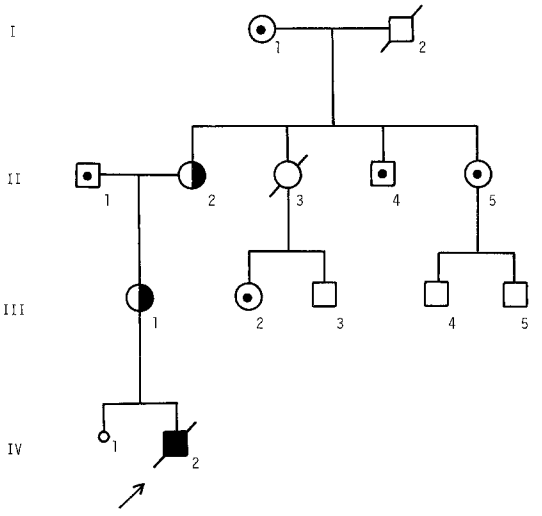
He died when 11 months old. Additional pathological findings at autopsy: peripheral and pulmonary edema; ascites (1500 ml); a small fenestration of the foramen ovale; increased concentration of alveolar macrophages and a subpleural granuloma with giant-cell reaction in the right lower lobe; involuted thymus with an increased number of Hassall's corpuscles; ribs with evidence of rachitis; malrotation of the gut with cecum in the right upper quadrant; some fibriotic adherances between the stomach, the bowel, and the abdominal wall; biliary cirrhosis of the liver with substantial proliferation of the biliary ducts; splenomegaly.

Family 2, Stockholm, Sweden. The propositus (Fig. 2b) was referred because of multiple malformations. Born at term after normal pregnancy and delivery. Length at birth, 50 cm; head circumference 34 cm. After birth, failure to thrive. Asymmetrical head with malformed left external ear, cleft soft palate, luxation of the left hip joint, right inguinal hernia, atrophic left gonad. At 1½ years, retarded psychomotor development, head circumference at the lower limit (-3σ) of normal. X-rays of heart, lungs, esophagus, and stomach normal.

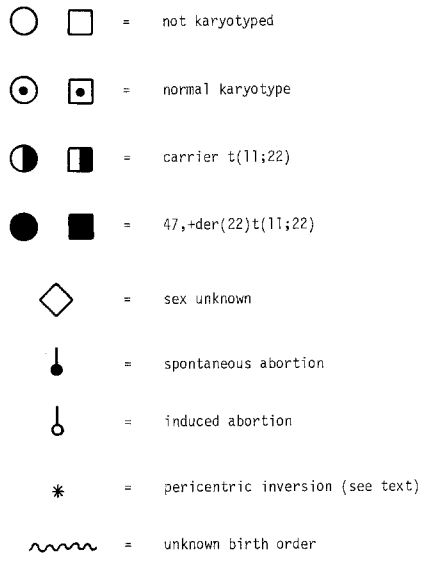
Family 3, Pavia, Italy. The propositus (Fig. 3b) was referred because of multiple malformations. Uneventful pregnancy. Caesarean section at 42 weeks. At birth: length 51 cm; head circumference, 35 cm; short period of asphyxia; slight hypotonia but normal reflexes; trigonocephaly with anterior fontanel 2 × 2 cm and open lambdoid fontanel; antimongoloid slant of the eyes; malformed external ears; hypoplastic mandible with bird profile; narrow palate; long slender fingers; cryptorchidism on the left.

At 2½ years of age: retarded psychomotor development, head circumference 49 cm, no amnioaciduria. Normal electrophoretic pattern of plasma proteins, sweat test, Guthrie test, ECG, EEG and ocular fundi. X-rays showed normal heart shadow and some signs of craniostenosis.

Slow psychomotor development during the following years. He sat at 30 months and walked with help at 6 years. He then showed ataxia. Affective relations began at 3 years of age. At 5 years of age he made use of only four words and communicated mainly with gestures. The dermatoglyphic pattern of his fingers



a



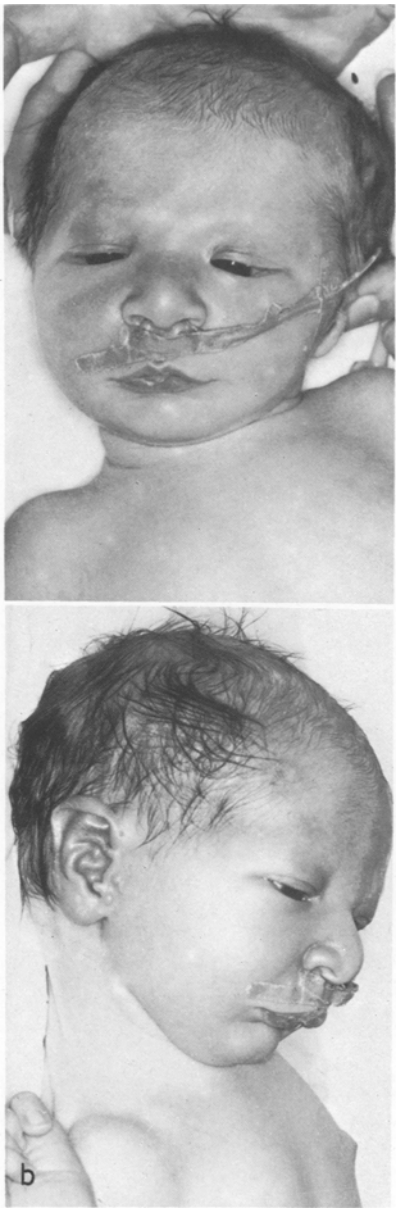


Fig. 1. Family 1—pedigree. A symbol with a diagonal in this and the following pedigrees indicates that the subject was dead at the time of investigation (**a**); Subject with an unbalanced 47,+der(22) karyotype (**b**)

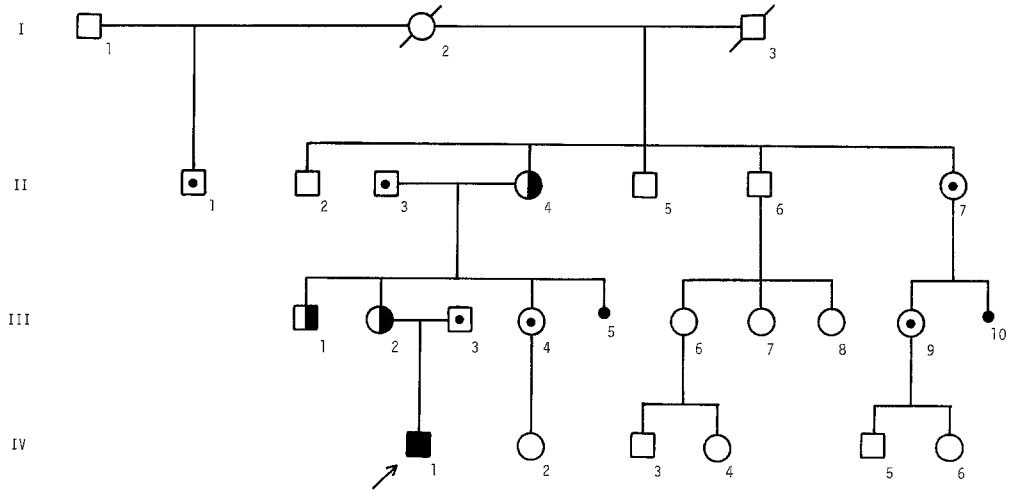
and palms showed some peculiarities but no striking abnormalities (Dr. A. Rodewald, Munich, Germany).

Family 4, Helsinki, Finland. The propositus was referred because of multiple malformations. The mother received two hormonal injections in the 10th week of gestation to induce menstruation (it was not suspected that she was pregnant). She was vaccinated against influenza in the 18th week of gestation. Caesarean section at 37 weeks because of toxemia, oligohydramnios, and weak fetal heart sounds. At birth, the infant needed artificial respiration. Pneumothorax appeared on the right side after 30 min, and the baby died subsequently. Normal placenta and umbilical vessels but short umbilical cord (26 cm). At autopsy: length 45 cm, low-set ears, small abnormal external ears and absence of auditory canals, cryptorchidism with normal testes in the abdomen, defective diaphragm on the left side with herniated intestines, hypoplastic lungs. Normal brain, cardiovascular system, intestines, and urogenital structures. Abnormal lobulation and shape of the liver and spleen.

The karyotype of the balanced carrier III-2 was established at prenatal diagnosis.

Family 5, Lund, Sweden. The proposita (Fig. 5 b) was referred because of severe mental retardadion, hypotonia, athetotic movements, and pupillary asymmetry. Length at birth 49 cm and head circumference 32 cm.

Family 6, Lund, Sweden. The propositus (Fig. 6 b) was referred because of multiple malformations: broad nose, poorly developed external ears, micrognathia, hypotonia, and retarded psychomotor development. The parents had previously had infertility of 17 years duration.



a

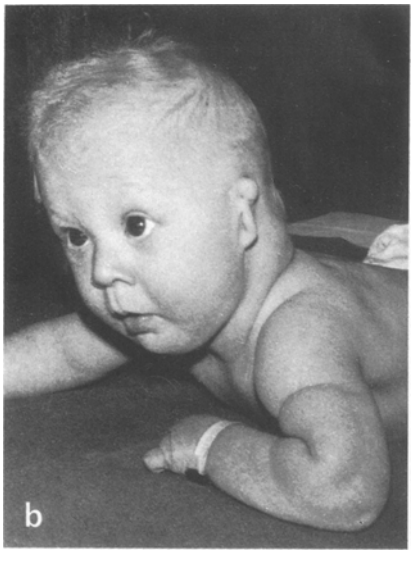


Fig. 2. Family 2—pedigree (**a**), for explanation see Fig. 1 a. Subject with an unbalanced 47,+der(22) karyptype (**b**)

Family 7, Oxford, England (mentioned in Addendum to Lindenbaum and Bobrow 1975 and in de la Chapelle et al. 1978). The proposita (Fig. 7b) was referred because of mental retardation. At birth breathing difficulties, cleft soft palate, and anal stenosis. Feeding problems. Slow psychomotor development; she was first noted to reach for objects at 18 months, and she smiled rarely before 2 years. She could sit unsupported but not walk or speak at 5 years.

At 3 years, height between the 10th and 25th percentiles, weight below the 3rd. Head circumference below the 3rd percentile. Large ear pinnae on the left with a fistula at the upper anterior margin. Sunken nasal bridge, normal eye separation. Pale blue nevus over the right mastoid; a similar nevus above the right eyebrow drained into prominent veins towards the ear. Teeth crowded and irregularly spaced. Slender trunk, low-set nipples, slightly depressed sternum. Thin legs ended in somewhat inverted feet. Left bridged transverse palmar crease, rather low ridge count including two digits with arch patterns not present in either parent.

At 5¼ years: height 96.5 cm, weight 11.35 kg, and head circumference 46.4 cm (below the 3rd percentile, −4 SD, and −3 SD, respectively).

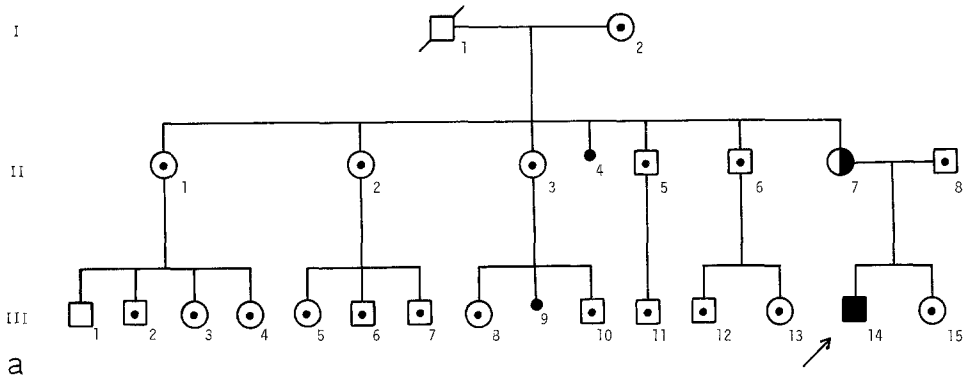
Eventually several translocation carriers were identified in groups of this family living in England, Denmark, and Sweden. One malformed male child (VI-7), offspring of a known carrier, died at 4 days in 1960. He had cleft palate, micrognathia, widely spaced skull sutures, and unspecified deformities of the thorax. Autopsy revealed no left kidney and a right kidney "the size of a coffee bean." Penis was small and the lungs were very atelectatic.

Family 8, Copenhagen, Denmark (reported in Danish by Petersen and Dahl 1977). The proposita (Fig. 8 b) was ascertained when 16 years old during a survey of patients with amenorrhea in an institution for mentally retarded. Delivered in breech presentation at 38 weeks. Length 49 cm and head circumference 30 cm.

At 1 year psychomotor retardation (developmental age 5–6 months). Dysplastic acetabulum in both hips. Microcephaly (42.5 cm), small eyes, hypotelorism, alternating convergent strabismus, normal ocular fundi. Large protruding ears and anterior helices, preauricular fistulas with secretion of pus. Hyperplastic mandibula with prominent, underhung jaw. Hypotonic and hypoplastic muscles. The shoulder joints were hyperextensive and the hips subluxated. Normal EEG, ECG, and blood, urine, and CSF examination.

At 20 years she still could not walk. Height 159 cm and head circumference 52 cm. Very susceptible to infections. Beginning development of secondary sex characteristics, but no menstruation.

Family 9, Odense, Denmark. The propositus (Fig. 9 b) was referred because of congenital malformations. Born by Caesarean section 4 weeks before the expected date of birth, dysmature, length 44 cm, head circumference 31.5 cm, peculiar face, micrognathia, broad-bridged nose, big and broad mouth, thick upper lip, and abnormal labial commissures. High-arched palate and broad alveolar processes. Large and dysplastic ears with prominent anterior parts corresponding to the tragi. Bilateral preauricular tags and submandibular cystic bag left. Flattened occiput, abundant skin folds at the back of the neck. Systolic heart murmur. Hypoplastic scrotum and undescended testes. Both upper extremities were kept in a supinated position, and all the fingers showed ulnar deviation. Moderate flexion and adduction contractures in the hips. Thick palmar skin. Small toes with clinodactyly on the left foot. Edematous hands and feet.



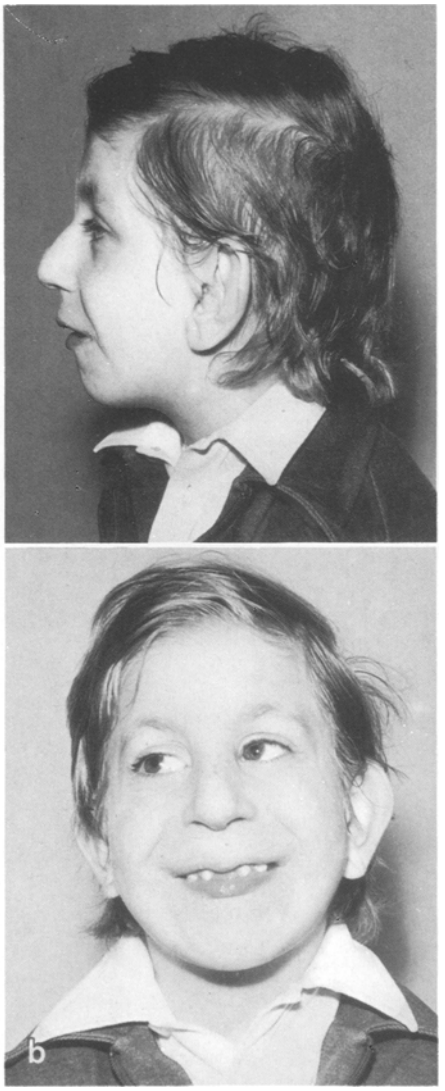


Fig. 3. Family 3—pedigree (**a**), for explanation see Fig. 1 a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

Psychomotor retardation was obvious at 6 months (At 2½ years she was considered seriously mentally retarded). Hypotonia.

A maternal aunt (III-7, examined at the age of 13 months, no karyotype obtained) was severely mentally retarded with uncoordinated movements of the upper extremities, rolling of the head and eyes, smacking of the lips, intermittent convergent strabismus, preauricular pit right, and delayed dentition. Normal physical growth but slender extremities, small hands and feet, marked genu valgus, hypotonia. Delayed bone maturation. At 15 years scoliosis and severe mental retardation. She died of pneumonia. No internal malformations were noted at autopsy.

Subject II-1 (carrier of the balanced translocation) is moderately mentally retarded.

Family 10, Copenhagen, Denmark. The family was ascertained in 1962 through III-7 by the late B. Hall, and the clinical description is taken from his publication (Hall 1963). The propositus (Fig. 10 b) showed cleft soft palate, left preauricular tag, small penis and mental retardation; he was susceptible to infections and obstipation. At 7 years: height 108 cm, head circumference 48 cm, large protruding ears, flat occiput, scanty and straight hair, myopia and alternating convergent strabismus, long and slender hands and feet with fingers tapered distally, transverse simian crease in one hand, hypoplastic scrotum, and cryptorchidism. He also had severe hypotonia and was unable to sit, stand, or walk alone. He had no language but reacted to sounds.

