Institute of Genetics of the University, Bari [1]
(Director: Prof. E. Battaglia)

Chromosomal Survey in 298 Normal Subjects and 1,253 Cases of Congenital Disorders during 1966-1970

E. Battaglia, G. Guanti, P. Barsanti, P. Petrinelli

SUMMARY

A survey of chromosomal abnormalities has been carried out in Italy since 1966. Among the 1,551 subjects examined, the following abnormalities were found: 2 cases of C/C translocation, 1 of D/C, 5 of D/D, and 9 of D/G; 2 cases of Patau's syndrome with D trisomy; 4 cases of Edwards' syndrome; 176 cases of Down's syndrome, of which 163 with regular trisomy, 4 with mosaicism, 7 with D/G translocation, 1 with G/G translocation, and 1 with C/G translocation; 10 cases with 47,XXY complement; 1 case with 46,XY/47,XXY/48,XXXY mosaicism; 4 cases with 45,XO karyotype; 3 with 45,XO/46,XX, 1 with 45,XO/46,XY, 2 with 45,XO/46,XX_r and 1 with 45,XO/46,XX_i mosaicism; 2 cases with 47,XYY complement; 2 phenotypic females with 46,XY karyotype; and 5 leukaemic patients with Ph chromosome.

Furthermore, several kinds of normal variants were observed, such as no. 9 prominent secondary constriction, chromosome-D or -G enlarged short arm, 16-pair heteromorphism, Y-chromosome polymorphism, and satellited E chromosome.

Within the past ten years, through the application of new cytological techniques to human subjects with various congenital diseases, a series of significant relationships has been established between chromosomal mutations and diseases. Data on chromosomal aberrations constitute a new approach to the etiological analysis of the cause or occurrence of such diseases; furthermore, they have proved of great importance as criteria for clinical diagnosis of various congenital disorders. This has met with some success in a number of instances, such as abnormalities of the sex chromosome complement, or trisomy for one member of a limited number of groups of autosomes, in which it is possible to predict the physical appearance of the affected individuals with considerable accuracy.

The importance, however, of other abnormalities of the karyotype is at a more primitive stage of assessment. These include various chromosome rearrangements, in their balanced or unbalanced forms, and variations in the morphology of one homologue of a pair by comparison with the other, and where there is no evidence that any other chromosome is abnormal. Many chromosome rearrangements are presumed to be balanced because they appear to be unassociated with any physical

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disability on the part of the carrier. Furthermore, unbalanced forms of rearrangements have been discovered, which do not appear to be harmful to their carriers, but may materially increase the risk of meiotic errors. In other instances, structural rearrangements have been ascertained from the study of abnormal subjects which are clearly unbalanced, while the balanced forms of the rearrangements have been detected in either parent.

Since 1966, a survey on chromosomal abnormalities in the Italian people has been conducted by the authors in cooperation with clinicians working in many medical fields. Many subjects of these studies have been already described (Battaglia, 1966; Guanti, 1968; Guanti and Balacco-Gabrieli, 1968; Racanelli et al, 1968; Balacco-Gabrieli and Guanti, 1969; Guanti et al, 1969; Schettini et al, 1969; Torelli and Guanti, 1969; Vecchio and Guanti, 1969; Vecchio et al, 1969; Guanti and Barsanti, 1970; Tannoia et al, 1970; Guanti et al, 1970a; Guanti and Petrinelli, 1970b; Guanti et al, 1970c; Guanti et al, 1970d; Morea and Guanti, 1970; Pansini et al, 1970; Rutigliano et al, 1970).

The present article summarizes these cases in cytogenetic terms (see Table). Its principal aim is to supply the basic information available for understanding the relationship of clinical conditions to cytogenetic features, as well as to serve as a future clue for better criteria in the differential diagnosis of abnormal development in man.

Materials and Methods

A total of 1,551 subjects of both sexes and all ages have been examined and karyotyped.

Most studies were exclusively made on cells derived from short-term cultures of peripheral blood, using a modification of Hungerford's technique. The remainder were carried out with short-term cultures of bone marrow in suspension. The number of metaphases analyzed was 25 on nearly every subject. The reconstruction of karyotype followed the Denver and Chicago systems of nomenclature.

Sexing was carried out in all subjects by studying smear preparations from the buccal mucosa.

In some instances, the chromosome identification and characterization have been possible with the aid of autoradiographic techniques (Guanti and Petrinelli, 1970b).

Results

A. Normal Subjects

Out of the 1,551 subjects examined, 298 (187 males and 111 females), ranging in age from 2 days to 84 years, were clinically normal.

It seems desirable to provide a summary of the findings for three classes of subjects:

(1) Subjects with normal karyotype (the most part).

(2) Subjects with a change confined to one chromosome, for which there was

no evidence that it was the result of an exchange of material, either between the different parts of a single chromosome or between two chromosomes. These changes, regarded as normal variants, involve either a single autosome or the Y. Two subjects showed a prominent secondary constriction on both members of pair 9 (Fig. 1).

A difference in size between the homologue of pair 16 was found in six individuals; the larger member of the pair was comparable in length to the smallest chromosome of group C. Twenty-one subjects were identified by a D or G acrocentric chromosome with the short arm considerably longer than normal (Figs. 2, 3, and 4). Sixteen males were found to have an unusually large or unusually small Y chromosome (Figs. 5 and 6). The variation in length of the Y chromosome was quantitated by estimating the Y/E value, i.e., the ratio of the length of the Y to the average length of group E chromosomes (normal range 0.30-0.64). All these changes only appear to affect secondary constriction regions. Family studies have shown that these varriants are transmitted as heritable traits. The most common interpretation is that they may be due to genetically determined alterations in coiling.

(3) Subjects with structural rearrangements: thirteen phenotypically normal subjects were shown to be carriers of balanced translocations. All but one were detected in the course of cytogenetic investigations on the relatives of abnormal subjects, carriers of unbalanced translocations. Therefore, they will be mentioned in connection with the index case, while the only case in which familial investigations were not possible is described hereafter.

Karyotype analysis in a female subject, submitted to our attention as mother of a probable carrier of Patau's syndrome (died a few hours after birth), revealed a modal number of 45 chromosomes; two acrocentric chromosomes were lacking in group 13-15, whereas an additional large metacentric autosome was present, similar in size and shape to the members of pair 3. This abnormal chromosome is regarded as being formed from the two missing acrocentric autosomes following a reciprocal translocation, the translocation chromosome composed of short-arm material having been lost.

For the identification of the translocation chromosome, autoradiographic analyses were carried out. The following replicating patterns were consistently observed (Fig. 7): one (no. 13) was labelled over the distal portion of the long arm; one (no. 14) showed labelling over the centromeric and proximal region of the long arm; while two (no. 15) were very lightly labelled. The translocation chromosome was characterized by one arm with centromeric and proximal parts clearly labelled. The data provided by autoradiography strongly suggest that the translocation occurs between chromosomes 13 and 14.

B. Abnormal Subjects

Among the 1,551 subjects examined, a large number of abnormalities were found in 1,253 patients. Although, as already pointed out, the most relevant of these cases have already been described in previous works, it is deemed worth-while to summarize them hereafter, mainly on the cytogenetic ground.

PATAU'S SYNDROME (two cases)

CASE 1: female, 2-day-old. No family history of congenital malformations; father aged 40, mother 42; pregnancy complicated by polyhydramnios; placenta 400 g; at birth, head circumference 35 cm, length 47 cm.

Clinical features: deep cyanosis; weak cry; feeble reflexes; generalized hypotonia; small palpebral fissures for blepharophimosis; bilateral microphthalmus; unilateral (right) cleft lip and palate; low-set malformed ears; bilateral polydactily of the hands; flexion deformity of both thumbs; clinodactily of the fifth finger; bilateral polysyndactily of toes; cutaneous and osseous aplasia of the vertex; congenital heart disease, probably septal defect " typus ostium primum "; hypertrophy of clitoris. Died at 12 days.

Dermatoglyphs: distal axial triradius; simian crease on both palms.

Sex-chromatin-positive. Chromosomes 47,XX,D+ (Fig. 8). (Guanti et al, 1970a).

CASE 2: female, 1-day-old. Father aged 28, mother 24; pregnancy and delivery normal; birth weight 2,800 g; conditions at birth poor.

Clinical features: paleness of cutis; perioral cyanosis; generalized hypotonia; wide anterior fontanel; flat triangular nose; wide-set eyes; low-set ears; right knee dislocation; left calcaneo-valgus foot; bronchopneumonia. Died.

Dermatoglyphs: distal axial triradius; simian crease on both palms.

Sex-chromatin-positive. Chromosomes 47,XX,D+.

EDWARDS' SYNDROME (five cases)

CASE 1: female, 19-day-old. Pregnancy normal, spontaneous delivery; birth weight 2,290 g.

Clinical features: micrognathia; slight hypertelorism; prominent occiput; blepharophimosis; downward slanting eyes; low-set malformed ears; wide-spaced nipples; flexion deformity of the 2nd and 3rd finger; short halluces; hypoplastic fingernails; flexion deformity of foot; hypoplastic labia majora; jitteriness; systolic murmur.

Sex-chromatin-positive. Chromosomes, 47,XX,E+ (Fig. 9).

CASE 2: female, 2-day-old. No family history of congenital malformations or mental defects; pregnancy and delivery normal; birth weight 1,800 g.

Clinical features: micrognathia; short neck; small low-set malformed ears; flexion deformity of fingers; feet abnormal: left equino-varus, right talo-varus deformities; mesocardial systolic murmur; bronchopneumonia. Died at 23 days.

Sex-chromatin-positive. Chromosomes, 47,XX,E+.

CASE 3: female, 3-day-old. Two previous pregnancies resulted respectively in a stillbirth and in an abortion at 12 weeks. Pregnancy and delivery normal; birth weight 2,500 g.

Clinical features: anoxia; micrognathia; flexion deformities of fingers; right clubfoot; mesocardial systolic murmur; generalized tonic-clonic convulsions. Died at 4 days with neonatal haemorrhagic disease.

Sex-chromatin-positive. Chromosomes 47,XX,E+.

CASE 4: female, 1-day-old. Father aged 42, mother 38; four sibs well; birth weight 2,900 g.

Clinical features: cyanosis; weak cry; laxity of skin; micrognathia; wide sagittal suture; slanting palpebral fissures; slight epicanthus; mandibular hypoplasia; sorth neck; low hairline on the neck; first and second toes flexion limited; joint hyperflexibility.

Dermatoglyphs: simple arches on all fingers; positions of palmar triradii not seen; two palmar creases bilaterally.

Sex-chromatin-positive. Chromosomes 47,XX,E+.

CASE 5: female, 2-day-old. Father aged 49, mother 44; birth weight 3,000 g; conditions at birth poor.

Clinical features: micrognathia; low-set ears; narrow high-arched palate; short neck; recto-vaginal fistula; anal atresia; renal anomalies. Died at 8 months.

Dermatoglyphs: simple arches on all fingers; positions of palmar triradii not seen; two palmar creases bilaterally.

Sex-chromatin-positive. Chromosomes 47,XX,E+.

DOWN'S SYNDROME

A total of 177 cases of Down's syndrome (93 females and 84 males) came under study for chromosomal analysis. In a small number of them, the chromosomal screening was additionally carried out on the parents of the patients.

Clinically, all patients showed the typical facial configuration and mental retardation characteristic of this syndrome. In some instances, congenital cardiopathy, simian crease, short curved fifth finger, and generalized hypotonia were present.

In 163 cases regular G-trisomy was detected (Fig. 10). Among these, however, 5 cases exhibited Y polymorphism, 6 cases enlarged satellites in one chromosome of group D or G, and 2 cases 16-heteromorphism. Chromosome examination in the parents of some patients of this group revealed no anomalies.

Four patients have been found, showing a mosaic of two different cell populations, one trisomic for chromosome 21 and the other normal:

Case 1: 46,XY(10%)/47,XY,G+(90%)
Case 2: 46,XX(15%)/47,XX,G+(85%)
Case 3: 46,XX(12%)/47,XX,G+(88%)
Case 4: 46,XX(22%)/47,XX,G+(78%)

This condition is usually suspected when the phenotypic expression of mongolism is not fully delineated, or when the intelligence of the patient is higher than expected.

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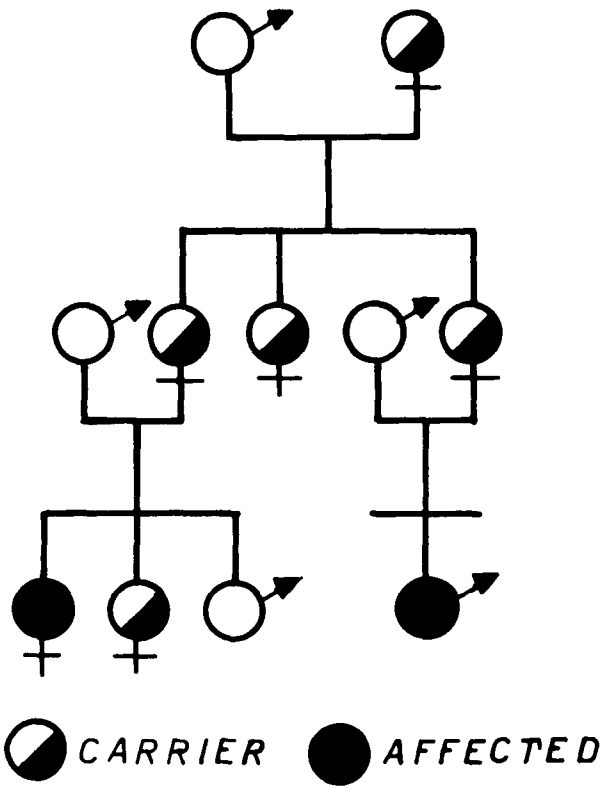
A total of 9 cases of translocation mongolism have been found: 7 D/G (Fig. 11), 1 G/G (Fig. 12), and 1 C/G. The G/G translocation and 2 cases of D/G translocation were sporadic, while 4 cases of D/G translocation were inherited from the mother (Fig. 13), and the seventh one was familial (see pedigree).



Pedigree of Down's syndrome

The term, " sporadic ", indicates that the parents of the affected child had normal karyotype; " inherited " means that one of the parents was a translocation carrier; " familial " will apply only to cases where more than one affected person occurs in the same family or where a sib of the propositus is affected.

The case of C/G translocation mongolism is of particular cytogenetic interest (Guanti, 1968); brief accounts of the clinical findings in this case are given below.

The patient was a 36-year-old woman, the second of two sibs. At birth, her mother was 18 and her father 19. She measured 132 cm, had an I.Q. of 30 (by Terman-Merrill's method), and the following signs of Down's syndrome: brachycephaly, furrowed tongue, hyperflexibility of joints, simian crease on both hands, low-set ears, oblique palpebral fis-

sures, epicanthal folds. Furthermore, she had destructive, defiant, and autolesionist behaviour.

Chromosome analysis revealed in all cells a modal number of 47 (Fig. 14). The extra chromosome was a small metacentric, indistinguishable from the two pairs of group F. Furthermore, a C chromosome, tentatively identified as a 12, showed a deletion of the distal part of the long arm, so that the supernumerary chromosome was interpreted as the result of a translocation C/G. This rearrangement accounts for the mongoloid features of the proposita. Sex-chromatin-positive.

The patient's parents and sister were not available for clinical and cytogenetic examinations.

Seventy-two patients, clinically defined as suspected mongoloids, showed neither trisomic condition nor evidence for translocation.

MULTIPLE MALFORMATIONS

A total of 56 patients with multiple malformations of different types and degrees underwent chromosome analysis. All but 3 cases showed regular karyotypes; among these, however, 5 cases exhibited normal variants. An abnormal karyotype was shown by the following 3 cases.

CASE 1: 4½-year-old male, first child of healthy unrelated parents.

Clinical features: psychomotor retardation; hypertelorism; broad and flattened nose; low-set ears; simian crease; suspected congenital cardiopathy.

Chromosome analysis revealed a constant number of 46 chromosomes (Fig. 15). Three members — one no. 3, one from group C, and one from group D — were missing. Three abnormal elements were present: a large submetacentric chromosome resembling a no. 2; a medium-sized element, nearly metacentric, resembling a no. 10; and an acrocentric satellited chromosome of a size intermediate between that of the chromosomes of groups D and G. Sex-chromatin-negative.

The parents and brother of the propositus were karyotypically normal.

No further investigations were made, after finding out that this case had already been published by Nuzzo et al (1968).

CASE 2: newborn male, second child of unrelated parents.

Clinical features: paleness of cutis and mucosae; perioral cyanosis; marked hypotonia; generalized dystrophy; large fontanelles; right parieto-occipital cephalhematoma; shield-shaped chest; congenital heart disease.

Chromosome examination revealed a modal number of 47; the extra chromosome was a small metacentric, indistinguishable from the two pairs of group F (Fig. 16). Sex chromatin negative.

Karyotype analysis was also carried out on the phenotypically normal father: the modal number of 46 chromosomes was observed (Fig. 17), but two group-C chromosomes were missing (tentatively identified as 9 and 12), while two new chromosomes were present (one apparently identical to the additional chromosome found in the propositus; the other similar to a 3). The two abnormal chromosomes have been interpreted as the result of a balanced reciprocal translocation between a chromosome 9 and a 12. The mother and the brother of the patient resulted karyotypically normal.

The clinical findings in the propositus were supposed to be the result of a partial trisomy for 9 and 12. (Guanti et al, 1970c).

CASE 3: 13-year-old boy, third sib of unrelated parents; hospitalized for a recurrent sepsis.

Physical and clinical features: height 150 cm; weight 49 Kg; mongoloid facies; paleness of cutis; scleral subicterus; multiple dental caries; prognathism; high-arched palate; systolic murmur; hepatosplenomegaly; epileptic seizures; mental retardation (I.Q. 58).

The presence of a beta-thalassemia was ascertained through haematological findings: microcytosis; anisopoikilocytosis; target cells; increased resistance of red cells to haemolysis in hypotonic saline solutions; increased resistance to alkali denaturation; increased A_2Hb. Furthermore, immunoelectrophoresis detected hypogammaglobulinemia (IgG 300 mg%; IgA 20 mg%; IgM 10 mg%).

Dermatoglyphs: total ridge count 59; atd angle 98°.