The chromosomes of the propositus and those of his family were examined in Copenhagen in 1972. One normal brother of the propositus was found to be a carrier of the balanced translocation. When his wife was pregnant, amniocentesis was twice attempted unsuccessfully in the second trimester. A girl with multiple malformations was born after 43 weeks of gestation (September 9, 1977) (Fig. 10 c). She was found to have an unbalanced karyotype. Birth weight 3260 g, length 53 cm, and head circumference 32 cm; hypoglycemia during the first day of life. Hypotonia, weak grasping reflex, and absent sucking reflex. Preauricular pits and tags, closure defect in the left side of the mouth and a fold of mucous membrane on the right cheek. There was a diastasis of 1 cm of the cranial bones and a deep skin pit in the sacral region. Normal ECG, EEG, echo-encephalography. Normal X-rays of the skull, spine, pelvis, heart, lungs, esophagus, and urinary tract. Flexion contractures in the elbows, hips and knees noted at the age 10 days. Tendency to a right-sided torticollis.

A maternal uncle (II-3 translocation carrier) has dwarfism (height 131 cm) of unknown etiology. A sister (III-3) who had cleft palate, was abnormally suseptible to infections and died when she was 8 months old. Another sister (III-6), who died when she was 12 months old, was reported to have Down's syndrome.

Family 11, Odense, Denmark. The proposita (Fig. 11 b) was referred because of congenital malformations. She was born by Caesarean section at 42 weeks of gestation; dysmaturity; length 48 cm, head circumference 31 cm, short (35 cm) but otherwise normal umbilical cord. Asymmetric skull with prominent right

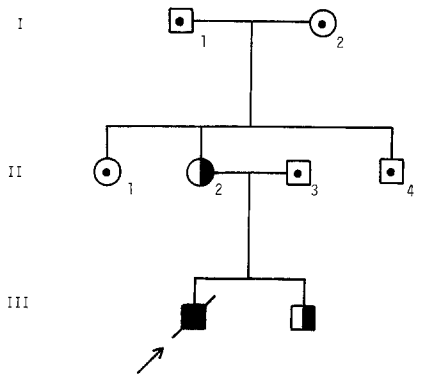


Fig. 4. Family 4—pedigree, for explanation see Fig. 1a

half. Cleft soft palate and posterior part of the hard palate, right preauricular tag, long philtrum.

At 11 months: small for age, microcephaly, brachycephaly, normal body proportions, weight 6200 g, length 67 cm, head circumferences 40 cm, diminished interocular distance, enophthalmus, convergent strabismus, pointed nose, micrognathia, retarded psychomotor development, hypotonia with normal reflexes, and a cardiac murmur suggestive of a ventricular septal defect. X-rays showed dextroconvex scoliosis, slight enlargement of the heart, and increased central pulmonary vascularity. Ptosis on the right and bilateral degenerative changes of the retina.

During the following years retarded (height and weight below −3 SD) and retarded bone age. At 5 years severe mental retardation, no speech. Marked psychotic reactions with limited contacts.

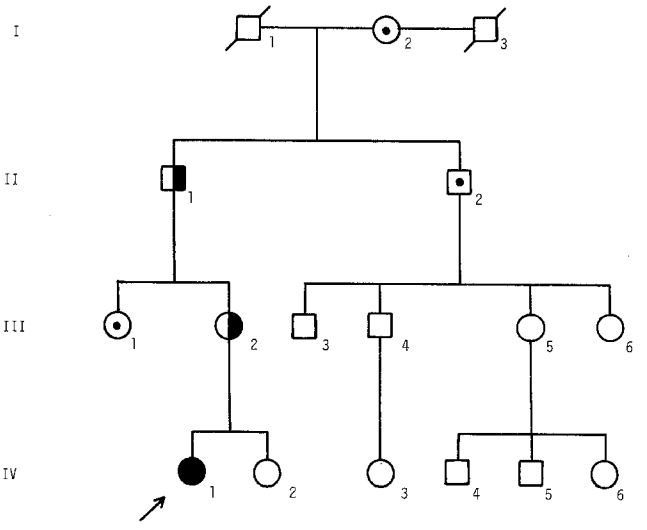
Her younger sister's (III-2) normal karyotype was found at prenatal diagnosis.

Family 12, Leiden, The Netherlands. The proposita (Fig. 12b) was referred because of congenital malformations. Born full term, length 49 cm, small head circumference, broad sagittal suture extending up to the glabella, wide anterior fontanel extending to the posterior fontanel, an area of necrotic scalp, encircled by long hair. Low-set ears with pits, broad nasal bridge, cleft palate, uvula agenesis, short neck with abundant skin, and small firm elevations under both heels.

At 5 years (Fig. 12c): severe mental retardation, height and weight below the 3rd percentile, microcephaly, bilateral sensorineural and conductive hearing loss (60–79 dB). On X-rays, herniation of both lung apexes. Incomplete right bundle-branch block and left ventricular hypertrophy. Normal angiocardiogram.

One brother of the proposita (III-3) died when 2 weeks old from peritonitis in connection with intestinal malrotation. He also had congenital heart disease, retrognathia, a broad nasal bridge, and cleft palate.

Family 13, Leiden, The Netherlands. The propositus was ascertained in a survey of mentally retarded persons with congenital anomalies. Born 4 weeks prematurely. Severe mental retardation, no speech. At 19 years height was below the 3rd percentile; small head circumference, turricephaly, asymmetrical face with smaller right side, normally set but large ears, prominent anthelix and antitragus left, mongoloid slant of the eyes, cleft palate and uvula agenesis, ventricular septal defect and pulmonary stenosis, cryptorchidism, right foot and toes small. No dermatoglyphic anomalies except that there were eight arches on the finger tips.



a

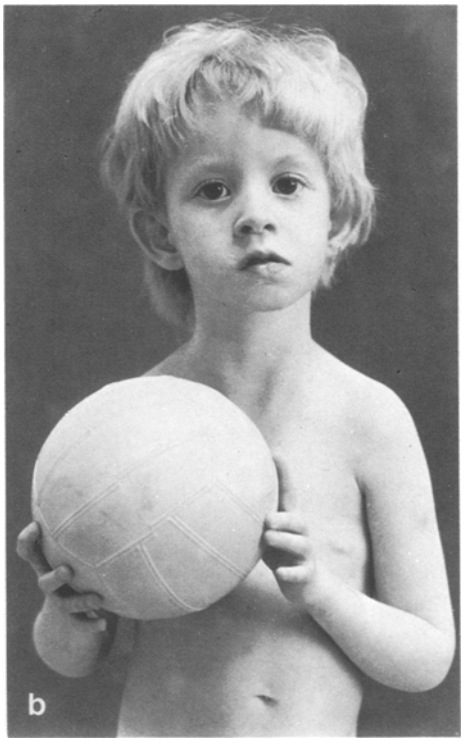
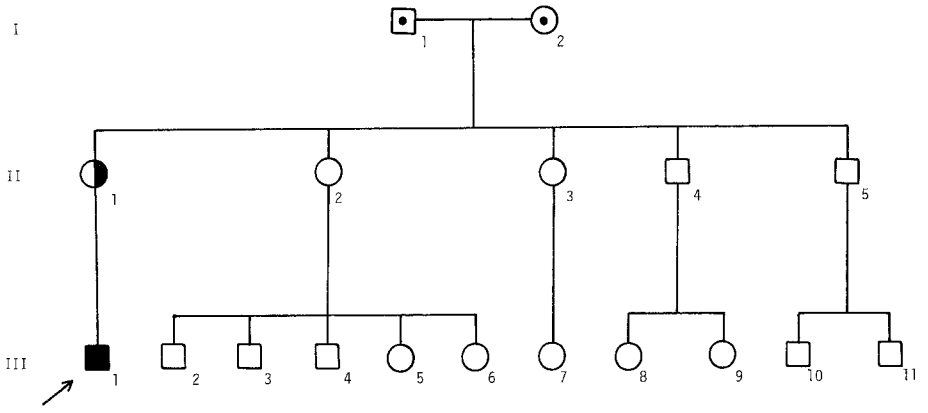


Fig. 5. Family 5—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

Family 14, Nijmegen, The Netherlands. The proposita (Fig. 14b) was referred because of congenital malformations, especially anal atresia and rectovulvar fistula. At 9 months weight, length, and head circumference were below the third percentile. Severe mental retardation. Several dysmorphic features were present: slight facial asmmetry, bilateral preauricular pits, large normally formed ears, short palpebral fissures with scanty eyebrows, curved nose with and abrupt transition to a long upper lip, long philtrum, retrognathia, bifid uvula, bilateral dislocation of the hip joints, posterior dislocation of the coccyx, sacral pit, hypo-



a

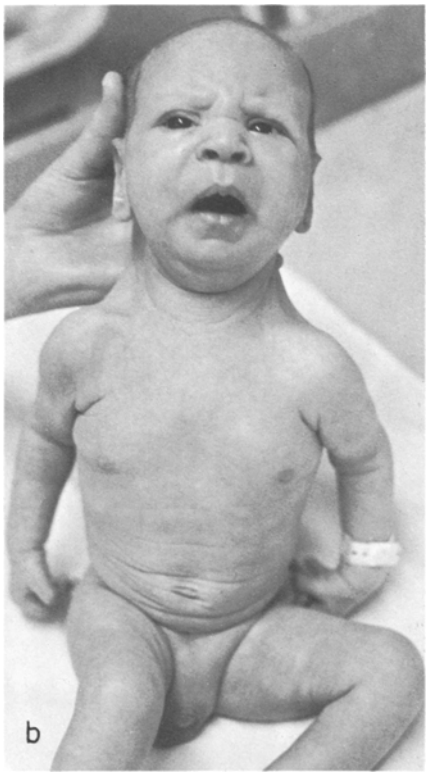


Fig. 6. Family 6—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

tonia. Pneumoencephalography revealed dilatation of the ventricles.

A maternal uncle (II-3) diet at the age of 5 weeks. According to his parents he had anal atresia, hydrocephalus, and cleft palate.

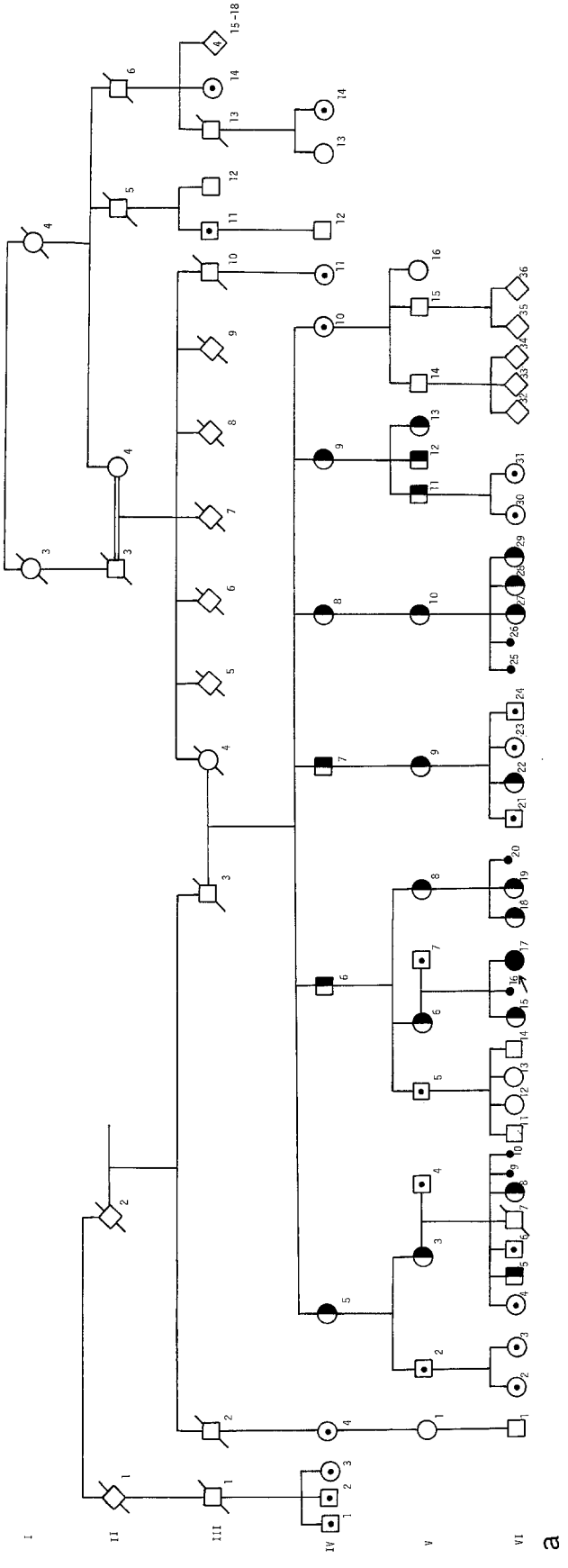
Family 15, Edinburgh, Great Britain. The propositus was referred for perinatal postmortem examination, as part of which routine chromosome studies were undertaken. This was after a forceps delivery for deep transverse arrest. The baby had survived 4 h. The infant was odd looking with webbed neck, edema of the neck tissues, beak-shaped nose, and a cleft palate plus bifid uvula. The scrotum was small and contained no testes. The brain showed bilateral arhinencephaly with absence of both olfactory nerves. There was a large left-sided posterolateral diaphragmatic defect with the left thorax containing a great part of the small intestine, spleen, part of the pancreas, and a portion of the right lobe of the liver. As a consequence both lungs were hypoplastic, the left more so than the right. The heart was displaced into the right thorax and showed a persistent common atrioventricular canal and also a smaller interventricular septal defect halfway down the septum. The ductus artiosus was widely patent. The liver was enlarged and lay far down in the abdomen with portion in the left thorax. The right kidney was smaller than usual with moderate hydronephrosis. The right ureter was dilated and thickened with stenosis at the ureterovesical junction. The left kidney was smaller than usual but showed no hydronephrosis. Both testes were intraabdominal and their polarity was reversed.

I-1, II-1, II-2, and III-10 all have a pericentric inversion of chromosome 2 (p11q13). The karyotype of the balanced carrier III-10 was established at prenatal diagnosis.

Family 16, Glasgow, Great Britain (mentioned in Ferguson-Smith 1978). The proposita (Fig. 16b) was referred at 2 years of age because of multiple malformations associated with psychomotor retardation. Noted to have several apneic attacks and was in an incubator for some days after birth. Delay in development at about 2–3 months. Could not sit unsupported until 1 year of age. At $2\frac{1}{2}$ years of age was not walking and had no speech. Malformations including cleft palate, bilateral preauricular tags and sinuses and angular mouth pits. She died suddenly at $8\frac{1}{2}$ years from an upper respiratory illness.

The karyotypes of the balanced carrier IV-2 was determined at prenatal diagnosis. II-5 was stillborn and noted to have cleft palate.

Family 17, Birmingham, Great Britain. The propositus (Fig. 17b and c) was referred for cytogenetic studies after birth because of ambiguous genitalia. Malformations included a small phallus with hypospadias, cryptorchidism, underdeveloped scrotum, bilateral inguinal hernia, odd facies with micrognathia, bilateral preauricular sinuses, bilateral congenital dislocation of the hip, small nails, and probable ventricular septal defect. A 12-month period of hospitalization was required for treatment of dislocated hips. He is now $5\frac{1}{2}$ years old and has severe psychomotor retardation. He has no speech, can scarcely, and does not feed himself; no formal psychomotor tests have been possible, but he is considered to be functioning at the 11–12 month level. His parents refuse further investigation and decline to discuss the family history.



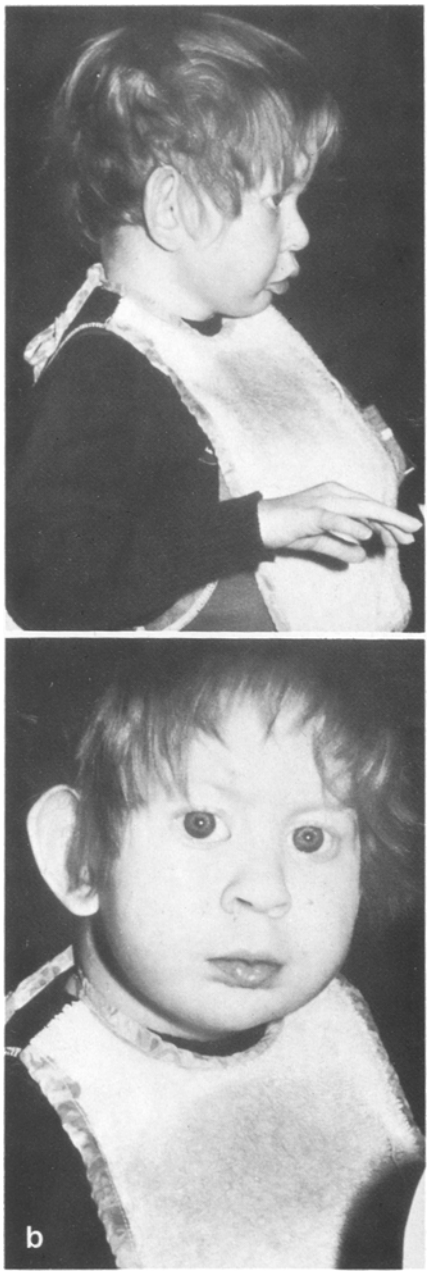
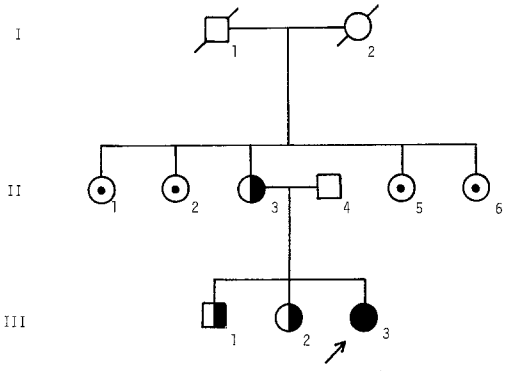


Fig. 7. Family 7—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

Family 18, New Zealand. The propositus ascertained at postmortem because of congenital abnormalities. Born at term, died after 1 h from cardiorespiratory insufficiency. He had microcephaly (occipital circumference 25 cm), micrognathia, rocker-bottom deformity of the right foot. A postmortem (Dr. R. J. Molony, New Plymouth) revealed a massive left-sided diaphragmatic hernia, resulting in generalized compressive atelectasis of the ipsilateral lung, and marked displacement to the right of the heart and great vessels. The whole of the left lobe and the bulk of the right lobe of the liver, the spleen, and part of the pancreas were in the thorax. There was no hernial sac. Subdural, sub-



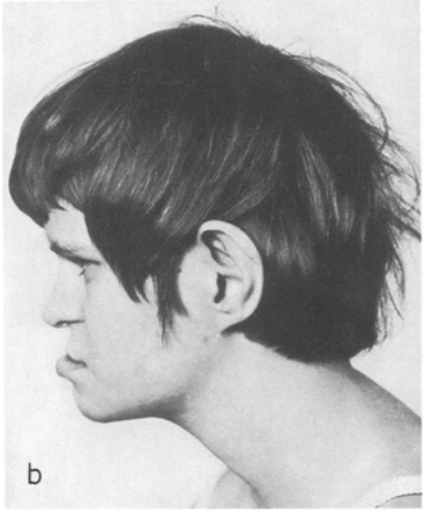
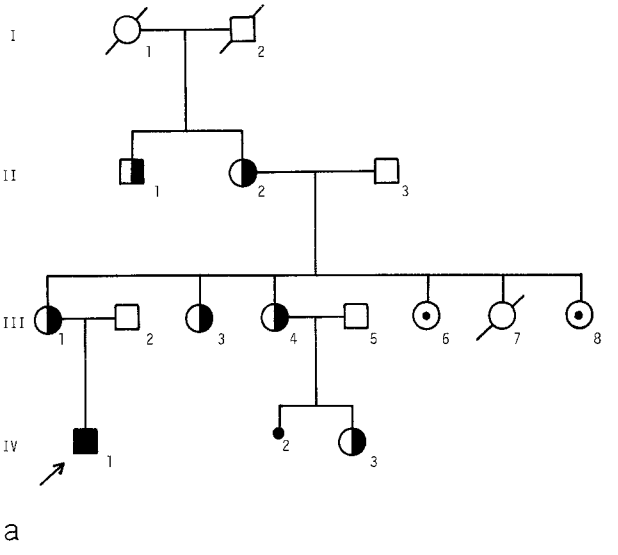


Fig. 8. Family 8—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

arachnoid, and intraventricular hemorrhage in the brain. No malformations of other organs.

Family 19, Zagreb, Yugoslavia. The propositus (Fig. 19b) was referred because of anal atresia, which was operated upon shortly after birth. During hospitalization the child got osteomyelitis in the femur and sepsis. After discharge from the hospital he had diffuculties with defection, feeding problems, anorexia, and psychomotor retardation. He also had bilateral inguinal hernia, and dolicho- and megacolon. At 5 months: weight 4160 g, height 56 cm, head circumference 38 cm, pale, hypotonia. Prominent forehead; hypertelorism; epicanthus; antimongoloid slant of the eyes; convergent strabismus; large, low-set, poorly shaped ear lobes. Small mandible; cleft palate. Heart and lungs normal. Small penis (about 2 cm), descended testes (about 12 mm long). Hyperflexibility and hypermotility of joints. Feet in calcaneovalgus position.

Family 20, Zagreb, Yugoslavia. The propositus (Fig. 20b) was referred for chromosome analysis because of congenital malformations. Respiratory and feeding difficulties after birth. At 3 months muscular hypotonia, weight 4600 g (below 10th percentile), height 56.5 cm (below 3rd percentile), head circumference 37 cm (below 3rd percentile). Slightly overlapping parietal bones. Slight antimongoloid slant of the eyes. Hypertelorism. Wide nasal bridge, low-set and poorly developed ears. Preauricular



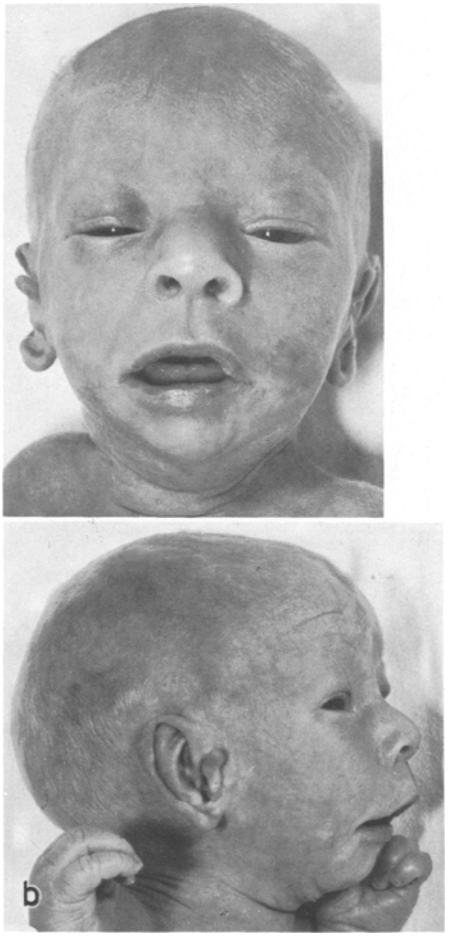
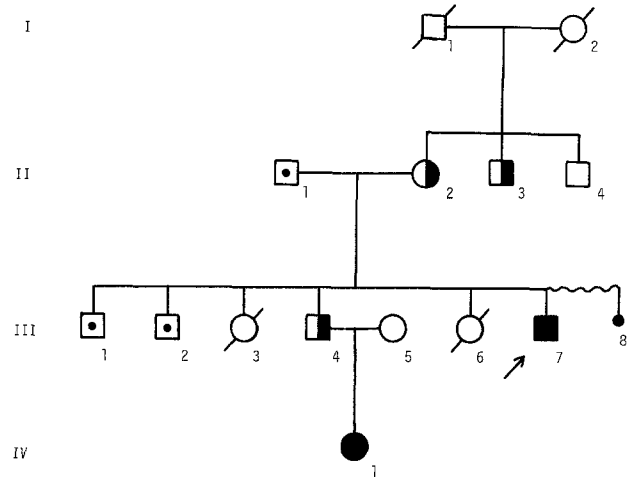


Fig. 9. Family 9—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

tags, micrognathia, cleft palate. Bilateral inguinal hernia. Cryptorchidism. Pseudoedema on the backs of the feet. Flexion contractures of the fingers. Slightly protruding heels. Enlarged heart on X-rays. ECG showed hypertrophy of the right ventricle. Normal EEG. Lateral ventricular asymmetry and dilata-



a

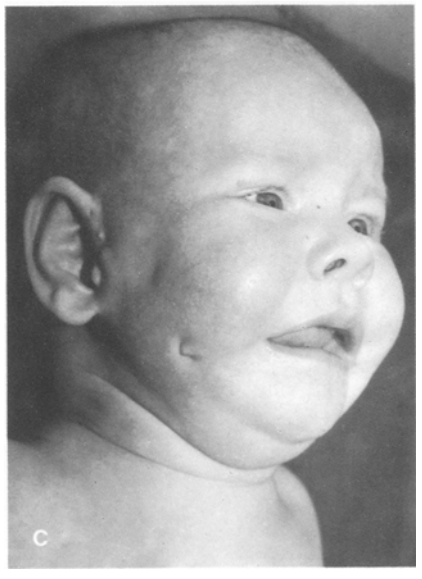
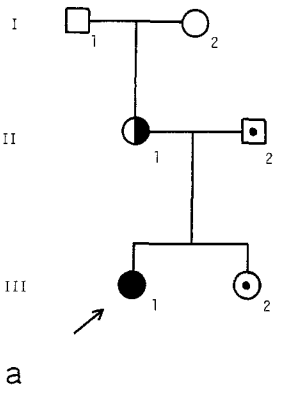


Fig. 10. Family 10—pedigree (**a**); for explanation see Fig. 1a. Subjects with an unbalanced 47,+der(22) karyotype (**b**, **c**)



a

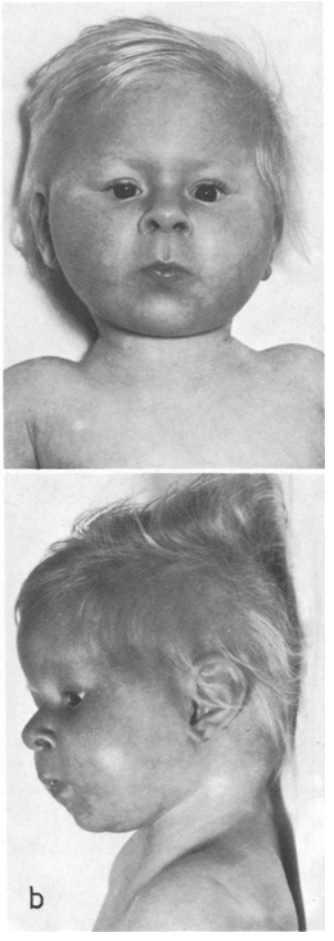
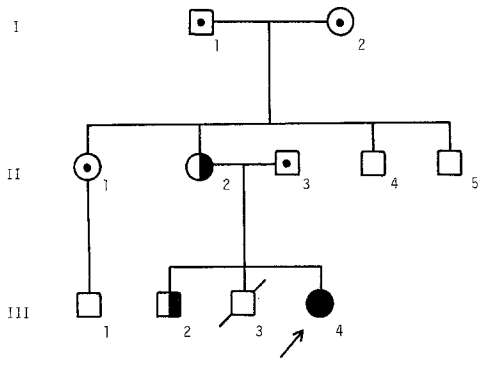


Fig. 11. Family 11—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

tion of the 3rd and 4th ventricles of the brain (computed tomography). Malformed hemispheres of cerebellum with dilatation of the subarachnoidal space. Delayed psychomotor development. I-1, II-3, and II-4 had pericentric inversion of a chromosome 9 [inv(9)(p1q13)].

Family 21, Verona, Italy. The proposita (Fig. 21 b) was referred because of congenital malformations. Born at term by Caesarean section because of flexed breech presentation. Length 48.5 cm,



a

head circumference 34.5 cm. Round face, hypotelorism, small nose and mouth, slight micrognathia, lowset ears with tags and pits, short and broad neck with skin folds. Limitation of extension in elbows, hips, and knees. Small clitoris and labia majora. Anal stenosis. Systolic heart murmur, slight muscular hypertonia. X-rays showed no skeletal abnormalities and a normal heart and gastrointestinal tract. Normal EEG, ECG, and amino acid levels in blood and urine. At 7 months: weight 9.2 kg (90th percentile), length 67 cm (95th percentile), and head circumference 43.5 cm (50th percentile). Psychomotor retardation and hypotonia, developmental quotient 0.66 (Brunet-Lezine's test).

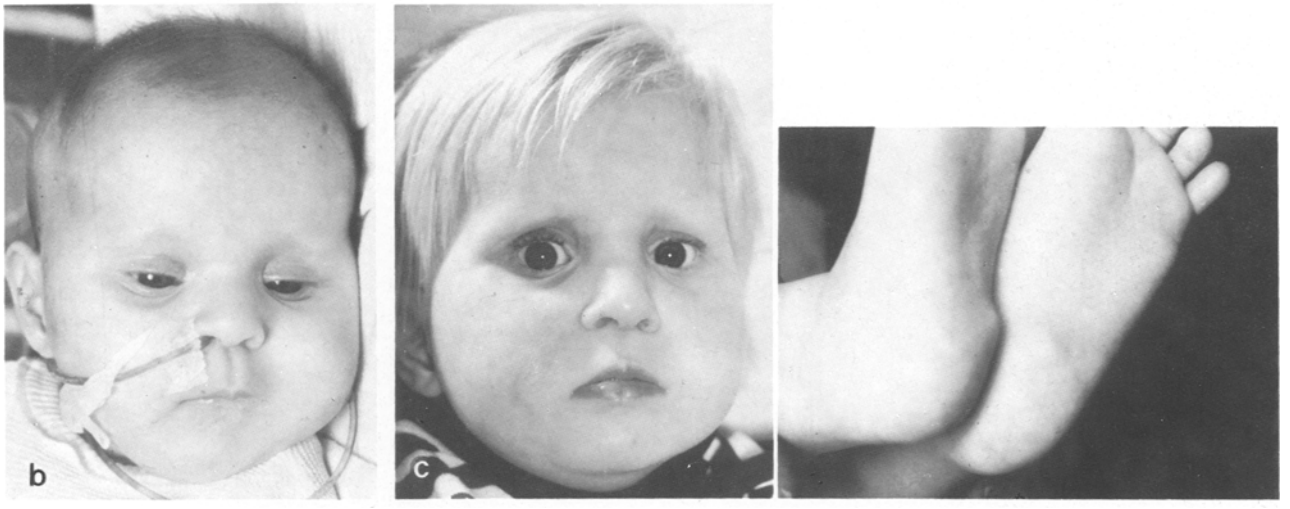


Fig. 12. Family 12—pedigree (**a**); for explanation see Fig. 1a. Subjects with an unbalanced 47,+der(22) karyotype (**b**, **c**)

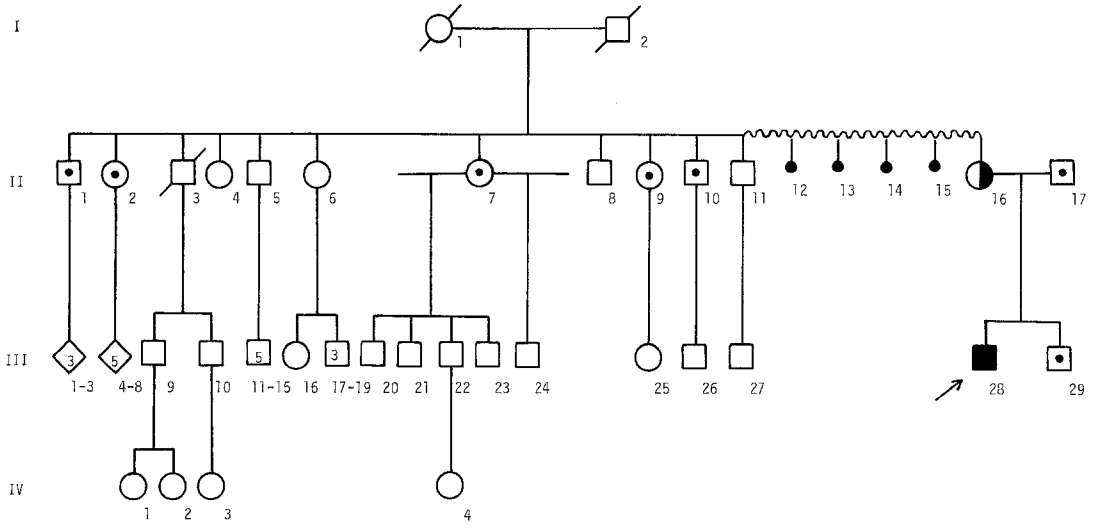
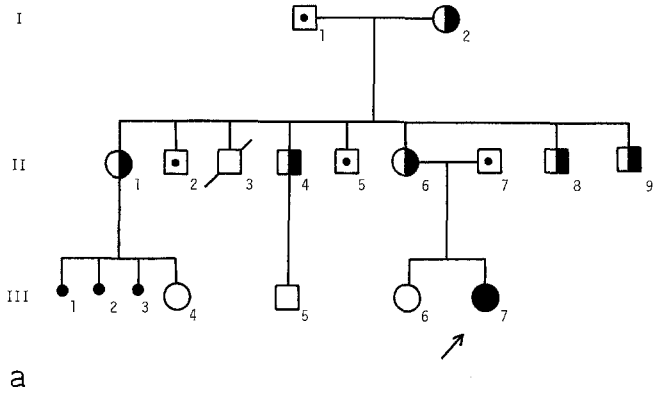


Fig. 13. Family 13—pedigree, for explanation see Fig. 1a



sed nasal bridge, flat and beaked nose, long philtrum, micrognathia, macrostomia with downturned commissures of the mouth, high-arched palate and bifid uvula, low-set and malformed ears, bilateral preauricular pits and tags on the right. Low-set nipples, undescended testes, bilateral dislocation of the hip joints. Shortly after birth recurrent gastroenteritis and upper respiratory tract infections complicated by bronchopneumonia. Mental and motor development were greatly retarded. Underdeveloped muscles and hypotonia, marked lumbar kyphosis, flexion of the flexed hips. Dermatoglyphics not remarkable except for the presence of hypoplastic ridges in both hypothenar regions. Optic nerve atrophy. Intravenous pyelography and scintigraphy revealed left renal aplasia. At 4 months low