Karyotype investigations revealed in all cells the 47,XYY complement (Fig. 18). Sex-chromatin-negative. (Tannoia et al, 1970).

CONGENITAL MALFORMATIONS OR DISEASES OF ORGANS AND SYSTEMS

Under this heading chromosome constitutions are described, associated with metabolic disorders and diseases or malformations of the following organs and systems: nervous system, eye, skeletal and muscular system, dermal tissue, excretory system, heart, hemic system, endocrine system, and reproductive system. The results of chromosomal analysis are summarized in the Table.

Nervous System

A total of 160 male and 58 female psychotic patients were studied. Of these, 8 males and 3 females had enlarged short arm on a D chromosome; 1 male showed 16 heteromorphism; 1 male and 3 females had enlarged short arm on a G chromosome; Y polymorphism was detected in 11 males; prominent satellites were present on one chromosome 17 of a male (Fig. 19).

One patient, an 18-year-old man, had XYY sex chromosome constitution. He was repeatedly hospitalized for hysteric crises. Height 171 cm; facial acne; dental malocclusion; right testicle, undescended, surgically brought down; I.Q. 97; no criminal records nor aggressive nature. Sex-chromatin-negative. (Guanti and Barsanti, 1970; Rutigliano et al, 1970).

Among the 54 male and 74 female epileptic patients examined the following cases were found: 3 females with prominent secondary constriction on the long arm of a chromosome 9; 2 male and 2 female carriers of an enlarged D short arm; 4 males with Y polymorphism; 1 male and 4 females with enlarged G short arm; 1 female carrier of a D/D translocation.

The latter, a 28-year-old patient, was the first of five children, born from healthy unrelated parents. Height 150 cm; weight 48 Kg; head circumference 57 cm; mesocephaly; psychosomatic hypoevolutism.

Karyotype analysis revealed a chromosome count of 45, and only 4 large acrocentric group-D chromosomes were present, instead of the 6 normally found; there was, however, a large metacentric chromosome, slightly smaller than the no. 3 chromosomes. This was interpreted as having been formed from the major part of two group-D chromosomes which had become translocated. Sex-chromatin-positive.

No familial investigations were carried out.

Eight male and 10 female patients with mental deficiency generally showed a normal complement. Among these, however, 1 male and 2 females showed enlarged short arm of a G chromosome, and 1 male with large Y was observed. One male and 4 females with microcephaly, 2 males and 1 female with Sturge-Weber syndrome, and 1 male and 1 female with Charcot's syndrome underwent chromosome analysis. It was found that their metaphases contained a normal complement of 46 chromosomes. The karyotype of 5 male and 1 female hydrocephalous patients was found to be normal; but 2 males showed large Y, and 1 had an enlarged D short arm.

One male with Buerger's disease and 1 with Hirschsprung's disease exhibited normal karyotype, except for the presence of a Y larger than normal. Two males affected by Bergeron's disease were found: one showed a normal chromosome complement, the other was carrier of a D/D translocation.

This patient, a 4-year-old child, was born after normal pregnancy and delivery from unrelated, phenotypically normal parents. He had a 7-year-old brother, phenotypically normal. His mother's first pregnancy resulted in spontaneous abortion.

Chromosome studies in the propositus consistently revealed a modal number of 45 chromosomes and the presence of a 13/14 translocation, ascertained through autoradiographic investigations; furthermore, a large Y was present. (Fig. 20). Sex-chromatin-negative.

Cytogenetic investigations were carried out in all members of the family available for study. The father and the brother of the patient had the same chromosomal rearrangement and the same normal variant found in the propositus. The mother and the paternal grandmother were karyotypically normal.

We have examined one male affected with Wilson's disease; his karyotype was normal, except for the presence of an enlargement of D short arm.

Eye

The study of 30 male and 20 female patients with retinitis pigmentosa gave negative findings: all presented normal karyotype. Among them, however, 3 males showed large Y, 2 males an enlarged D short arm, and 4 females an enlarged G short arm (Guanti and Balacco-Gabrieli, 1968).

In a series of 26 index cases, 16 males and 10 females, affected with ocular albinism, we found no abnormal karyotype, except for normal variants: 3 males were carriers of an enlarged G short arm, and 1 of large Y; and 2 females showed an enlarged D short arm. (Balacco-Gabrieli and Guanti, 1969).

Also, 11 male and 12 female patients with myopia were examined. In this group, 3 males and 4 females, all members of the same family, showed 16-pair heteromorphism (Guanti et al, 1969); 1 male exhibited a Y shorter than normal; and the remainder resulted perfectly normal.

A group of 10 individuals, 8 males and 2 females, with congenital cataract, 1 female with Fuchs's dystrophy and 1 with congenital ptosis, and 2 males with Marchesani's syndrome failed to reveal any chromosomal change or variation.

Out of 7 cases with congenital nystagmus (1 female and 6 males), 2 subjects showed large Y, the others being chromosomally normal. Karyotype was normal also in 3 females with congenital strabismus, except for 1 who showed an enlarged D short arm.

Skeletal and Muscular System

The patients here considered were: 7 males and 1 female with osteogenesis imperfecta, 2 males and 3 females with congenital dislocation of hip, 2 males and 1 female with achondroplasia, 3 males with multiple exostoses, 1 female with turricephaly, 1 male with hand-flexion deformity, 1 male with Holt-Oram syndrome, 1 female with Klippel-Feil syndrome, 2 females with myositis ossificans progressiva, 11 males and 5 females with polysyndactily, 1 female with Ellis-Van Creveld syndrome. All of them were karyotypically normal. Furthermore, 1 female with polysyndactily showed an enlarged D short arm, and 1 male with Ellis-Van Creveld syndrome exhibited 16-pair heteromorphism.

Dermal Tissue

In the course of the investigations we have observed: 2 males and 2 females with epidermolysis bullosa dystrophica, 2 males and 2 females with Hebra's syndrome, 1 male and 2 females with xeroderma pigmentosum, 1 female with collodion skin, 1 with congenital ichthyosiform erythroderma, 1 with Ehlers-Danlos syndrome, 2 with ichthyosis congenita, 1 with incontinentia pigmenti, 1 with pseudoxanthoma elasticum, 2 males with cutis verticis gyrata, 2 males and 2 females with Sabouraud's syndrome. All of them were karyotypically normal. Also examined were 2 males wih Rothmund-Thompson syndrome, who presented occasional aneuploidy (Vecchio et al, 1969); and 1 male with Sabouraud's syndrome, who exhibited short Y.

Excretory System

No chromosomal anomalies were found in 2 females with complete reduplication of kidney, 1 male with hereditary nephropathy, 5 males with medullary sponge kidney (Racanelli et al, 1968), and 12 males with polycystic disease of the kidney.

Heart

A total of 6 patients were examined: 4 males and 1 female, carriers of congenital cardiopathy, were karyotypically normal, while the remaining male showed an enlarged D short arm.

Hemic System

No chromosomal anomalies were found in the following disorders associated with the hemic system: hemophilia (1 male), Cooley's anaemia (1 female), Jaksch-Hayem-Luzet syndrome (1 male), Letterer-Siwe disease (1 male), Vaquez's disease (1 male), chronic lymphocytic leukaemia (2 males), acute lymphocytic leukaemia (1 female), eosinophilic leukaemia (1 male and 1 female). The only case of Hodgkin's disease observed showed an unusually long Y. A high frequency of structural chromosomal aberrations — gaps, breaks, fragments, chromatid exchanges, endoreduplications — was found in lymphocytes of a 10-year-old female patient, affected with Fanconi's anaemia (Guanti et al, 1970d).

Bone-marrow examination in a female with acute myeloid leukaemia revealed the presence of various aneuploid metaphases. In a series of 14 index cases (8 males and 6 females), affected with chronic myeloid leukaemia, chromosome analysis carried out on bone-marrow cells revealed the presence of Ph chromosome in 3 males and 2 females (Fig. 21), and the existence of aneuploidy in 1 male and 3 females (Schettini et al, 1969).

Endocrine and Metabolic Disorders

Normal chromosome constitution was found in 3 males and 1 female with hypothyroidism, 1 female with Albright's syndrome, 1 male with congenital agenesis of thyroid, 2 males with Lorain-Levi syndrome, 2 females with Pellizzi's syndrome, 2 females with Simmonds' disease, 2 males and 2 females with progeria, 1 male and 1 female with Hurler syndrome, 1 male with celiac syndrome, 1 female with congenital hypokalemic syndrome, 1 male with Sanfilippo's syndrome, and 2 males with Tay-Sachs disease.

Among the 4 patients, carriers of adrenogenital syndrome, the male had an enlarged D short arm, while the 3 females were normal. One female in the group of the 6 dwarf patients examined showed an enlarged D short arm; the other female and the 4 males were karyotypically normal. One female and 6 out of the 7 males with Fröhlich's syndrome invariably showed 46 normal chromosomes; in the remaining male a short Y was found.

Three females and 1 male affected by hypopituitarism had a normal chromosome complement, except for an enlarged D short arm found in the male. One of the 2 female patients with Russell's syndrome showed an enlarged D short arm in the otherwise normal karyotype.