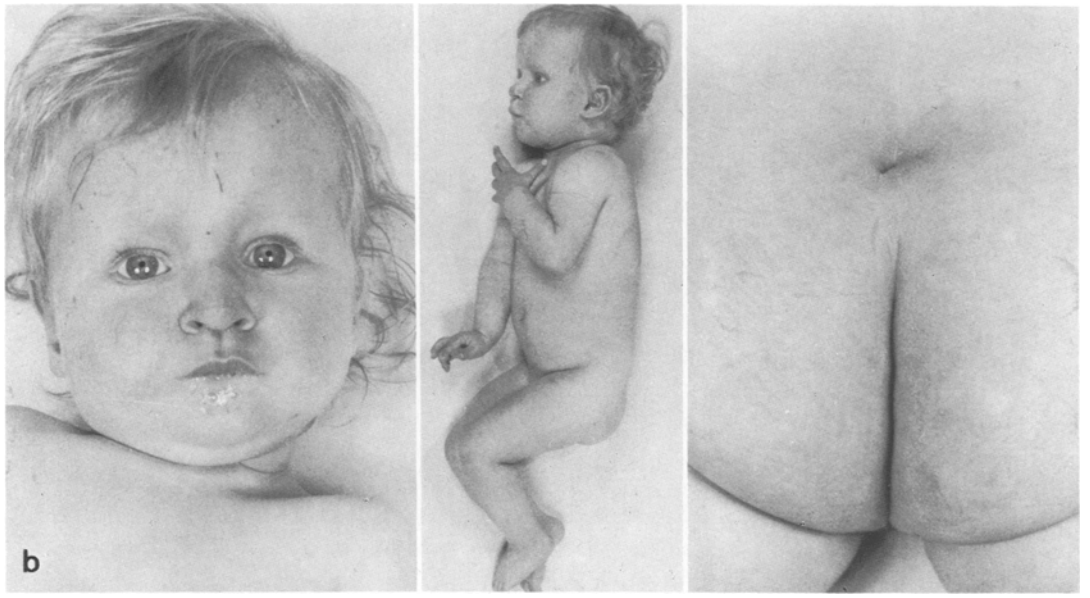


Fig. 14. Family 14—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

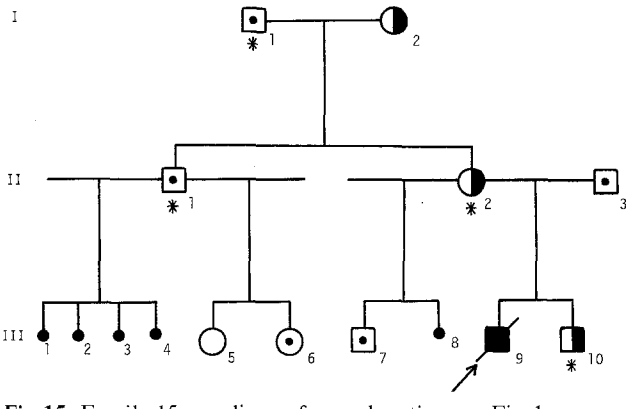


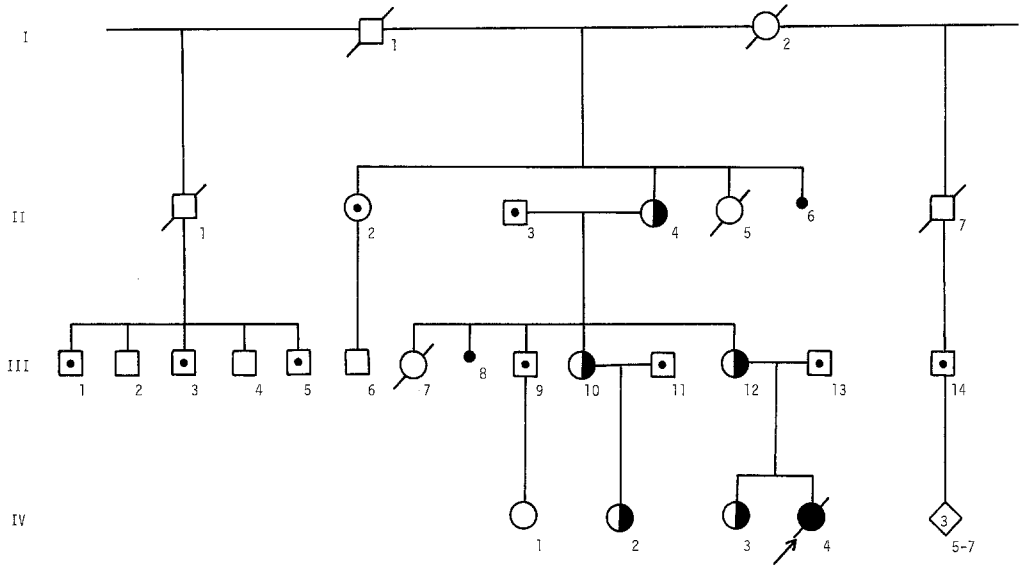
Fig. 15. Family 15—pedigree, for explanation see Fig. 1a

Family 22, Genova, Italy. The propositus (Fig. 22b) was ascertained in Torino because of congenital malformations diagnosed as being due to trisomy 22. The description to follow was kindly provided by Dr. P. Franceschini: facial asymmetry, mild hypertelorism, semicircular eyebrows with peculiar orbital morphology, convergent strabismus, right epicanthus, depressed nasal bridge, flat and beaked nose, long philtrum, micrognathia, macrostomia with downturned commissures of the mouth, high-arched palate and bifid uvula, low-set and malformed ears, bilateral preauricular pits and tags on the right. Low-set nipples, undescended testes, bilateral dislocation of the hip joints. Shortly after birth recurrent gastroenteritis and upper respiratory tract infections complicated by bronchopneumonia. Mental and motor development were greatly retarded. Underdeveloped muscles and hypotonia, marked lumbar kyphosis, flexion of the flexed hips. Dermatoglyphics not remarkable except for the presence of hypoplastic ridges in both hypothenar regions. Optic nerve atrophy. Intravenous pyelography and scintigraphy revealed left renal aplasia. At 4 months low IgG (230 mg/dl) and at 8 months IgE was too low to be measured. Normal IgM and IgA levels. Cellular immunity was seriously impaired. The child died at 2 years of age. A detailed study of this case will be published by Dr. P. Franceschini.

The mother (III-3) of the propositus asked for prenatal diagnosis in Genova, and on this occasion shed was found to be a carrier of the balanced translocation t(11;22)(q23;q11), which she in turn received from her mother. Prenatal diagnosis revealed a male fetus (IV-3) with normal chromosomes.

Family 23, Helsinki, Finland. The propositus was ascertained because of severe psychomotor retardation at the age of 5 years. Born at term. Cleft palate and an abnormally shaped skull, but no other abnormalities were noted. At 17 years his weight was 12.7 kg, height 115 cm. He could neither talk nor stand nor walk. Bird-like face, scanty hair, scaphocephaly, hyperflexible joints arachnodactyly, left-sided cryptorchidism, small penis, systolic heart murmur but no other sign of a cardiac defect.

A cousin of the propositus (III-19) was delivered in breech presentation, birth weight 2940 g, abnormal ears and cleft palate. He developed slowly and at 7 years he was severely retarded, unable to sit or stand. No vocabulary. Scanty hair growth , "baby-like" face. Bilateral cryptorchidism. No obvious heart malformation.



a

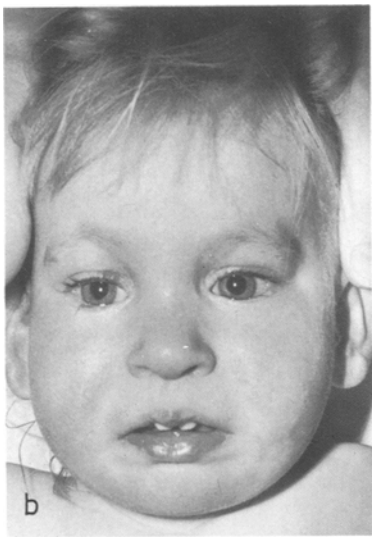


Fig. 16. Family 16—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

The karyotype of IV-1 was established at prenatal diagnosis.

Family 24, Rome, Italy. The propositae, two girls, were ascertained because of multiple malformations. III-2 (Fig. 24b) was born after an uncomplicated pregnancy and delivery. At birth: weight 3000 g, micrognathia, ogival palate, bifid uvula, epicanthus of the right eye, low-set ears, right-sided preauricular blind fistula, bilateral preauricular tags, bilateral dislocation of the hip joint, club feet. At 11 years she had the following additional findings: weight 28 kg, height 130 cm, head circumference 49 cm, mild growth retardation, hypertonia of lower limbs, angioma of the skin, flattening of the posterior skull, strabismus, normal ocular fundi, prominent nose, prominent upper lip, long slender fingers, proximally implanted thumbs, absence of toe nails. X-rays showed osteroporosis of the hands, dorsolumbar scoliosis and hypocalcification of the lower limbs. Normal ECG. EEG showed diffusely abnormal pattern with an epileptic focus. Psychomotor retardation.

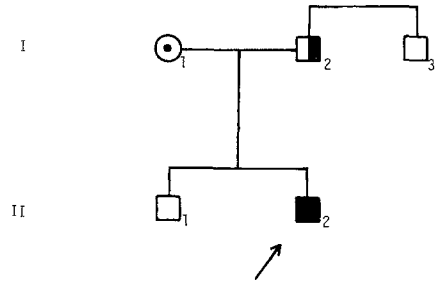
III-3 (Fig. 24c) was born after 43 weeks of gestation. At birth: weight 3000 g, cleft palate, micrognathia, large and low-set ears, left preauricular tag, right-sided preauricular blind fistula, and bilateral dislocation of the hip joint. When she was $2\frac{1}{2}$ years old the following additional findings were made: weight 12 kg, height 84 cm, head circumference 45 cm, hypotonia of the lower limbs, dry skin with angioma, flattening of the posterior skull, strabismus, normal ocular fundi, long and welldefined philtrum, prominent upper lip, protruding calcaneus. X-rays showed the rudiment of a supernumerary rib (seventh cervical vertebra). Normal ECG; EEG showed a diffusely abnormal pattern. Psychomotor retardation.

Family 25, Chambéry, France. The proposita and part of the family were described by Noel et al. (1976). The study of the pedigree was extended with the results shown in Fig. 25. At 3.9 years the proposita had retarded psychomotor development, facial dysmorphosis, preauricular pit, long philtrum, bilateral club foot, hypoplastic left kidney, diaphragmatic hernia.

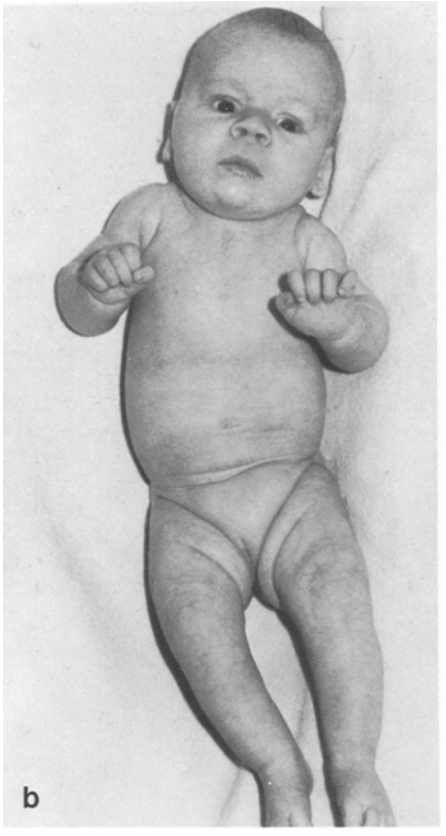
Family 26, Chambéry, France. The proposita was referred for chromosome analysis because of multiple malformations. Born at term after an uneventful pregnancy, weight 3130 g, length 50 cm, head circumference 34 cm. She had a large nose, long philtrum, microretrognathia, cleft palate, large malformed low-set ears, systolic heart murmur interpreted as due to an atrial septal defect. Intravenous phyelography showed a small malformation of the left renal pelvis.

The child subsequently showed obvious psychomotor retardation and a small head circumference (−2 SD).

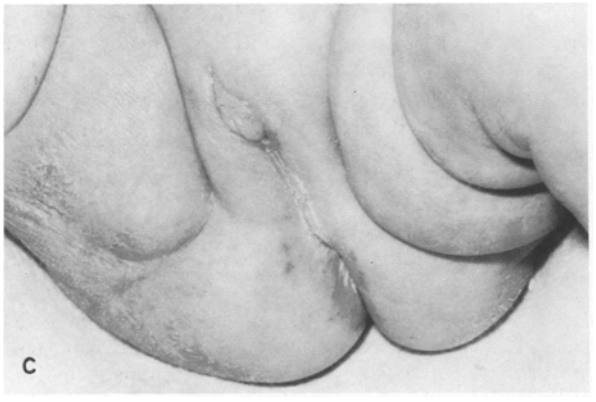
Family 27, Chambéry, France. The propositus (Fig. 27b) was referred for chromosome analysis because of multiple malformations. He showed muscular hypotonia and was unable to hold his head upright at 5 months of age. He also had an odd face with a very long philtrum, retrognathia, small cleft palate, ventricular septal defect, inguinal hernia, and psychomotor retardation.



a



b



c

Fig. 17. Family 17—pedigree (**a**); for explanation see Fig. 1a. Subjects with an unbalanced 47,+der(22) karyotype (**b**, **c**)

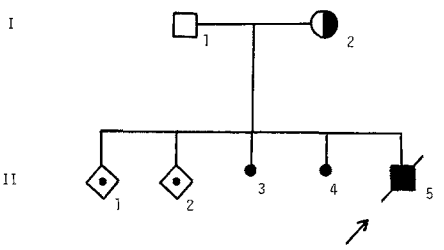
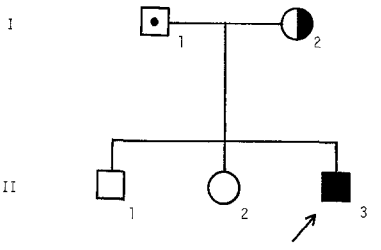
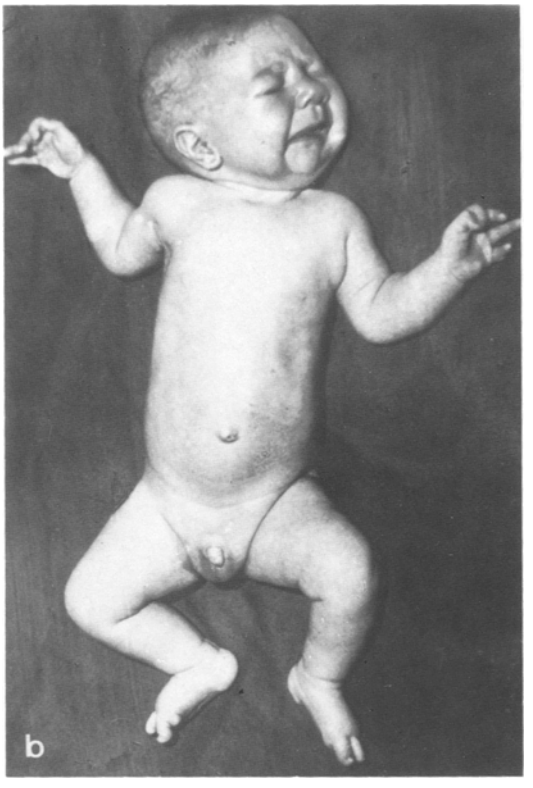


Fig. 18. Family 18—pedigree, for explanation see Fig. 1a



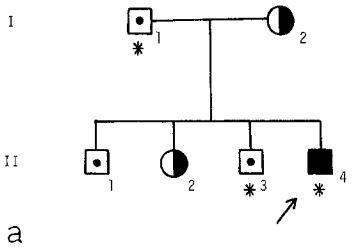
a

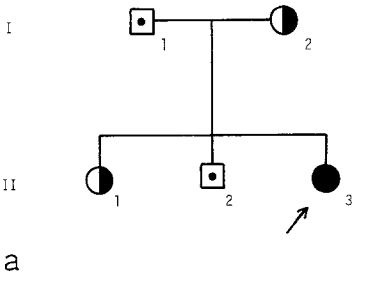


b

Fig. 19. Family 19—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

Family 28, Prague, Czechoslovakia. The propositus (Fig. 28 b) was ascertained because of multiple malformations. Born 14 days after term, weight 2900 g, length 49 cm. Severe psychomotor retardation, brachycephaly, cleft palate, short neck, muscular hypotonia, dislocation of the hip joints, stenosis of the pulmonary artery with secondary hypertrophy of both ventricles. No anal stenosis or preauricular tags or pits. Died at the age of 2 years.





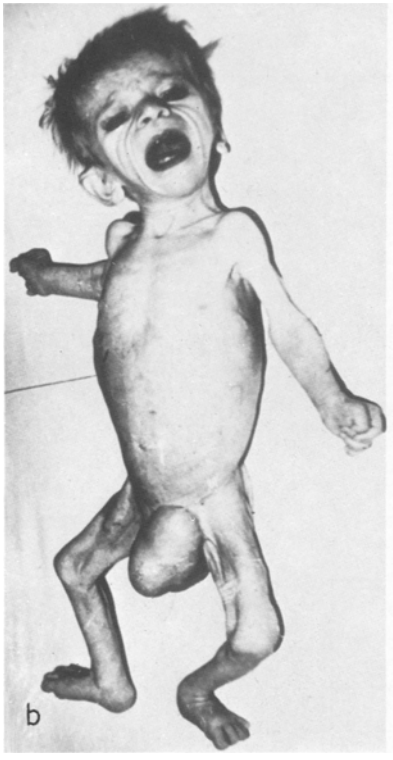


Fig. 20. Family 20—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

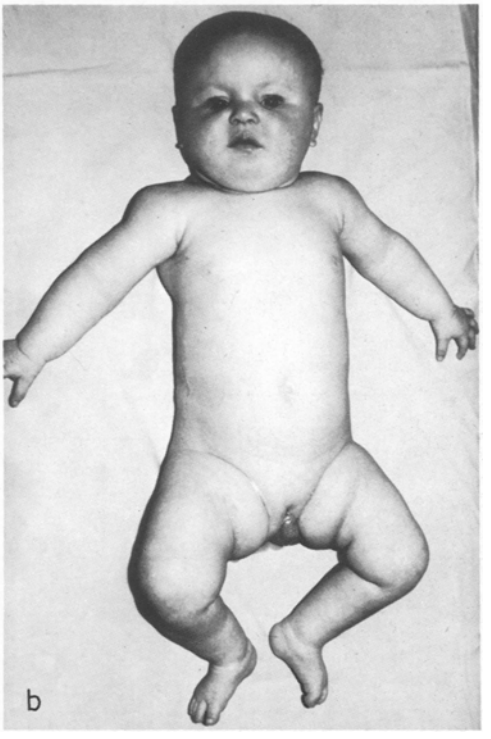


Fig. 21. Family 21—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

Family 29, Prague, Czechoslovakia. The propositus was ascertained because of multiple malformations. At birth: weight 3130 g, length 50 cm. Examination of the age of 9 years (Fig. 29b) revealed mental retardation (IQ 20–30); height 124.5 cm (normal for age, 132.5 cm); head circumference 53 cm. Antimongoloid slant of the eyes. Large ears with preauricular tags on the left. First tooth appeared at age 1 year. Inguinal and umbilical hernias. Hypoplastic penis. Athetotic movements of hands; hypotonia with hyperreflexia. EEG showed diffuse abnormalities. Retarded bone age.

Family 30, Rotterdam, The Netherlands. The propositus was referred for chromosome analysis because of multiple malformations and mental retardation. He showed delayed growth, scoliosis and atrophy of the lower extremities, club feet, cleft palate, pronounced caries, strabismus, one preauricular fistula (left ear), and cryptorchidism. He was premature (birth weight 2200 g) and spent the first 4 months of his life in the hospital for treatment of pyelonephritis and other repeated infections.

Family 31, Rotterdam, The Netherlands. The propositus (Fig. 31b) was referred for chromosome analysis because of multiple malformations. He showed psychomotor retardation, muscular hypotonia, microcephaly, micrognathia, impaired hearing, pulmonary valve stenosis, ventricular septal defect, abnormal clavicles on X-rays, limited hip abduction. Normal genitalia. Growth is delayed: length 81 cm, weight 8650 g at 2 years.

The family turned out to be related to family 32 through I-1.

Group B (Ascertained Through Balanced Carriers)

Age, mode of ascertainment, origin of the translocation, and reproductive history of the probands are given in Table 2. All the probands had a 46,XX or XY,t(11;22) karyotype, with the breakpoints as entered in Table 2. Below, those probands who are not specified as otherwise were clinically normal.

Family 32, Rotterdam, The Netherlands. The propositus was referred for chromosome analysis because his wife had had

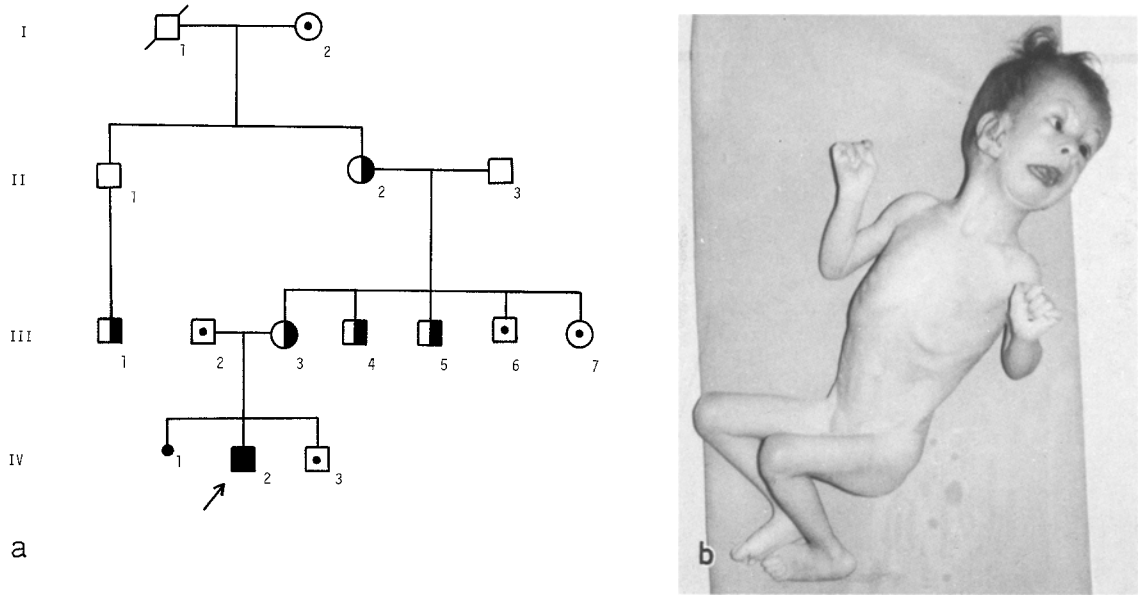


Fig. 22. Family 22—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

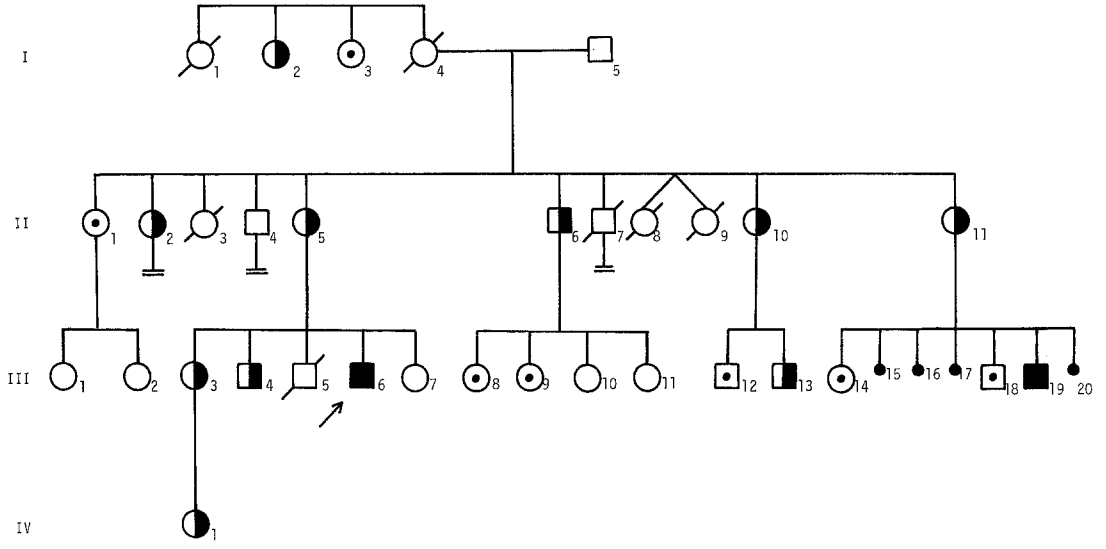


Fig. 23. Family 23—pedigree; for explanation see Fig. 1a

three miscarriages. The family turned out to be related to family 31 through I-2.

Family 33, Rotterdam, The Netherlands. The proposita (IV-8) was referred for chromosome analysis because of epilepsy, moderate mental retardation, and other neurological problems. She was found to have a pericentric inversion of chromosome 2: inv(2)(p12q14). This prompted an analysis of the relatives, and it was then discovered that the 11;22 translocations was also segregating in this family. III-28 was the first family member found to have this translocation.

The karyotype of IV-10 was established at prenatal diagnosis. The child was born at term; birth weight 2700 g, with severe cyanosis and dyspnea due to heart defect: atresia of the tricuspid valve, pulmonary hypoplasia, and ventricular septal defect. II-11, IV-1, and IV-2 were found to be slightly mentally retarded.

Family 34, Rotterdam, The Netherlands. The propositus was referred for chromosome analysis because of infertility, impotence, and hypogonadism. Further investigation of the patient and his family was refused.

Family 35, Pavia, Italy. The proposita was ascertained because she had had two spontaneous abortions and a stillborn child (III-5) with no apparent malformation. Her balanced carrier mother and sister were both normal.

Family 36, Stockholm, Sweden. The proposita had had two spontaneous abortions in the 2nd and 3rd months of gestation,

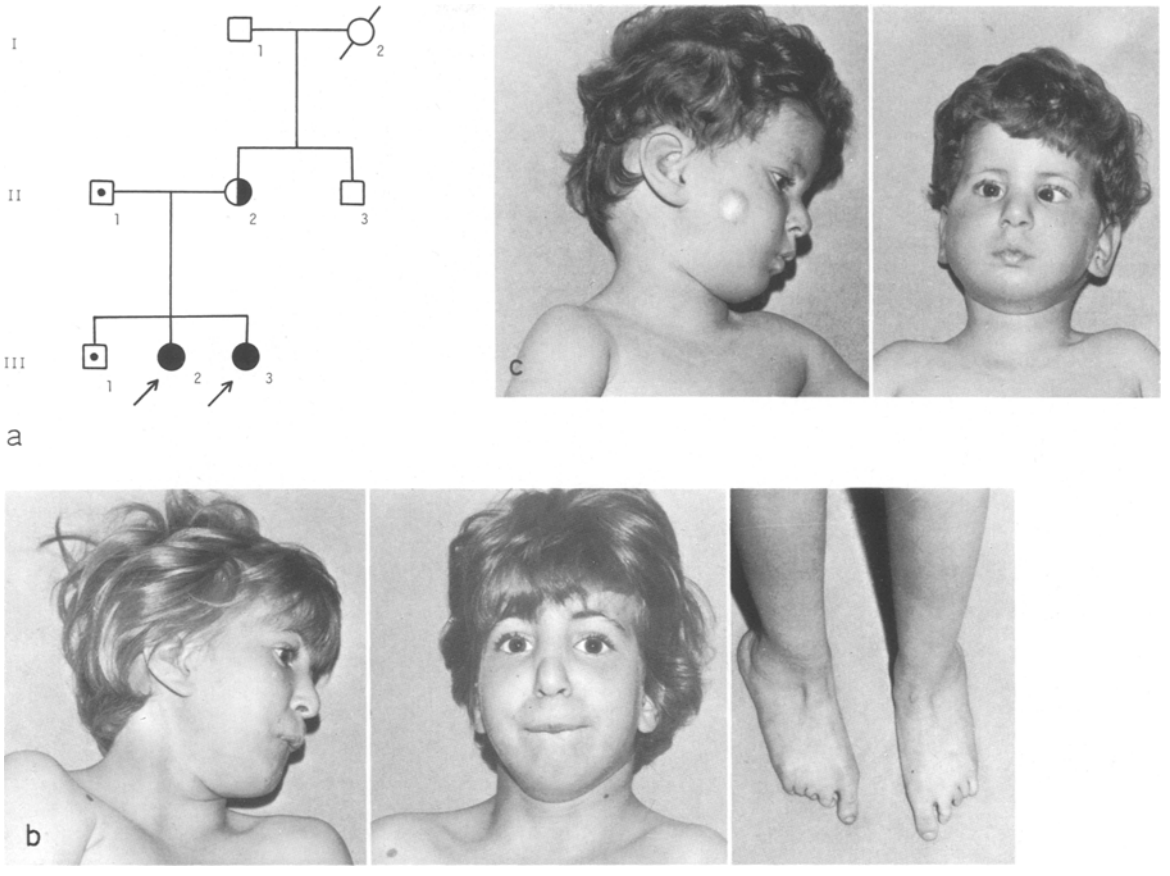


Fig. 24. Family 24—pedigree (**a**); for explanation see Fig. 1a. Subjects with an unbalanced 47,+der(22) karyotype (**b, c**)

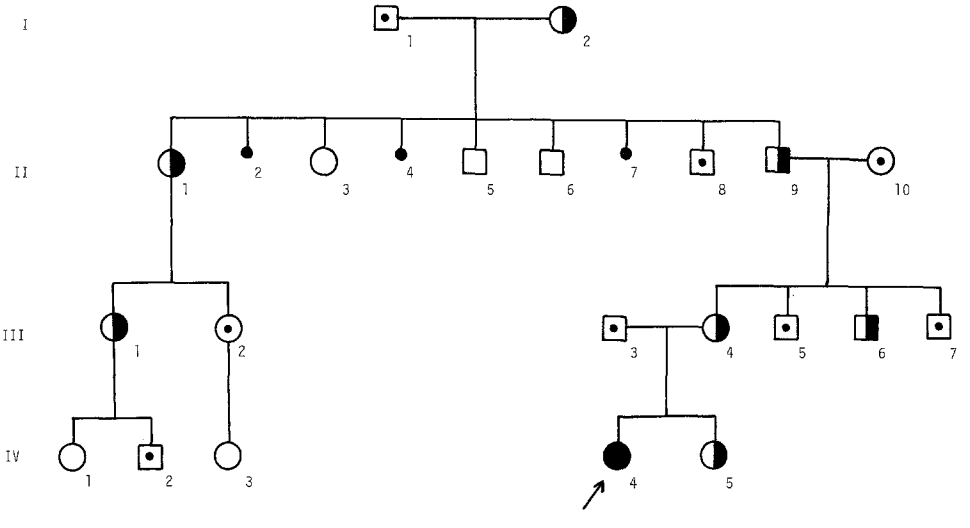


Fig. 25. Family 25—pedigree, for explanation see Fig. 1a

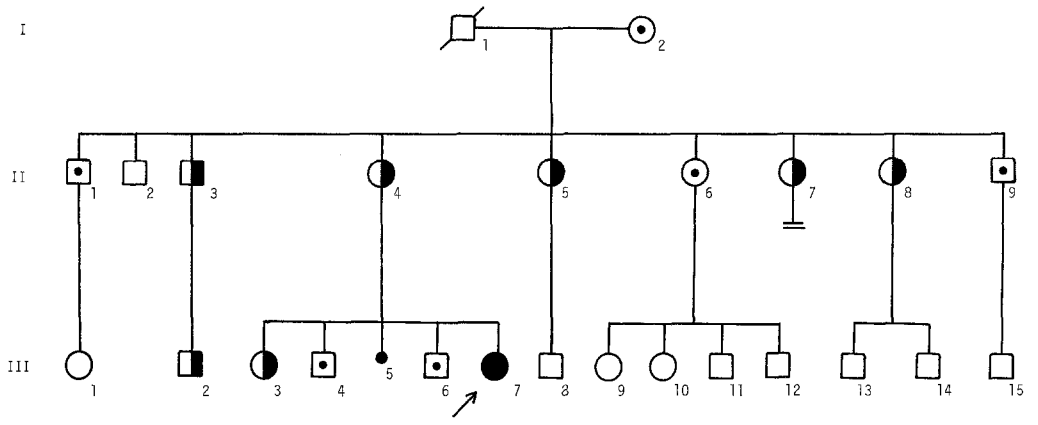
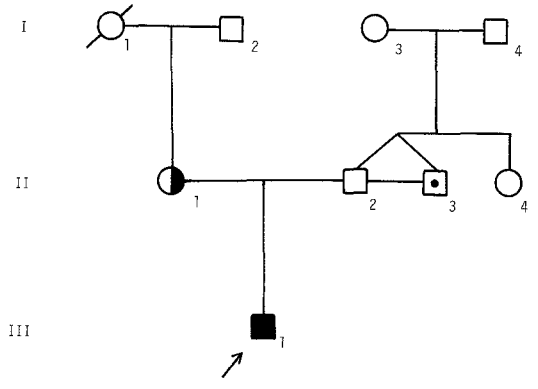


Fig. 26. Family 26—pedigree, for explanation see Fig. 1a



a

respectively. A daughter of the proposita's half-brother (III-1), born in 1930, has mental retardation of unknown etiology.

Family 37, Stockholm, Sweden. The proposita had one stillborn girl (III-1) and one stillborn boy (III-3). The boy had a ventricular septal defect (4 mm in diameter) and aplasia of the right kidney and ureter. The normal karyotype of the last child (III-4) was determined at prenatal diagnosis. Toxemia during all pregnancies.

Family 38, Helsinki, Finland. The propositus was ascertained at 17 years of age because of short stature and hypogonadism. Height 157 cm, weight 37 kg, no development of secondary sex characteristics, prepubertal testes (2–2.5 cm), infantile external genitalia. Skeletal age (Greulich and Pyle) 13.5 years. X-rays of skull and thorax normal, normal sella turcica. Urinary excretion of gonadotrophins (FSH) 2.8 I.U./24 (normal range 5–25 I.U./24). The patient was considered to have hypogonadotrophic hypogonadism.