The 10 females with Marfan's syndrome were chromosomally normal; among the 15 males with the same syndrome, 3 presented enlargement of a D short arm, and 1 had a Y chromosome shorter than normal (Pansini et al, 1970). An unusually long short-arm on a D chromosome was found in 1 male and in 1 female with Morquio-Ullrich syndrome; the other affected male showed no karyotypic anomalies. (Torelli and Guanti, 1969).

SEXUAL ANOMALIES

Phenotypic Males

Out of the 39 patients with tall stature, obesity, scanty hair, gynecomastia, and small testes, diagnosed as Klinefelter's syndrome, 10 cases showed 47 chromosomes (Fig. 22), having an XXY determining mechanism as regular Klinefelter's syndrome, and were sex-chromatin-positive. Another case, characterized by mosaicism represented by a 46,XY/47,XXY/48,XXXY complex, is particularly interesting (Figs. 23, 24, 25). This patient, aged 30 years, married, was the last-born of four siblings. Maternal age at birth was 40 years, paternal age 50. Height 181 cm, weight 82 Kg. Slight gynecomastia; small testes.

The remaining 28 cases had 46 chromosomes associated with an XY sex constitution; one of these had an unusually short Y, found also in his normal brother. Out of 3 males with azoospermia, 1 had a Y longer than normal, while the remaining 2 were karyotypically normal.

Cytogenetic investigations in 1 male with congenital phymosis, 10 males with hypogonadism, and 1 case of " Turner phenotype " in male revealed the normal male karyotype 46,XY.

Among 5 cases of cryptorchism, all with 46,XY complement, 3 were found to have normal variants: 1 showed enlargement of a D short arm, 1 exhibited long Y, and the last-one presented an enlarged G short arm and long Y.

Phenotypic Females

Out of 16 patients with sexual infantilism, short stature, webbed neck, cubitus valgus, and primary amenorrhea, diagnosed as carriers of Turner's syndrome, 11 had chromosome abnormalities of different types, while the remaining 5 cases showed no deviation from the normal female complement, except for 1 subject with an enlarged D short arm and 1 with an enlarged G short arm. The following is the detailed description of the chromosome abnormalities in the 11 cases.

Four patients showed a modal number of 45. Karyotype analysis (Fig. 26) detected the loss of an element from group 6-12-X; buccal smears showed negative sex-chromatin counts. Thus, it is evident that the patients have an XO sex-chromosome constitution, characteristic of Turner's syndrome.

Three patients had two different cell populations, one with an XO and the other

with a normal XX sex complement. The clinical spectrum of XO/XX mosaicism is wide and may vary from cases quite typical of Turner's syndrome to cases with normal gonads and normal stature in relation to the different relative frequency of the two cell populations. Two of our patients showed typical features of Turner's syndrome, the last-one being only affected with primary amenorrhea.

In another patient with features of Turner's syndrome a 45,XO/46,XY mosaicism was present.

In a subject with short stature, pterigium colli, cubitus valgus, multiple cutaneous nevi, hypothyroidism, mental retardation, and primary amenorrhea, two stem-lines were found with 45 and 46 chromosomes respectively. Karyotype analysis (Fig. 27) revealed the presence of only one X in the first cell population; in all cells with 46 chromosomes there were 15 chromosomes, instead of 16, in the 6-12-X group, and an extra metacentric chromosome similar to those of pair no. 3; these cells were interpreted as having one normal X chromosome and a presumptive isochromosome for the long arm of the X.

Two cases of 45,XO/46,XX_r mosaicism were found. One patient showed many features of Turner's syndrome, the other had only short stature and hypertrophy of clitoris (Vecchio and Guanti, 1969). In both subjects two distinct cell populations were present: a 45-cell line, with a chromosome of group C missing; and a 46-cell line, which included a small element varying in size and shape, but often similar to a ring (Fig. 28). This structure was interpreted as derived from an X chromosome. The different phenotype of these two patients may be explained considering that different regions with different genic contents might be lost in the ring-X formation.

Normal female karyotype was observed in 4 patients with hypertrophy of clitoris, in 2 with hypogonadism, in 3 with secondary amenorrhea, and in 3 with hirsutism.

Two cases of Morris' syndrome were found. The patients were of female legal sex; completely feminine habitus; well-developed breasts; scanty axillary and pubic hair; external genitalia female, but with a blind vagina; testes of almost normal size in the inguinal canals. Cytogenetic investigations revealed a negative sex-chromatin pattern and a normal male 46,XY karyotype in both patients.

In a series of 11 patients with primary amenorrhea, all with a normal female complement, 2 subjects showed an enlarged G short arm; the same normal variant was present in a patient with bipartite uterus and in 1 of the 7 subjects with pure gonadal dysgenesis.

Pseudohermaphroditism

Five newborns with male pseudohermaphroditism were studied; in all cases external genitalia were predominantly female with prominent skin folds resembling labia majora, a finger-sized phallus, common external orifices of the urethra and vagina, testes undescended. Karyotype analysis revealed in all these subjects the existence of a normal male 46,XY complement.

One subject, aged 24 years, was examined for male pseudohermaphroditism.

Height 160 cm, weight 49 Kg, scanty axillary and pubic hair, gynecomastia, testes surgically descended in labia majora, small penis. Chromosomal constitution 46,XY. Sex-chromatin-negative.

Two newborn infants and 3 children, aged 6 to 14 years, came under study for female pseudohermaphroditism. They presented the following characteristics of external genitalia: a small penis; a scrotum-like organ consisting of fused labia majora; labia minora absent; common external orifice for both urethra and vagina. Radiological examinations showed adrenal hyperplasia in the 3 children. Cytogenetic investigations revealed a positive sex-chromatin pattern and a normal female 46,XX karyotype in all these subjects.

SPONTANEOUS ABORTIONS AND STILLBIRTHS

Wives and husbands from 17 couples, and 3 females whose husbands were not examined, with history of spontaneous abortions and stillbirths, were studied. All of them showed a normal karyotype, but 3 of the females had enlarged short arm on a G, and 2 on a D chromosome; and one male exhibited large Y.

Conclusions

The findings presented in this survey would indicate that some clinical syndromes are regularly associated with specific chromosomal abnormalities, and that several congenital malformation syndromes cannot be correlated with the identifiable chromosome variation present in the affected patients. It is evident that congenital defects in carriers of apparently normal karyotype could be caused by genic mutations or chromosomal rearrangements (minute loss, translocations, etc.), both of which are not identifiable through current cytological techniques. Since human cytogenetics is as yet at an early stage of development, the collection of karyological data is highly desirable in various disorders on a large scale, in order to discover the cause and occurrence of these diseases and to make possible their differential diagnosis.

Table. (*A*) Normal Subjects

N	Condition	Karyotype	
152 89	Regular karyotype	46,XY 46,XX	
	NORMAL VARIANTS		
1 1	No. 9 prominent secondary constriction	46,XY,9q+ 46,XX,9q+	Fig. 1
8 4	D enlarged short arm	46,XY,Dp+ 46,XX,Dp+	Fig. 3
6 3	G enlarged short arm	46,XY,Gp+ 46,XX,Gp+	Fig. 4
1 5	Pair 16 heteromorphism	46,XY,16q+ 46,XX,16q+	Fig. 2
12 4	Y polymorphism	46,XY,Yq+ 46,XY,Yq−	Fig. 5 Fig. 6
	STRUCTURAL REARRANGEMENTS		
1	C/C translocation	46,XY,C−,C−,t(9q12q)+,t(9p12p)+	Fig. 17
2 1	D/D translocation	45,XY,D−,D−,t(DqDq)+ 45,XX,D−,D−,t(DqDq)+	Fig. 7
9	D/G translocation	45,XX,D−,G−,t(DqGq)+	Fig. 13

Table. (*B*) Abnormal Subjects

N	Condition	Karyotype	
2	Patau's syndrome	47,XX,D+	Fig. 8
5	Edward's syndrome	47,XX,E+	Fig. 9
	DOWN'S SYNDROME		
76 87	Regular trisomy	47,XY,G+ 47,XX,G+	Fig. 10
1 3	Mosaicism	46,XY/47,XY,G+ 46,XX/47,XX,G+	
5 2 1 1	Translocation	46,XY,D−,t(DqGq)+ 46,XX,D−,t(DqGq)+ 46,XY,G−,t(GqGq)+ 47,XX,Cq−,t(CqGq)+	Fig. 11 Fig. 12 Fig. 14
29 43	Pseudomongolism	46,XY 46,XX	

Table. (*B*) – *Continued*

N	Condition	Karyotype	
		MULTIPLE MALFORMATION SYNDROMES	
25	Normal karyotype	46,XY	
24		46,XX	
1	Abnormal karyotype	46,XY,3p+q+,Cq–,Dq–	Fig. 15
1		47,XY,t(Cq–)+	Fig. 16
1		47,XYY	Fig. 18
2	Franceschetti's syndrome	46,XY	
1		46,XX	
1	De Lange's syndrome	46,XX	
		CONGENITAL MALFORMATIONS OR DISEASES OF ORGANS AND SYSTEMS	
	Nervous System		
158	Psychotic patients	46,XY	
58		46,XX	
1		47,XYY	
1		46,XY,E satellited	Fig. 19
54	Epilepsy	46,XY	
73		46,XX	
1		45,XX,D–,D–,t(DqDq)+	
8	Mental deficiency	46,XY	
10		46,XX	
1	Microcephaly	46,XY	
4		46,XX	
5	Hydrocephaly	46,XY	
1		46,XX	
2	Sturge-Weber syndrome	46,XY	
1		46,XX	
1	Charcot's syndrome	46,XY	
1		46,XX	
1	Buerger's disease	46,XY	
1	Bergeron's disease	46,XY	
1		45,XY,D–,D–,t(DqDq)+,Yq+	Fig. 20
1	Hirschsprung's disease	46,XY	
1	Wilson's disease	46,XY	

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Table. (*B*) – *Continued*

N	Condition	Karyotype
	Eye	
30 20	Retinitis pigmentosa	46,XY 46,XX
16 10	Ocular albinism	46,XY 46,XX
11 12	Myopia	46,XY 46,XX
8 2	Congenital cataract	46,XY 46,XX
6 1	Congenital nystagmus	46,XY 46,XX
3	Congenital strabismus	46,XX
2	Marchesani's syndrome	46,XY
1	Fuchs's dystrophy	46,XX
1	Congenital ptosis	46,XX
	Skeletal and Muscular System	
7 1	Osteogenesis imperfecta	46,XY 46,XX
2 3	Congenital dislocation of hip	46,XY 46,XX
3 3	Polysyndactily	46,XY 46,XX
2 1	Achondroplasia	46,XY 46,XX
1 1	Ellis-Van Creveld syndrome	46,XY 46,XX
3	Multiple exostoses	46,XY
1	Turricephaly	46,XX
1	Hand-flexion deformity	46,XY
1	Holt-Oram syndrome	46,XY
1	Klippel-Feil syndrome	46,XX
2	Myositis ossificans progressiva	46,XX

Table. (*B*) – *Continued*

N	Condition	Karyotype
11	Progressive muscular dystrophy	46,XY
5		46,XX
	Dermal Tissue	
2	Epidermolysis bullosa dystrophica	46,XY
2		46,XX
2	Hebra's syndrome	46,XY
2		46,XX
1	Xeroderma pigmentosum	46,XY
2		46,XX
3	Sabouraud's syndrome	46,XY
2		46,XX
1	Collodion skin	46,XX
1	Congenital ichthyosiform erythro-derma	46,XX
1	Ehlers-Danlos syndrome	46,XX
2	Ichthyosis congenita	46,XX
1	Incontinentia pigmenti	46,XX
1	Pseudoxanthoma elasticum	46,XX
2	Rothmund-Thompson syndrome	46,XY
2	Cutis verticis gyrata	46,XY
	Excretory System	
2	Complete reduplication of kidney	46,XX
1	Hereditary nephropathy	46,XY
5	Medullary sponge kidney	46,XY
2	Polycystic disease of kidney	46,XY
	Heart	
5	Congenital cardiopathy	46,XY
1		46,XX
	Hemic System	
1	Hemophilia	46,XY

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Table. (*B*) – *Continued*

N	Condition	Karyotype	
1	Cooley's anemia	46,XX	
1	Fanconi's anemia	46,XX	
1	Jaksch-Hayem-Luzet syndrome	46,XY	
1	Letterer-Siwe disease	46,XY	
1	Vaquez's disease	46,XY	
4	Chronic myeloid leukemia	46,XX	
3		46,XY,Ph	Fig. 21
2		46,XX,Ph	
1	Acute myeloid leukemia	46,XX	
2	Chronic lymphocytic leukemia	46,XY	
1	Acute lymphocytic leukemia	46,XX	
1	Eosinophilic leukemia	46,XY	
1		46,XX	
1	Hodgkin's disease	46,XY	
	Endocrine and Metabolic Disorders		
1	Andrenogenital syndrome	46,XY	
3		46,XX	
2	Dwarfism	46,XY	
4		46,XX	
7	Fröhlich's syndrome	46,XY	
1		46,XX	
1	Hypopituitarism	46,XY	
3		46,XX	
3	Hypothyroidism	46,XY	
1		46,XX	
1	Albright's syndrome	46,XX	
1	Congenital agenesis of thyroid	46,XY	
2	Lorain-Levi syndrome	46,XY	
2	Pellizzi's syndrome	46,XX	
2	Russell's syndrome	46,XX	
2	Simmonds' disease	46,XX	

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Table. (*B*) – *Continued*

N	Condition	Karyotype	
2	Progeria	46,XY	
2		46,XX	
1	Hurler's syndrome	46,XY	
1		46,XX	
15	Marfan's syndrome	46,XY	
10		46,XX	
2	Morquio-Ullrich syndrome	46,XY	
1		46,XX	
1	Celiac syndrome	46,XY	
1	Congenital hypokalemic syndrome	46,XX	
1	Sanfilippo's syndrome	46,XY	
2	Tay-Sachs disease	46,XY	
	SEXUAL ANOMALIES		
	Phenotypic Males		
10	Klinefelter's syndrome	47,XXY	Fig. 22
28		46,XY	
1		46,XY/47,XXY/48,XXXY	Figs. 23, 24, 25
3	Azoospermia	46,XY	
1	Congenital phimosis	46,XY	
5	Cryptorchism	46,XY	
10	Hypogonadism	46,XY	
1	Turner male	46,XY	
	Phenotypic Females		
4	Turner's syndrome	45,XO	Fig. 26
3		45,XO/46,XX	
1		45,XO/46,XY	
5		46,XX	
2		$45,XO/46,XX_r$	Fig. 28
1		$45,XO/46,XX_i$	Fig. 27
4	Hypertrophy of clitoris	46,XX	
2	Hypogonadism	46,XX	

Table. (*B*) – *Continued*

N	Condition	Karyotype
11	Primary amenorrhea	46,XX
3	Secondary amenorrhea	46,XX
7	Pure gonadal dysgenesis	46,XX
1	Bipartite uterus	46,XX
3	Hirsutism	46,XX
2	Morris' syndrome	46,XY
6	*Pseudohermaphroditism*	46,XY
5		46,XX
17	SPONTANEOUS ABORTIONS	46,XY
20		46,XX

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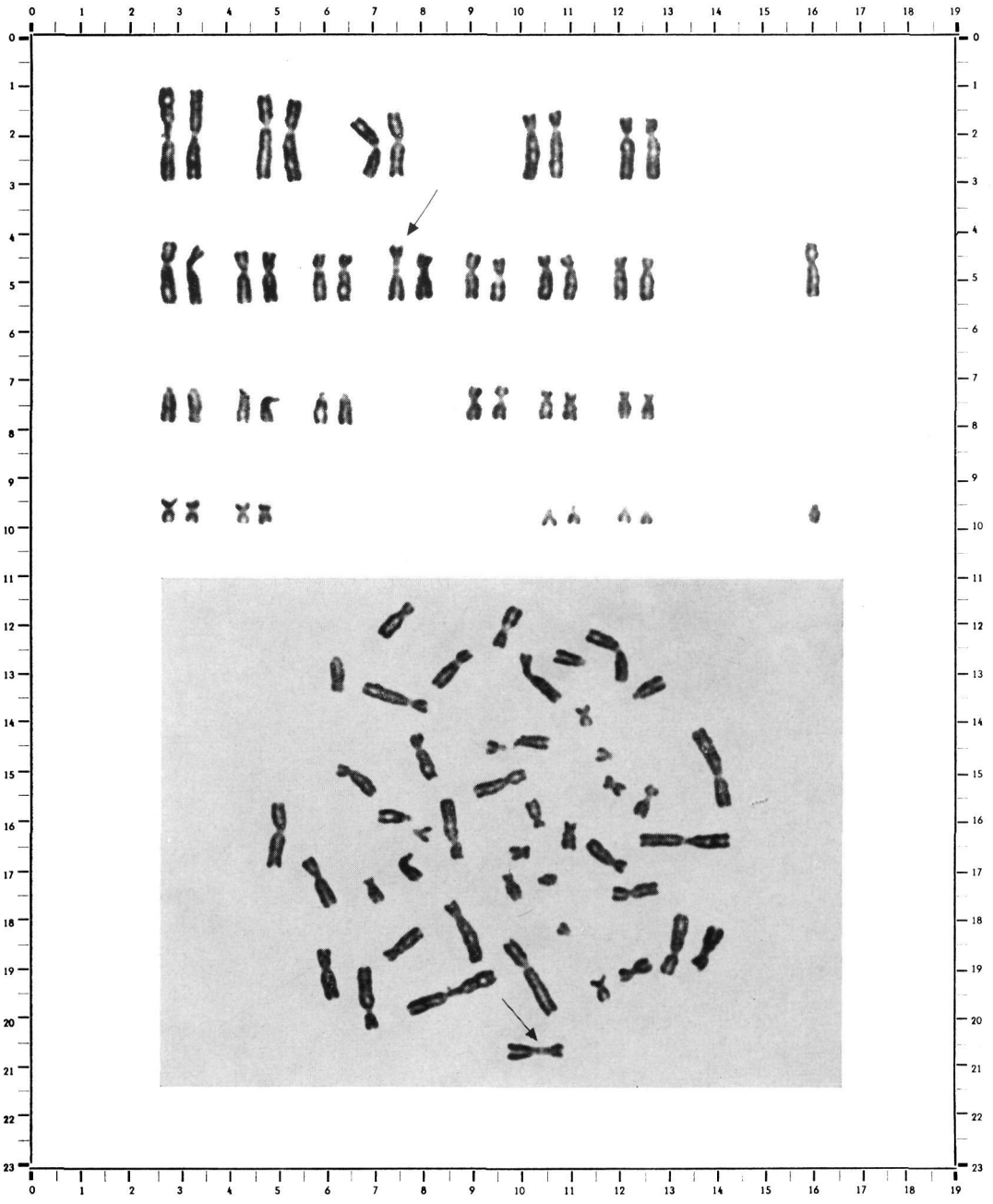