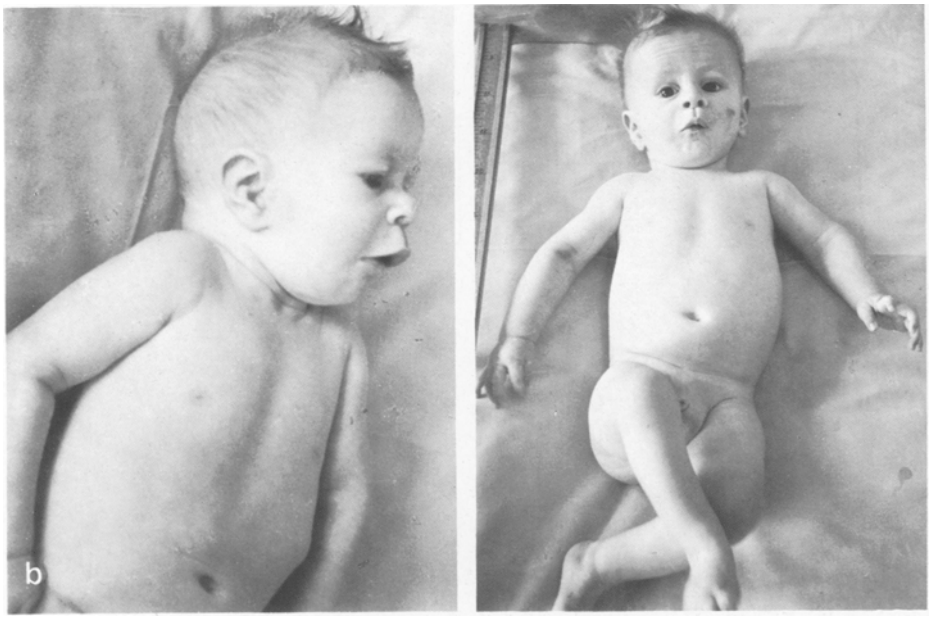
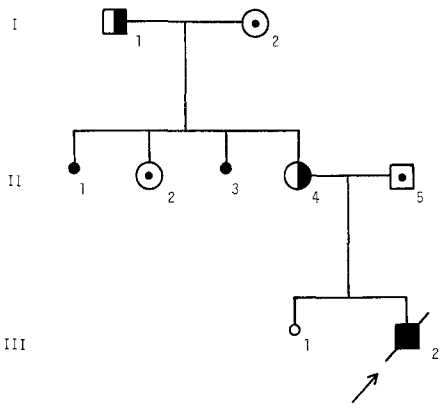


Fig. 27. Family 27—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)



a

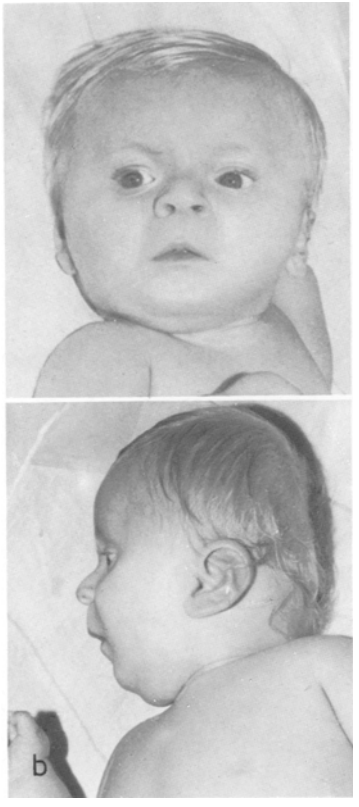
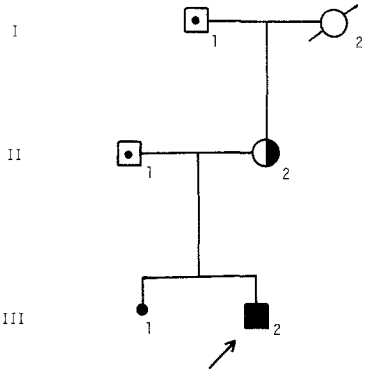


Fig. 28. Family 28—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

The patient also had inv(9)(p1q13), which he had inherited from his father. The incidence of this inversion in the Finnish population is approximately 2%.

Family 39, Essen, Germany. The proposita had had three spontaneous abortions, all in the 3rd month of pregnancy. Her mother (I-2), who was a carrier of the balanced translocation, developed cancer of the uterus at the age of 40 years.

Family 40, Paris, France. The propositus was ascertained during a survey of infertile males. He had not had ejaculations. Histology of the testes was reported to have shown "bilateral anomaly of the testes". No family studies were possible.



a

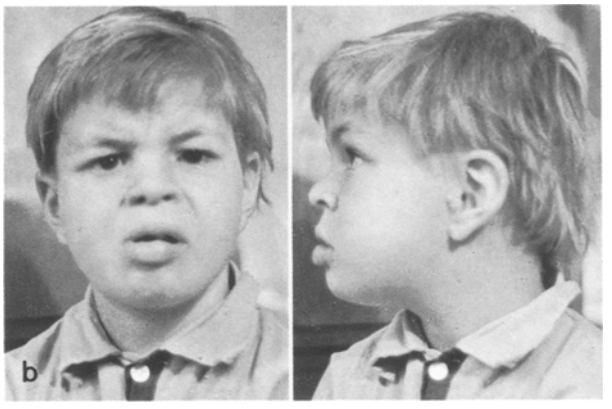


Fig. 29. Family 29—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

Family 41, Paris, France. The propositus was ascertained during a survey of infertile males. He had asthenoteratospermia. Histology of the testes revealed quantitatively normal spermatogenesis. The translocation was not apparently present at diakinesis of the examined meiotic cells from a testis biopsy. His wife (normal karyotype) had a spontaneous abortion in 1968. Family studies were not possible.

The case has been mentioned by Dutrillaux (1977).

Family 42, Paris, France. The propositus was ascertained during a survey of infertile males. Varicocele. Oligoasthenoteratospermia.

Family 43, Leiden. The Netherlands. The proposita was ascertained when 5 years old because of slight facial anomalies and mental retardation. Slightly delayed motor development; severely delayed speech development. At 7 years of age: I.Q. 46: normal height, weight, and head circumference. Frontal bossing, low anterior hair implantation, slightly low-set ears, flat nasal bridge. Slight webbing of the neck. Broad thorax with widely spaced nipples. Slight stenosis of the pulmonary valve found at angiocardiography. Slight cubitus valgus. Multiple lentigines. Normal female external genitalia. Normal extremities. The healthy mother (II-1) and brother (III-1) were carriers of the balanced translocation.

Group C (Published Cases)

Authors, age at last examination, birth weight, parental ages, parental transmission, and break points of the translocation of

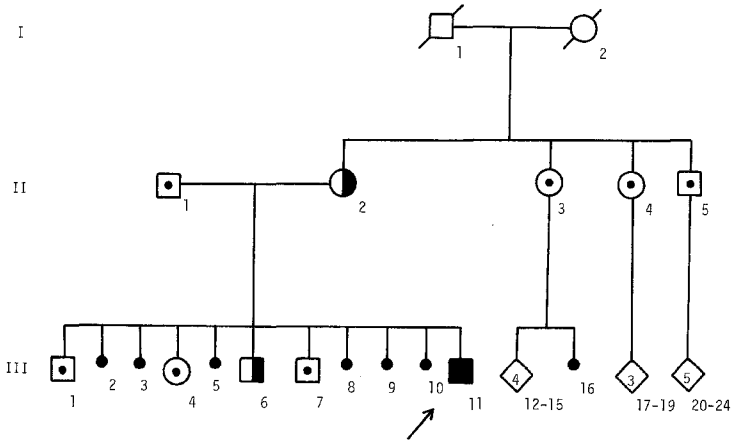
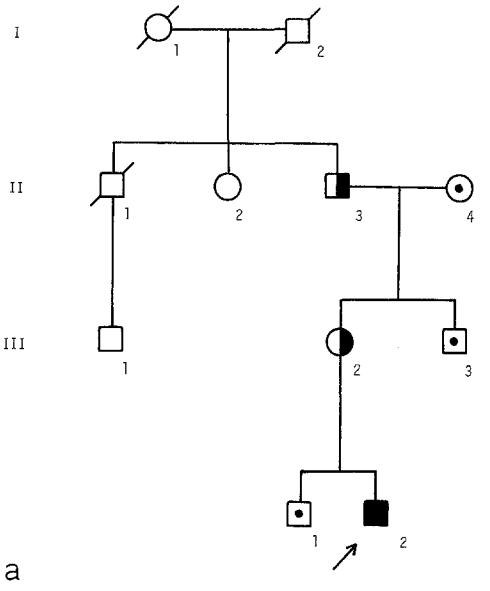


Fig. 30. Family 30—pedigree, for explanation see Fig. 1a



a

the cases ascertained through unbalanced carriers are given in Table 3, and the pertinent information on the cases ascertained through balanced carriers is given in Table 4. The case published by Noel et al. (1976) is not included in this group but was, after the extension of the pedigree and follow-up of the patient, referred to group A (no. 25).

Segregation Analysis of the 11/22 Translocation

The segregation ratios were calculated using only sibship born to known carrier parents, and the analysis was restricted to individuals with known karyotypes. To eliminate ascertainment bias, the probands and their direct ancestors were not used in the calculation. Ascertainment through a proband with an unbalanced or balanced karyotype was treated separately in the analysis (Tables 5 and 6). Probands ascertained because of repeated spontaneous abortions were excluded in the calculation of the abortion frequency.

In families ascertained through a proband with an unbalanced karyotype (published cases included), there were altogether 112 karyotyped offspring to carrier parents, including three with an unbalanced karyotype (Table 5). The ratio of balanced carriers to normal did not deviated significantly from 1:1 (54:55).

Data on sex and karyotype of the offspring of carrier parent derived from all pedigrees combined are presented in Table 7. When the fathers were the carrier parents, there was no indication that segregation of sex and the translocation were correlated, although there were few offspring. But the table shows that when the mothers were the carriers, the daughters showed a marked excess of balanced translocation karyotypes, and the sons a complementary excess of normal karyotypes, so that together they give the good approximation to the 1:1 ratio mentioned above. Formally the difference is significant (χ^2_1 corrected =

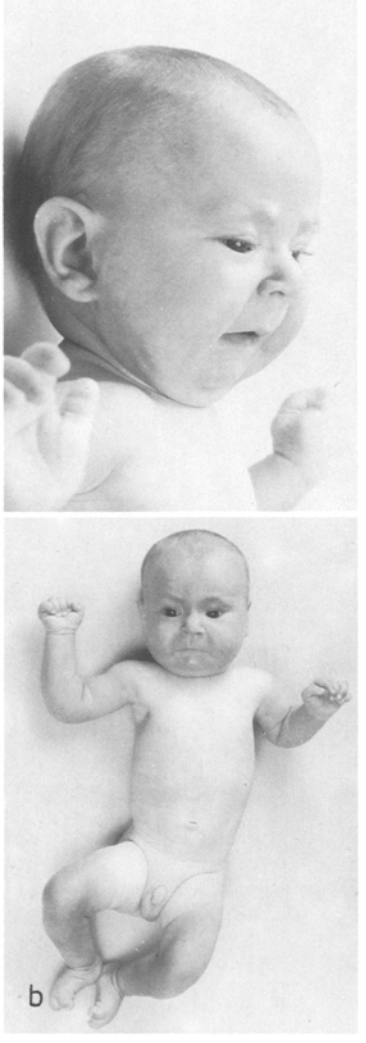


Fig. 31. Family 31—pedigree (**a**); for explanation see Fig. 1a. Subject with an unbalanced 47,+der(22) karyotype (**b**)

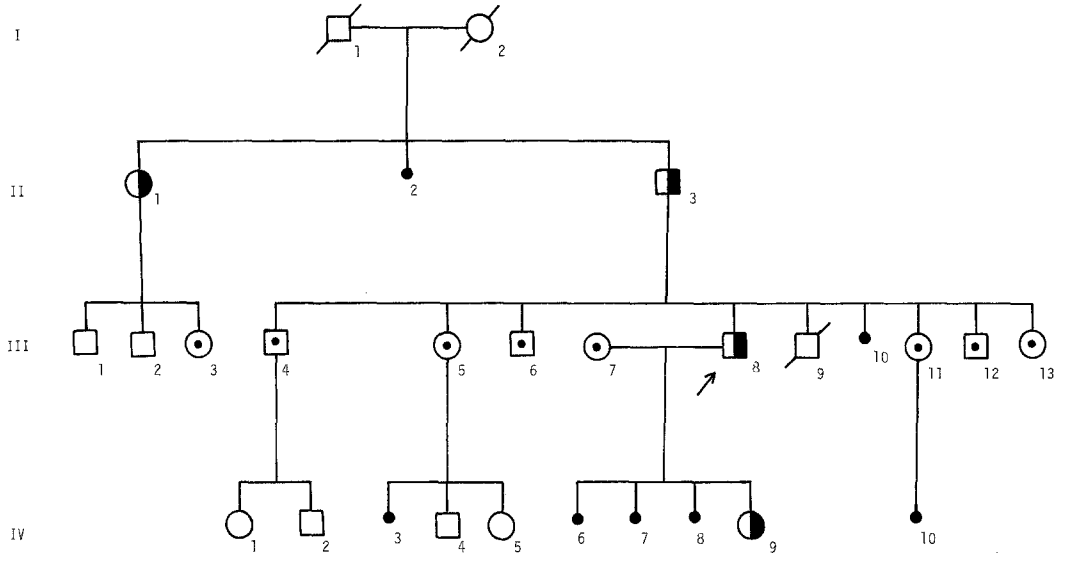


Fig. 32. Family 32—pedigree, for explanation see Fig. 1a

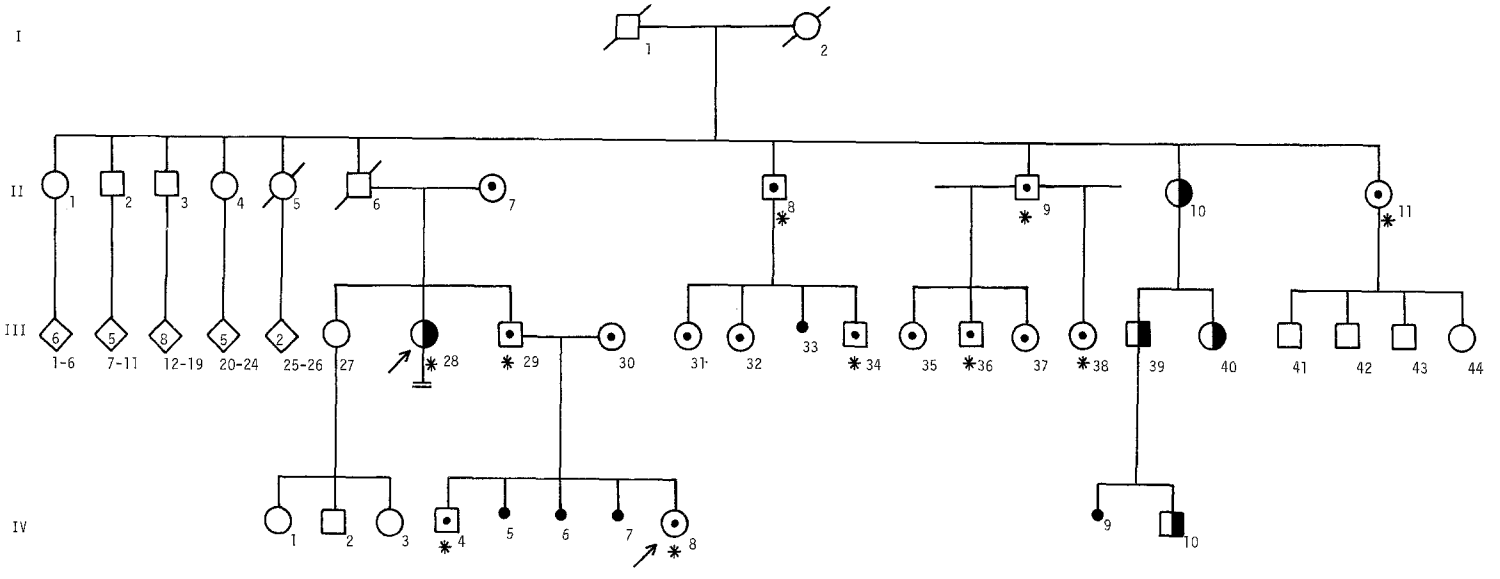


Fig. 33. Family 33—pedigree, for explanation see Fig. 1a

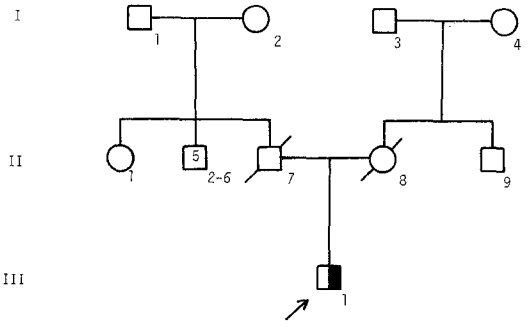


Fig. 34. Family 34—pedigree (**a**); for explanation see Fig. 1a.

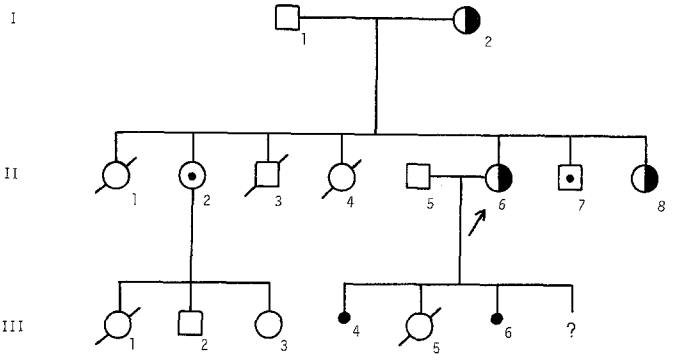


Fig. 35. Family 35—pedigree, for explanation see Fig. 1a

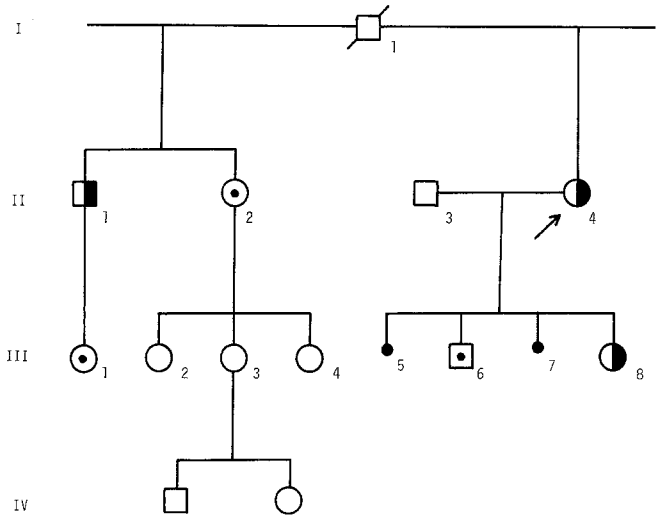


Fig. 36. Family 36—pedigree, for explanation see Fig. 1a

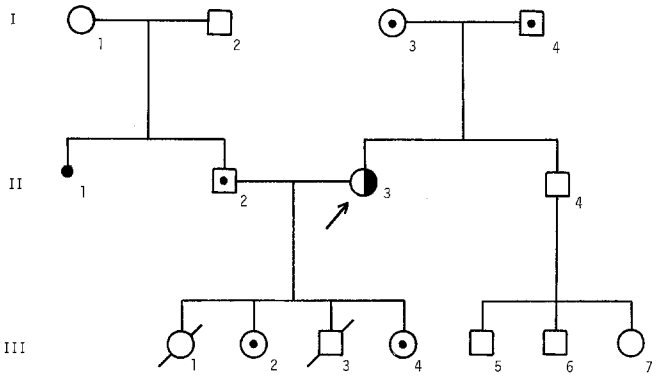


Fig. 37. Family 37—pedigree, for explanation see Fig. 1a

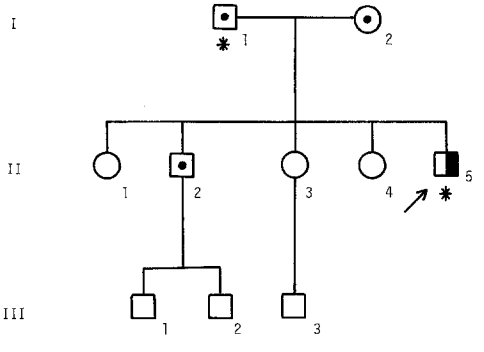


Fig. 38. Family 38—pedigree, for explanation see Fig. 1a

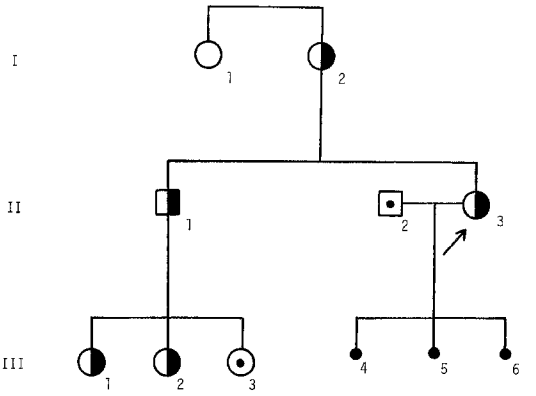


Fig. 39. Family 39—pedigree, for explanation see Fig. 1a

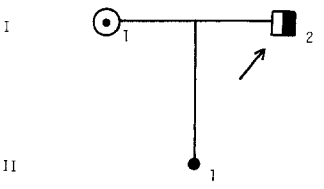


Fig. 40. Family 41—pedigree, for explanation see Fig. 1a

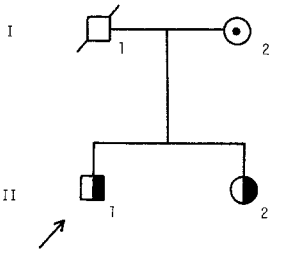


Fig. 41. Family 42—pedigree, for explanation see Fig. 1a

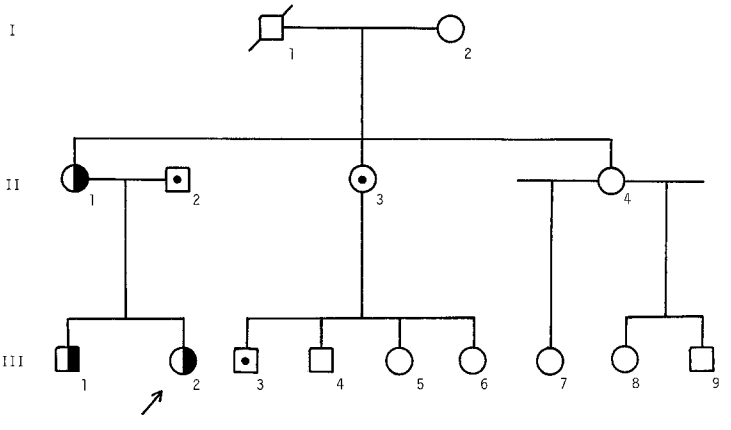


Fig. 42. Family 43—pedigree, for explanation see Fig. 1a

Table 3. Published cases ascertained as unbalanced carriers

Case no.	Reference	Sex	Date of birth			Age at last examination	Living or dead	Birth weight	Parental age		Parent carrier	Break-points 11;22
			yr	mo	d				Mo	Fa		
44	Lindsten et al. 1974	M	68	04	12	5 y	l	—	25	26	Mo	q23;q12
45	Aurias et al. 1975	M	73	02	14	1 m	l	2330	26	30	Mo	q23.1;q11
46	Aurias et al. 1975	F	72	—	—	2 m	d	—	24	23	Mo	q23.1;q11
47	Laurent et al. 1975	M	74	10	10	2½ y	l	2500	25	27	Mo	q23.1;q11
48	Giraud et al. 1975	F	—	—	—	24 h	d	2350	26	29	Mo	q23;q11
49	Ayraud et al. 1976	M	72	—	—	4 y		2380	27	26	Mo	q23.1;q11
50	Emanuel et al. 1976, Emanuel and Zackai 1978	F	—	—	—	6 w	d	2820	34	36	Mo	q2;q11
51	Kessel and Pfeiffer 1977	M	67	02	01	10 y	l	3250	22	—	Mo	q23;q12
52	Bofinger and Soukup 1977	F	—	—	—	20 m	l	2540	33	34	Mo	q25;q11
53	Nakai et al. 1979	F	—	—	—	14 m	l	2640	29	33	Mo	q23;q11
54	Feldman and Sparkes 1978	F	—	—	—	3 y	l	—	31	29	Mo	q25;q13
55	Kadotani et al. 1978[a]	F	—	—	—	5 y 8 m	l	2650	30	41	Mo	?;q13

[a] Although not reported as an 11;22 translocation, this case was confirmed as such in correspondence with the authors

Table 4. Published cases ascertained as balanced carriers

Case no.	Reference	Sex	Date of birth			Date and modality of ascertainment	Translocation received from	Reproductive performance[a]				Breakpoints 11;22
			yr	mo	d							
56	Fu et al. 1976	M	69	04	29	1975; mental retardation	Mother	—				q25;q11
57	Oakley et al. 1976	—	—	—	—	At birth; multiple malformations	Father	—				q23;q11
58	Fitzgerald 1976	M	46	—	—	1973; behaviour difficulties	Father	NM	BCM	BCF	A	q25;q13

[a] See footnote, Table 2

Table 5. Karyotypes of offspring to carriers of the 11;22 translocation ascertained through an offspring with an unbalanced karyotype

Source of data	Number of parents with balanced karyotype		Offspring						
			Total (abortions excluded)	Normal karyotype	Balanced translocation	Unbalanced translocation	Karyotype unknown		
							Alive	Dead[a]	Abortion
Present material	Fathers	10	18	10	3	1	4	—	2
	Mothers	49	107	40	44	1	14	8 (4)	31
Previously published families	Fathers	3	5	1	3	—	—	1	5
	Mothers	11	14	3	5	1	3	2 (1)	6
All families	Fathers	13	23	11	6	1	4	1	7
	Mothers	60	121	43	49	2	17	10 (5)	37
	Total	73	144	54	55	3	21	11 (5)	44

[a] Figures within parentheses indicate the number who where malformed

Table 6. Karyotype of offspring to carriers of the 11;22 translocation ascertained through a balanced carrier

Source of data	Number of parents with balanced karyotype		Offspring						
			Total (abortions excluded)	Normal karyotype	Balanced translocation	Unbalanced translocation	Karyotype unknown		
							Alive	Dead[a]	Abortion
Present material	Fathers	3	13	8	4	—	—	1	3
	Mothers	9	20	6	6	—	2	6 (1)	4
Previously published families	Fathers	2	2	1	1	—	—	—	6
	Mothers	1	2	—	2	—	—	—	1
All families	Fathers	5	15	9	5	—	—	1	9
	Mothers	10	22	6	8	—	2	6 (1)	5
	Total	15	37	15	13	—	2	7 (1)	14

[a] Figures within parentheses indicate the number malformed

Table 7. Sex and karyotype of offspring of carriers of the 11;22 translocation. All the present cases as well as previously published cases were included

Mode of ascertainment		Number of offspring[a]			
		Females		Males	
		Balanced translocation	Normal karyotype	Balanced translocation	Normal karyotype
Ascertained through proband with unbalanced karyotype	Mother carrier	32	13	17	28
	Father carrier	4	7	2	4
Ascertained through a proband with balanced karyotype	Mother carrier	5	5	3	1
	Father carrier	3	5	2	4
All cases	Mother carrier	37	18	20	29
	Father carrier	7	12	4	8
	Total	44	30	24	37

[a] Sex unknown in two cases

6.29; $P<0.025$). We are unable to suggest a plausible explanation for this effect. Despite the formal significance of the difference it might be an extreme product of chance sampling, though this is not to say that the observation should be dismissed.

There were three cases with an unbalanced karyotype corresponding to a recurrence risk of $3/112 = 2.7\%$. However, five of the eleven dead children with an unknown karyotype had anamnestical findings compatible with an unbalanced karyotype. The maximum recurrence risk would therefore be $8/144 = 5.6\%$. Seven of the eight offspring with a certain or probable unbalanced karyotype came from families where the mother was the carrier of the balanced translocation. This corresponds to a recurrence risk of $7/121 = 5.8\%$ for female carriers and $1/123 = 4.3\%$ for male carriers. The abortion frequency was $44/188 = 23.4\%$.

In the families ascertained through a proband with a balanced karyotype (published cases included), 28 offspring to balanced carrier parents were karyotyped: 15 were normal, and 13 were carriers (Table 6). This also is in good agreement with a 1:1 ratio. There were no children with an unbalanced translocation among the karyotyped offspring. However, one of the deceased individuals of unknown karyotype had had multiple malformations and might have had an unbalanced karyotype. This would lead to a maximum recurrence risk of $1/37 = 2.7\%$. The abortion frequency was $14/57 = 27.5\%$ which is not different from that found in the families ascertained through an offspring with an unbalanced karyotype ($P = 0.66$).

The pedigrees have also been used for an analysis of family size and the results are given in Table 8. Live-born children only were counted. The sibships of the

Table 8. Analysis of family size

Family size	Number of families in the offspring of subjects			
	with balanced karyotype		with normal karyotype	
	Males	Females	Males	Females
0	10	6	15	15
1	5	5	6	6
2	1	7	8	4
3	1	4	4	5
4	1	1	3	6
5	—	1	1	2
Sum	18	24	37	38
Mean	0.78	1.67	1.38	1.66

probands and families in directly ancestry of the probands were excluded. The last generation in each pedigree was also excluded. Although it is unavoidable that this analysis will have included incomplete families and even families that had not been started, ascertainment of families (and potential families) should be very similar for all parental classes shown in Table 8. Comparisons between parental classes should therefore be valid. This indicates that the mean family sizes of carrier and normal females were almost identical, although the distributions may be different ($P > 0.05$). It also suggests that heterozygosity for the translocation may reduce fecundity in males ($P < 0.001$, Mann-Whitney U-test).

Discussion

The Translocation

As seen from Table 9 there was an excess, although statistically not significant, of males among the 32 probands with the unbalanced 11;22 translocation in the present material. Furthermore, all the probands with an unbalanced karyotype had inherited the translocation, 31 from the mother and only 1 from the father. If previously published cases are included, the numbers are increased to 43 from the mother and 1 from the father. This very striking difference in transmission associated with the sex of the carrier parent can plausibly be attributed to differing conditions of meiosis in the oocyte and the spermatocyte.

Table 9 also shows that if Groups B and Cb are combined, 2 of the 15 probands with a balanced karyotype had a de novo and 10 a familial translocation, while the origin of the translocation was unknown in 3 cases. The translocation was of maternal origin in 4 of the familial cases and of paternal origin in 6. That the only 2 de novo translocations in the full series of 59 probands should be among the 12 ascertained as balanced carriers may also be a chance effect of sampling but deserves notice. The difference from the series ascertained through unbalanced carriers, where all of 43 were familial, is just significant ($P = 0.044$) on a Fisher's exact test.

The only type of unbalanced karyotype noted was 47,+der(22), which is the product of a 3:1 disjunction. The formal maximum recurrence risk for this unbalanced translocation was calculated to be 5.8% or 2.7% when the ascertainment was through a proband with an unbalanced or balanced karyotype, respectively. Formally also, there was a slight difference in the risk between male and female carriers. However, there was only one child with the unbalanced karyotype 47,+der(22) among the progeny of male carriers (other than those in the direct ancestry of the probands) in the pedigrees; so neither the calculated maximum recurrence risk for male carriers nor its comparison with that of female carriers is well substantiated. Subjectively,

Table 9. Summary of probands

		Number of probands		Status at last examination				Translocation received from		De novo translocation	
		M	F	Living		Dead					
				M	F	M	F	Mo	Fa	M	F
Group A		20	12[a]	13[b]	11	6	1	31	1	—	—
Group B		6	6	6	6	—	—	3	4[c]	1	1
Group C	a	5	7	5	4	1	3	12	—	—	—
	b	2[d]	—	2	—	—	—	1	1	—	—
Total		33[d]	25								

[a] In one family (No. 24) there were two probands
[b] In one case it was not reported whether the proband was alive
[c] In two of the cases a paternal origin was likely but could not be proven because the fathers were dead. Information on the origin of the translocation was missing in three cases
[d] In one additional case, in which the translocation was inherited from the father, the sex was not reported

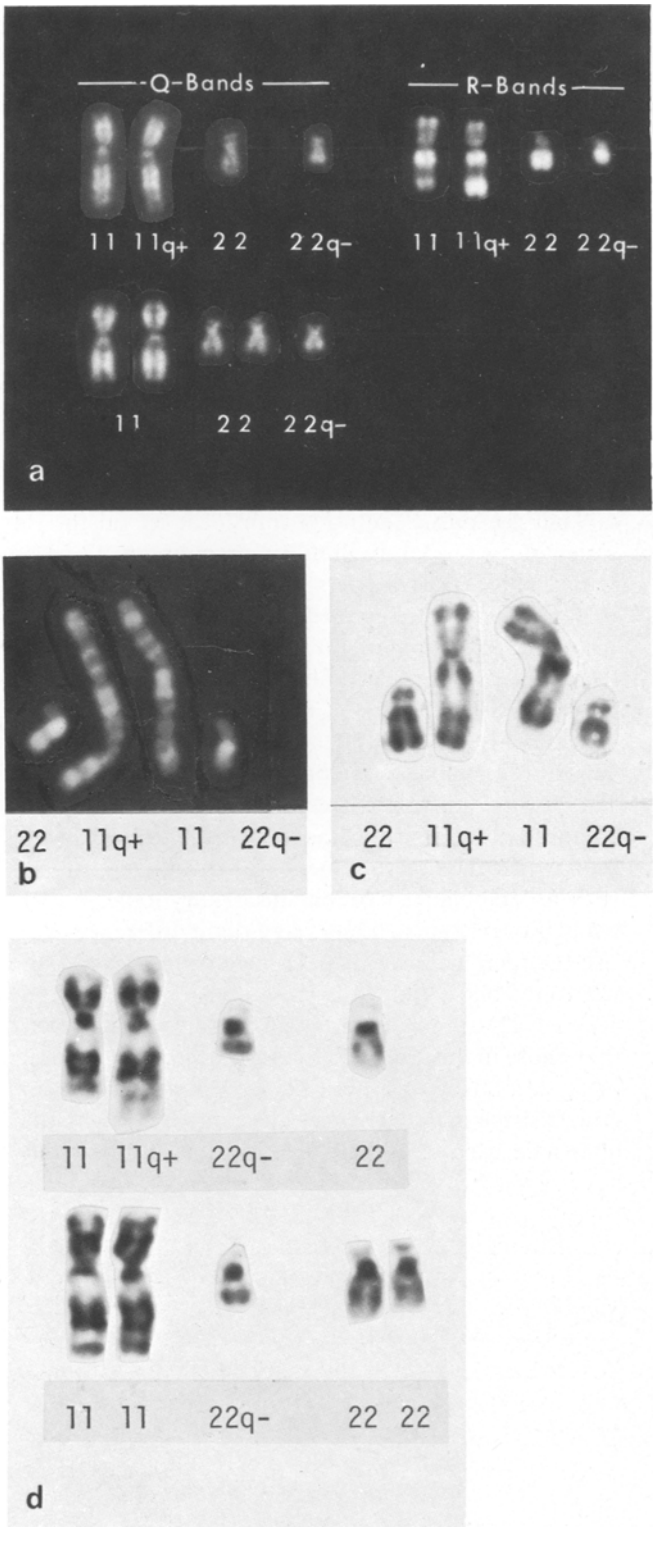


Fig. 43. The 11;22 translocation illustrated by different banding techniques. **a** Q-bands (QFQ) and R-bands with acridine orange (RFA): family 8, II-3 (*above,* balanced carrier) and III-3 (*below,* unbalanced); **b** R-bands by BrdU and acridine orange (RBA): family 42, II-1 (balanced carrier); **c** R-bands (RHG): family 40, propositus (balanced carrier); **d** G-bands (GTG): family 3, II-7 (balanced carrier) and III-14 (unbalanced)

furthermore, a lack of formal difference in recurrence risk between male and female carriers appears to conflict with the overwhelming excess of probands that received the translocation from their mothers as discussed above.