Fig. 1. 46,XY,9 prominent secondary constriction

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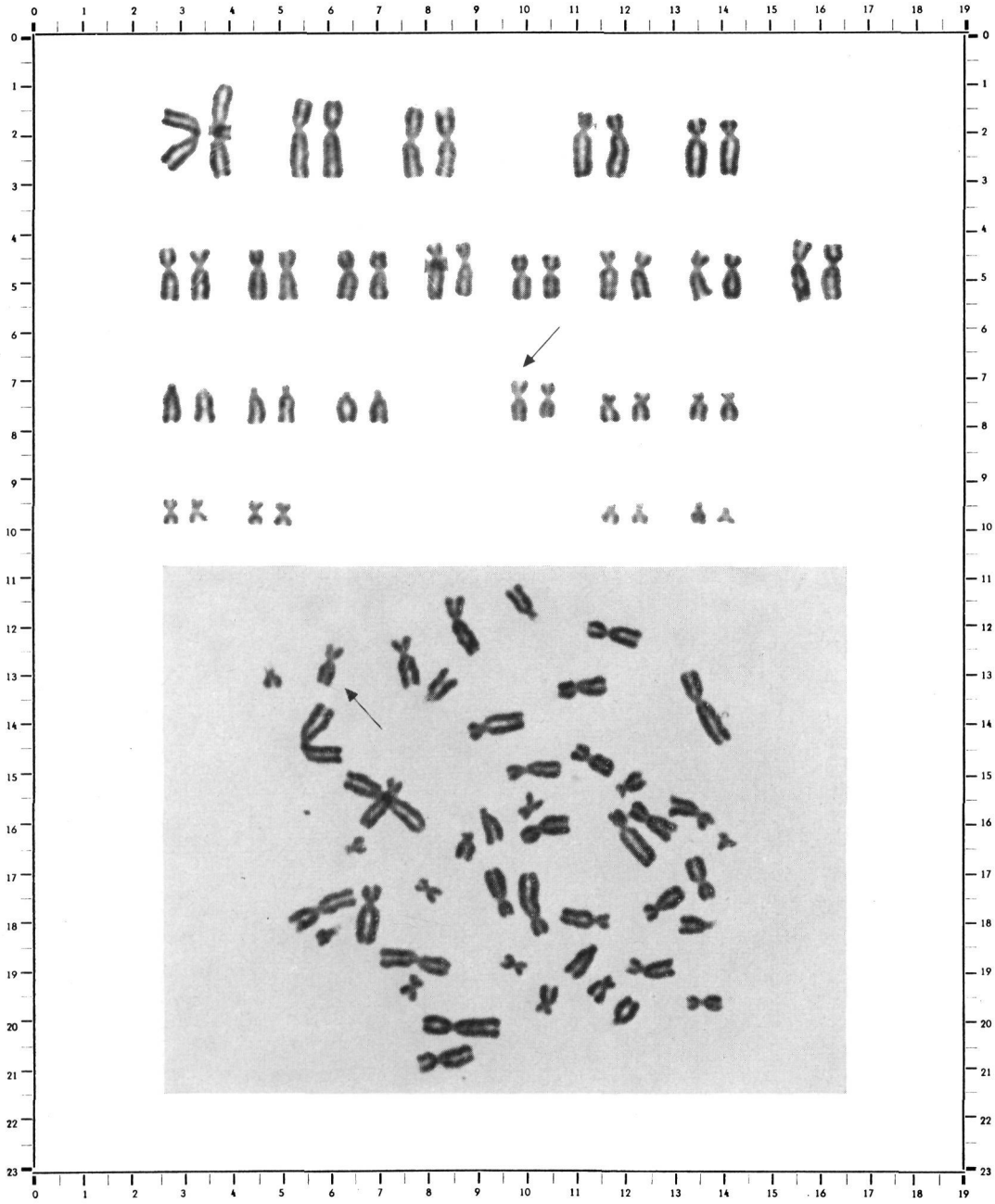

Fig. 2. 46,XX,16 heteromorphism

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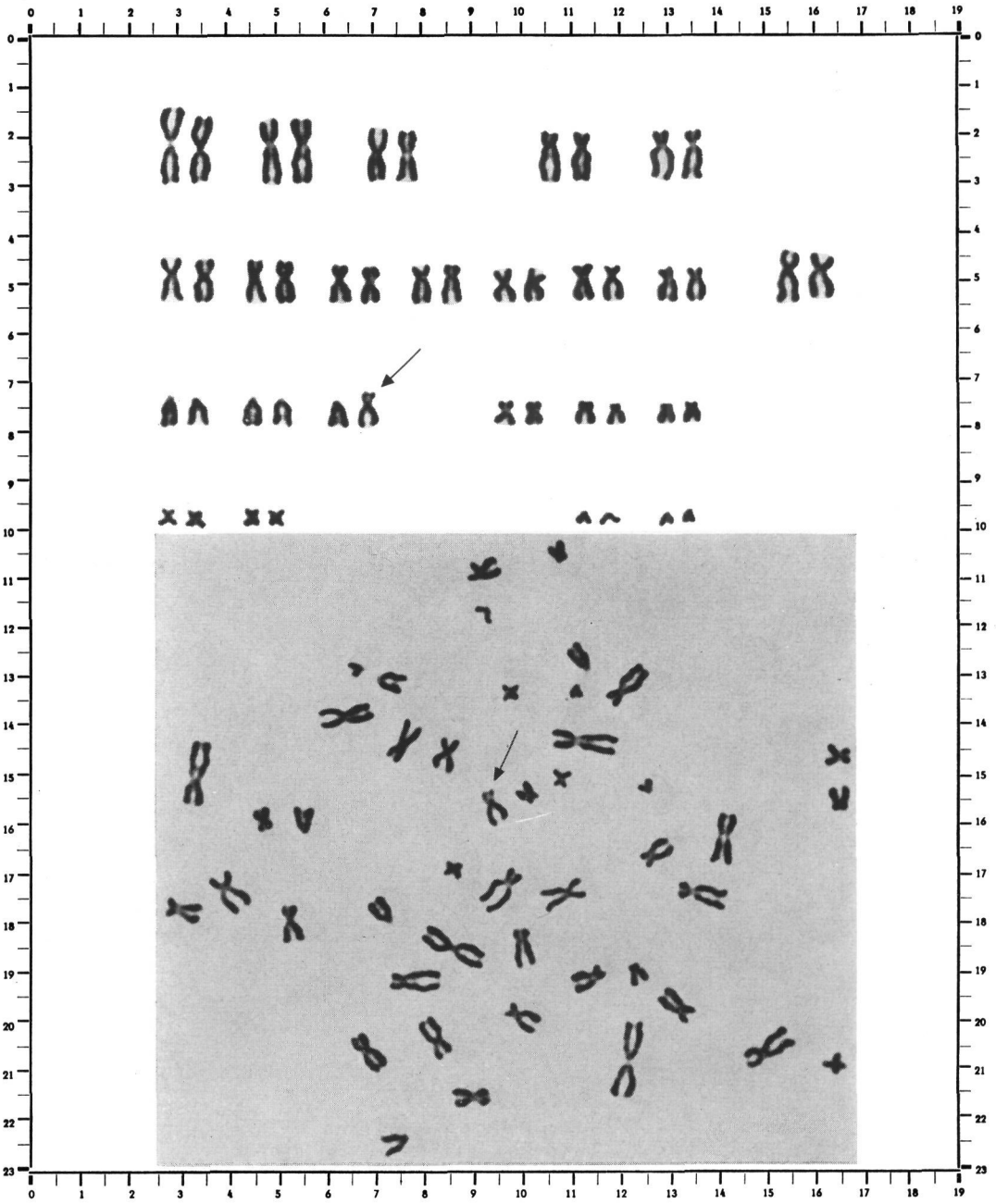