Although the present material about a specific translocation is unusually large, it did not allow a more detailed segregation analysis. However, it should be mentioned that there is a very strong theoretical expectation (based on the regular occurrence of a chiasma in the interstitial segment of 11q) that zygotes receiving a 24-chromosome gamete including der(11), der(22), and a normal 22 from the carrier parent should occur as a type complementary to, and equally as frequent as, the 47,+der(22) zygotes that give rise to the observed unbalanced-karyotype offspring. This expected class of zygotes would be balanced translocation carriers and, simultaneously, have trisomy 22. They might therefore be expected sometimes to survive to term. In analogy with the balanced translocation, it would be easy to miss the abnormal chromosome 11 and thus fail to make a diagnosis of trisomy 22. In turn, because of the similarity of the alleged phenotype of trisomy 22 with that considered typical of trisomy 11q, this product would not be distinguished by phenotype alone.

It should be noted that the incidence of spontaneous abortions appears to be high (18%–37%). It is also noteworthy that many of the probands ascertained as balanced carriers came to clinical attention because of subfertility or infertility (Table 2).

As seen from Table 1–4 breakpoints of the translocations indicated by the authors vary. The most frequent descriptions were 11q23;22q11 (25 cases) followed by q25;q13 (10 cases), while q25;q12 were regarded as breakpoints four times and q23;q13, q23;q12 and q24;q12 three times each. The breakpoints q2;q1, q2;q11, q24;q11, and q25;q11 were indicated three, one, one, and two times, respectively. All contributors seem to agree that the precise identification is difficult (see also Parslow et al. 1980). Two of us (B.D., Paris and B.N., Rome) made and ad hoc comparative study and concluded that the identification of the translocation was difficult and the exact localization of the breakpoints nearly impossible by the use of G- and/or Q-banding techniques. Conventional as well as high resolution R-banding makes the detection of the translocation easier, but the exact location of the breakpoints remains difficult to establish even with these techniques (Fig. 43). T-banding seems to be the technique that gives the best possibility of idenfication. With this technique, the breakpoints q23.1;q11.1 seem to be the more likely ones.

In view of these difficulties it is not esay to decide formally whether the breakpoints are the same in all

Table 10. Summary of malformations/defects in 13 previously published and 34 unpublished cases[a] with an unbalanced 11/22 translocation, 47,+der(22),t(11q;22q)[b]

Craniofacial		
Malformed ears, pits and tags		39
Cleft palate		25
Miero-/retrognathia		25
Craniofacial asymmetry		15
Microcephaly		14
Large/beaked nose		14
Long philtrum		9
Other abnormal shapes of the skull		9
High arched palate		7
Bifid uvula		5
Hypertelorism		4
Hypotelorism		4
Epicanthus		4
Antimongoloid eye slant		4
Mongoloid eye slant		3
Prominent upper lip		2
Cardiovascular		
Congenital heart disease	proved	13
	suspected	7
Gastrointestinal		
Anal stenosis or atresia		6
Urogenital		
Cryptorchidism		17
Renal aplasia/hypoplasia		9
Small penis		9
Skeletal		
Dislocation/dysplasia of hip joints		14
Joint contractures		5
Club foot		5
Long digits		4
Supernumerary ribs		3
Scoliosis		3
Skin		
Webbing of the neck		3
Abnormally set nipples		3
Angioma		2
Scanty hair		2
Sacral pit		2
Neuromuscular		
Delayed psychomotor development		40
Hypotonia		22
Strabismus		12
Diaphragmatic hernia		6
Inguinal hernia		6
Athetotic movements		3
Dilated ventricles of the brain		3
Torticollis		2
Hearing loss		2
Muscular hypertonia		2

[a] 26 males, 21 females
[b] Only malformations reported in more than one case are included in the table. For details see text

probands. However, if this is so, one has to conclude that at 11q23.1 and at 22q11.2 there are two "weak" points with a relatively high probability of concurrent breakage and reunion. In six cases of partial duplication of 11q in which the other chromosome involved in the translocation was not chromosome 22 (Francke 1977), the breakpoints on chromosome 11 were indicated as q23.1 (two cases), q23 (one case), q21 (one case), and q13 (two cases). Similar findings have been made by others (Leonard et al. 1979; Felding and Mitelman 1979). Only two cases are outside the ranges observed in the present study. We may thus conclude that the zone q23 of chromosome 11 has a high preferential predisposition to translocation.

As to chromosome 22, the breakpoint q11 was most frequently indicated (when the breakpoint on chromosome 11 was indicated at q23), and the second most frequent breakpoint was at q13 (when the breakpoint on 11 was q25). The breakpoint of the Philadelphia chromosome (Ph^1) is considered to be either at the interface between bands q11 and q12 or within band q11. Thus, the breakpoints in the 11;12 translocation and in the 9;22 translocation producing the Ph^1 chromosome may be similar, and the differences in size between the Ph^1 chromosome and the der(22) chromosome of the 11;22 translocation may be due to the varying amounts of chromosomes 9 and 11, respectively, translocated on to chromosome 22 (see also Fitzgerald 1976; Verma and Dosik 1979). We checked the cases of chronic myeloid leukemia (CML) reported or mentioned in the literature in which the Ph^1 chromosome originated through an 11;22 translocation, but none was informative, either because the translocation was 11p;22q or because the breakpoints were not stated (see Pasquali et al. (1979) for review). We observed one case of CML in which the Ph^1 chromosome originated

through a 11q;22q translocation. In this case the breakpoint was at 11q23 (Lindsten, unpublished). It should also be noted that recently Van Berghe et al. (1979) found that in two patients with refractory anemia with thrombocytosis and simultaneous 5q– and 21q–, 21q– was due to a t(11;21)(q25;q21).

It would be very important to be able to decide whether the breakpoint on 22q is always the same and in such a case whether it is on 22q11 or 22q13. In fact this difference could have important consequences, because in the first case the portion of 22q that is present in triplicate in the subjects with the unbalanced karyotypes would be much less than in the second case, giving therefore more importance to the partial trisomy 11q for the phenotype associated with balanced karyotypes. We feel that at the present stage it is not appropriate to attempt a comparison of the phenotypes associated with the unbalanced karyotypes indicated respectively as 22q11 or 22q13 (see also discussion below).

The present material provides no information regarding the number of original rearrangement events. On the other hand the geographical distribution of the families is so wide as to exclude a common early origin.

The Phenotype

As stated in the introduction, the course, quality, and quantity of the clinical data available on the subjects with an unbalanced karyotype are so variable that one cannot hope to draw definitive conclusions about the phenotypic expression, in spite of the size of the sample. In Table 10 approximation scoring of the various defects and symptoms found in probands of groups A and C have been entered. As seen from this table the following signs had been recorded in 10 or more of the 45 cases; low birth weight (mean 2730 g, $n = 40$), delayed psychomotor development, muscular hypotonia, microcephaly, craniofacial asymmetry, malformed ears with pits and tags, cleft palate, micro-/retrognathia, large beaked nose, strabismus, congenital heart disease, cryptorchidism, and congenital dislocation of the hip joints.

A comparison of this list of signs with those considered typical of the partial-trisomy-11q syndrome (e.g., Aurias and Laurent 1975; Francke 1977; de Grouchy and Turleau 1975) shows that the similarities are many. On the other hand, there is a formal concordance or, better, a nearly complete coincidence with the phenotypic manifestation of trisomy 22 (see *e.g.*, Hsu and Hirschhorn 1977). That the phenotypic manifestations of trisomi 11q22 and of trisomy 22 are indeed very similar was already pointed out by Kessel and Pfeiffer (1977), who stated, "... either several cases of trisomy 22 include a partial trisomy 11q2, or the manifestation of partial trisomy 11q2 associated with a translocation with a chromosome 22 is due to that chromosome." One way to get around this dilemma was suggested by Francke (1977), who stated that "... the combination of retracted lower lip, dysplastic clavicle with nonfused medial and lateral segments and micropenis in the male is most unusual and may become the hallmark of the dup(11q) syndrome." Assuming that this is so, are the rest of the symptoms due to the partial trisomy 22? One should incidentally note that among the 44 probands of groups A and C there was no case with coloboma, while the other symptoms of the cat-eye syndrome (anal atresia, preauricular tags and pits, renal aplasia) are found. Is this an indication that in the cat-eye syndrome the same segment of 22 is present in triplicate as in the unbalanced karyotype 47,+der(22) plus or minus another chromosome segment?

Acknowledgements. The authors would like to thank the following colleagues for their help in collecting data on some of the patients included in the present study: Drs. S. Berggren and G. Dahl, Copenhagen; Dr. H. Fisher, Hereford; Mrs. M. E. Ferguson-Smith and Dr. J. C. Maclaurin, Glasgow; Dr. B. G. A. ter Haar, Nijmegen; and Drs. J. Hubert, C. Iahns, and R. Meyer, Chambéry.

References

Aurias A, Laurent C (1975) Trisomie 11q. Individualisation d'un nouveau syndrome. Ann Genet (Paris) 18:189–191

Aurias A, Ture C, Michiels Y, Sinet P-M, Graveleau D, Lejeune J (1975) Deux cas de trisomi 11q(q23→qter) par translocation t(11;22)(q231;q111) dans deux familles différentes. Ann Genet (Paris) 18:185–188

Ayrand N, Galiana A, Lloyd M, Deswarte M (1976) Trisomie 11q(q23.1→qter) par translocation maternelle t(11;22)(q23.1;q11.1). Une nouvelle observation. Ann Genet (Paris) 19:65–68

Berghe H Van den, Petit P, Broeckaert-van Orshoven A, Louwagie A, de Baere H, Verwilghen R (1979) Simultaneous occurrence of 5q– and 21q– in refractory anemia with thrombocytosis. Cancer Genet Cytogenet 1:63:68

Bofinger MK, Soukup SW (1979) Cat eye syndrome. Partial trisomy 22 due to translocation in the mother. Am J Dis Child 131:893–897

Chapelle A De la, Simola K, Parli P, Lindenbaum RH, Robson EB, Cook PJL, Buckton K (1978) Linkage data on chromosome 11. Human Gene Mapping 4 (1977): Fourth International Workshop on Human Gene Mapping. Birth Defects XIV, 4. The National Foundation, New York; also in Cytogenet Cell Genet 22:1978

Dutrillaux B (1973) Chromosomal aspects of human male sterility. In: Caspersson T, Zech L (eds) Chromosome identification. Academic Press, New York San Francisco London

Emanuel B, Zackai EH (1978) Site specific reciprocal translocation t(11;22)(q23;q11) in numerous unrelated families with 3:1 meiotic disjunction. Am J Hum Genet 30:80A

Emanuel B, Zackai EH, Aronsson MM, Mellman WJ, Moorhead PS (1976) Abnormal chromosome 22 and recurrence of trisomy-22 syndrome. J Med Genet 13:501–506

Felding I, Mitelman F (1979) Deletion of the long arm of chromosome 11. Acta Paediatr Scand 68:635–638

Feldman GM, Sparkes RS (1978) The problem of partial trisomy 22 reconsidered. Hum Genet 45:97–101

Ferguson-Smith MA (1978) Human cytogenetics. In: Littlefield JW, De Grouchy J (eds) Birth Defects. Procedings of the fifth international conference, Montreal, Canada, 21–27 August, 1977. Excerpta Medica, Amsterdam-Oxford

Fitzgerald PH (1976) Evidence that chromosome band 22q12 is concerned with cell proliferation in chronic myeloid leukaemia. Hum Genet 33:269–274

Francke U (1977) Abnormalities of chromosome 11 and 20. In: Yunis JJ (ed) New chromosomal syndromes. Academic Press, New York San Francisco London

Fu W-N, Borgaonkar DS, Kadewig PP, Weaver J, Pomerance HH (1976) Structural aberrations of the long arm of chromosome no. 22. Report of a family with translocation t(11;22)(q25;q11). Clin Genet 10:329–336

Giraud F, Mattei J-F, Mattei M-G, Bernard R (1975) Trisomie partielle 11q et translocation familiale 11–22. Humangenetik 28:342–346

De Grouchy J, Turleau C (1977) Clinical atlas of human chromosomes. John Wiley & Sons, New York Chichester Brisbane Toronto

Hall G (1963) Mongolism and other abnormalities in a family with trisomy 21-22 tendency. Acta Paediatr Scand Suppl 146:77–91

Hsu LYF, Hirschhorn K (1979) The trisomy 22 syndrome and the cat eye syndrome. In: Yunis JJ (ed) New chromosomal syndromes. Academic Press, New York San Francisco London

Kadotoni T, Katano T, Murakami M, Shiote A (1978) An additional case of partial trisomy 22 with multiple clinical malformations. Proc Jpn Acad 54:623–627

Kessel E, Pfeifer RA (1977) 47,XY,+der(11;22)(q23;q12) following balanced translocation t(11;22)(q23;q12)mat. Remarks on the problem of trisomy 22. Hum Genet 37:111–116

Laurent C, Biemont M-Cl, Bethenod M, Cret L, David M (1975) Deux observations de trisomie 11q(q23.1→qter) avec la même anomalie des organes genitaux externes. Ann Genet (Paris) 18:179–184

Léonard C, Courpotin C, Labrune B, Lepercq G, Kachaner J, Caut P (1979) Monosomie partielle par délétion du bras long, du chromosome 11:del (11)(q23). Ann Genet (Paris) 22: 115–120

Lindenbaum RH, Bobrow M (1975) Reciprocal translocations in man 3:1 meiotic disjunction resulting in 47- or 45-chromosome offspring. J Med Genet 12:29–43

Lindsten J, Therkelsen AJ, Friedrich U, Jonasson J, Steenstrup OR, Wiquist N (1974) Prenatal cytogenetic diagnosis. Int J Gyn Obstet 12:101–111

Nakai H, Yamamoto Y, Kuroki U (1979) Partial trisomy of 11 and 22 due to familial translocation t(11;22)(q23;q11), inherited in three generations. Hum Genet 51:349–355

Noel B, Levy M, Rethoré M-L (1976) Trisomie partielle du bras long du chromosome 11 par malségrégation d'un translocation maternelle t(11;22)(q231;q111). Ann Genet (Paris) 19:137–139

Oakley JR, Asplin EP, Taitz LS (1976) Balanced translocation, impaired sperm motility, and offspring anomaly. Arch Dis Childh 51:638–640

Parslow M, Hoo JJ, Garry M, Rose F (1980) A deleted extra chromosome 22 identified by DNA replication banding. Hum Genet 53:323–326

Pasquali F, Casalone R, Francesconi D, Peretti D, Fraccaro M, Bernasconi C, Lazzarino M (1979) Transposition of 9q34 and 22(q11→qter) regions has a specific role in chronic myelocytic leukemia. Hum Genet 52:55–67

Petersen F, Dahl G (1979) Trisomi 22q–. Ugeskr Laeg 139: 3061–3062

Verma RS, Dosik H (1979) A case of chronic myelogenous leukemia (CML) with a translocation between chromosome 12 and 22, t(12;22)(q13;q13), resulting in a Philadelphia (Ph^1) chromosome. Cytogenet Cell Genet 23:274–276

Received April 16, 1980