Fig. 3. 46,XX,D enlarged short arm

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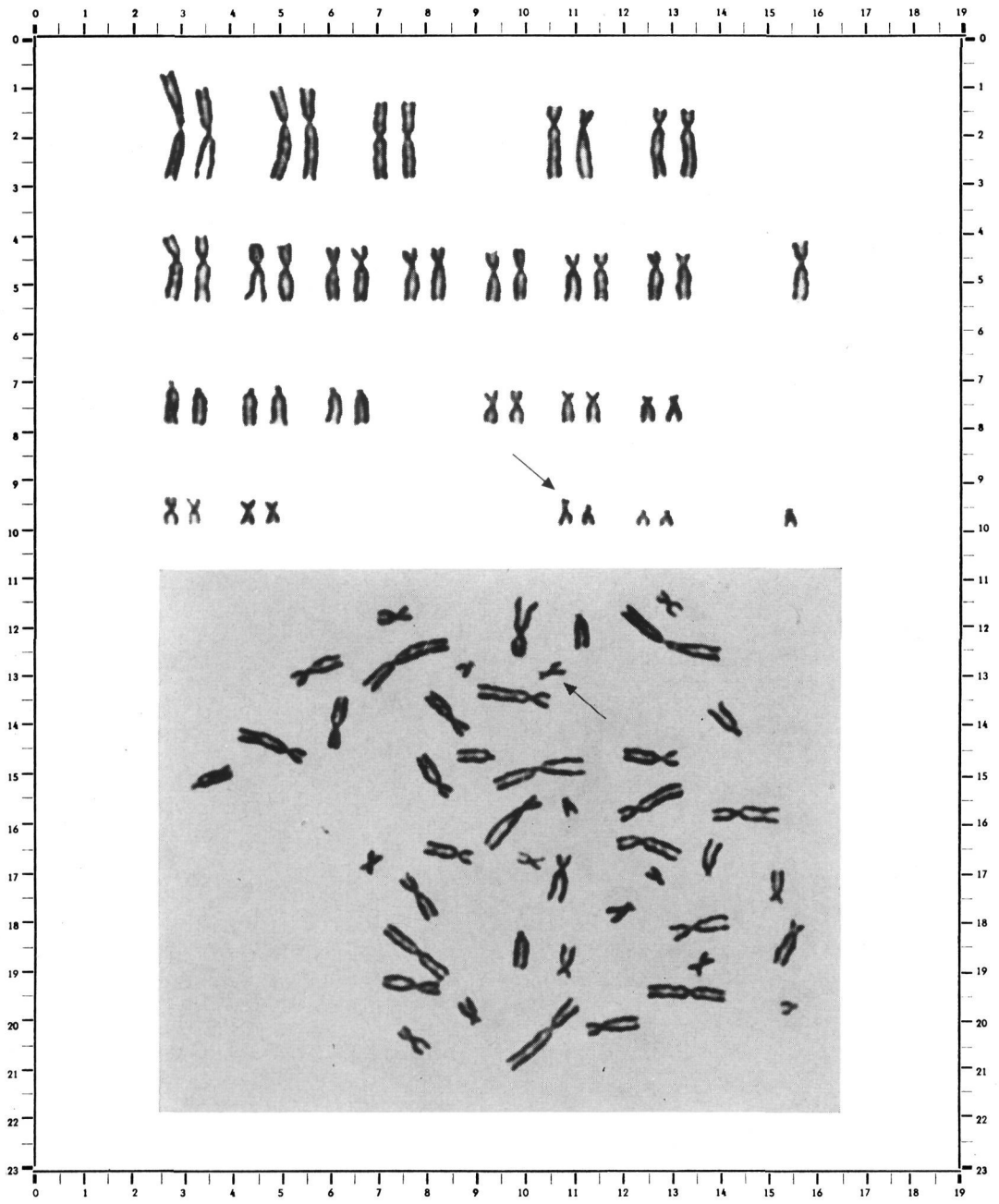

Fig. 4. 46,XY,G enlarged short arm

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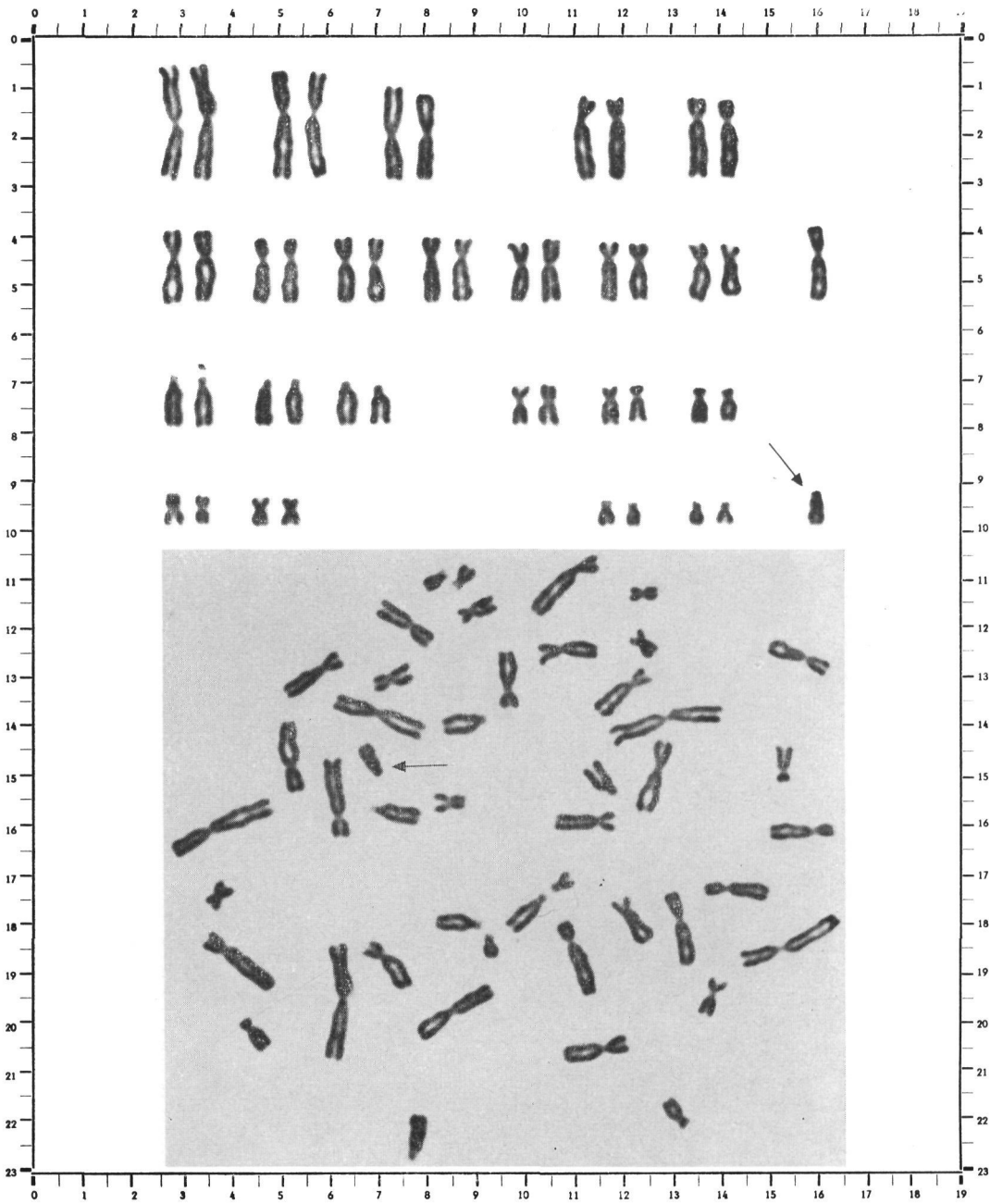

Fig. 5. 46,XY,Yq+

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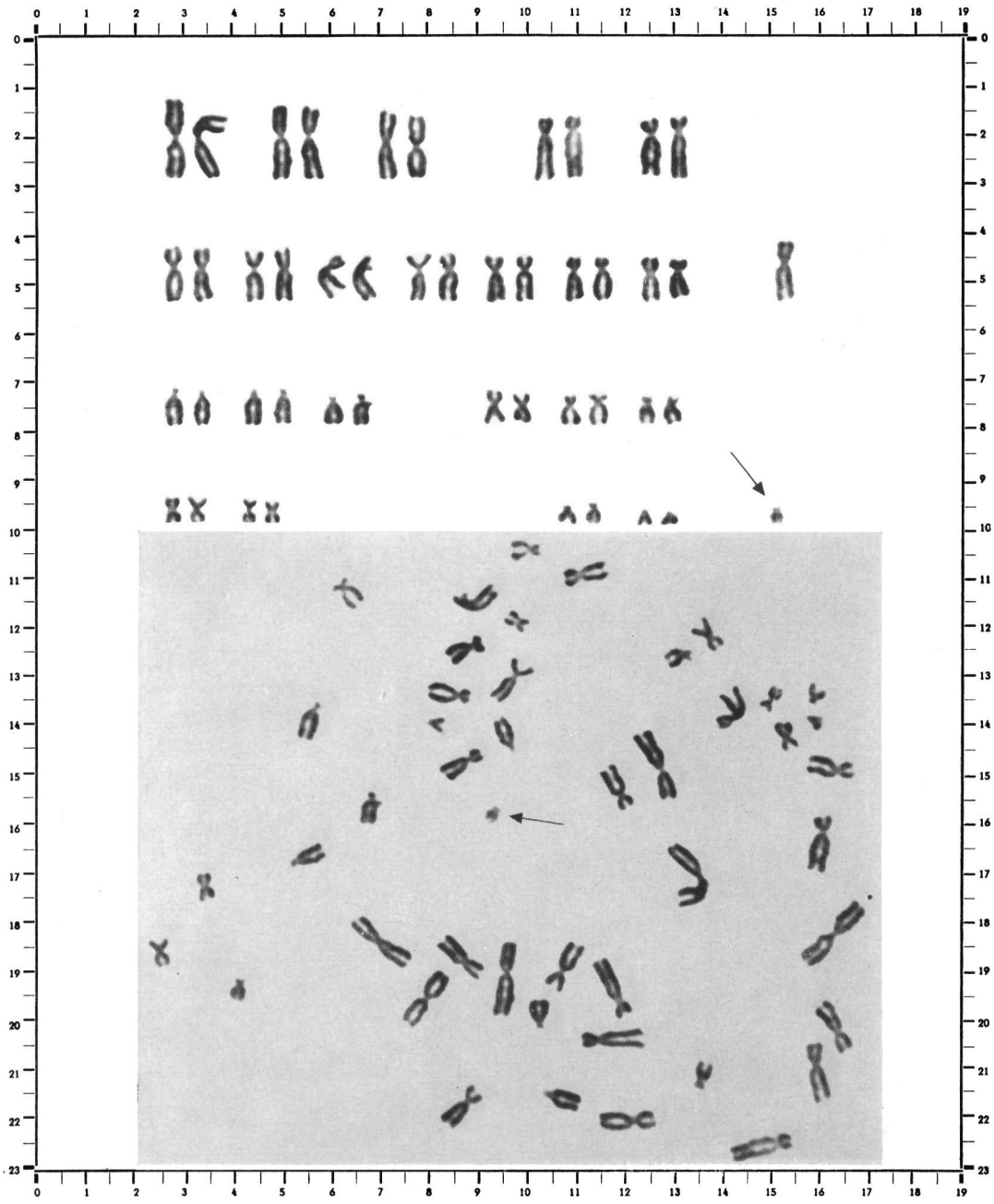

Fig. 6. 46,XY,Yq–

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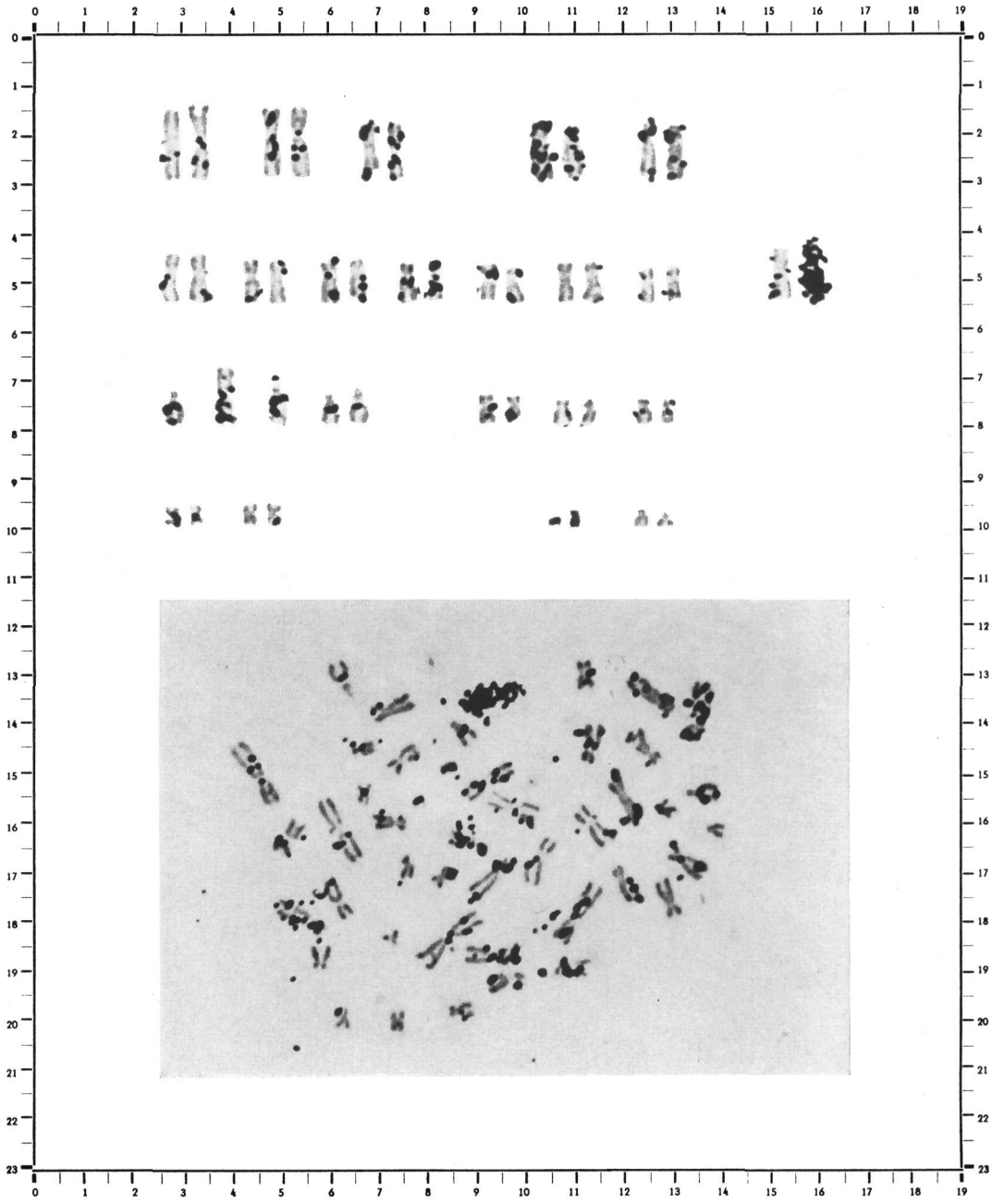

Fig. 7. 13/14 translocation

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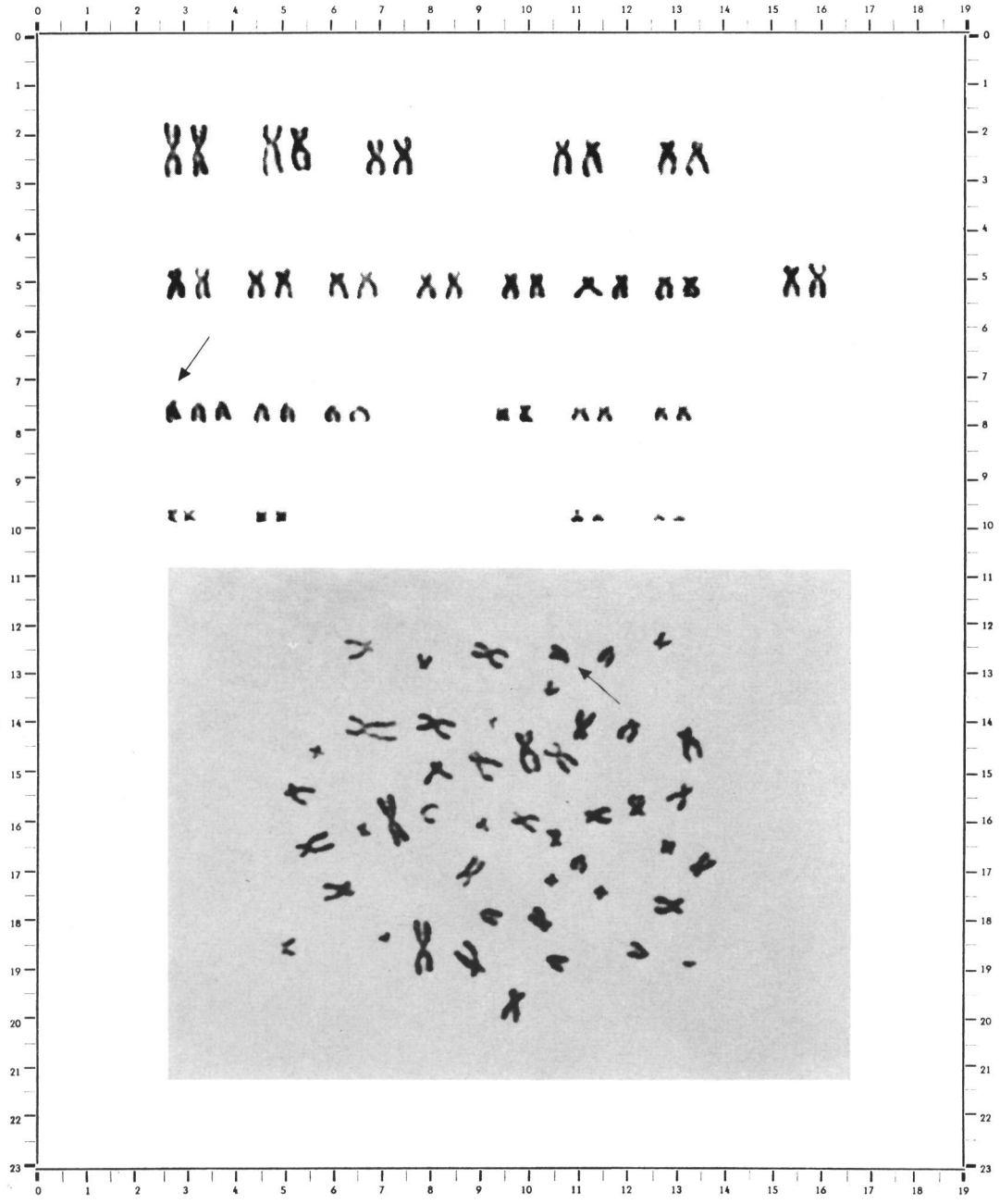

Fig. 8. 47,XX,D+

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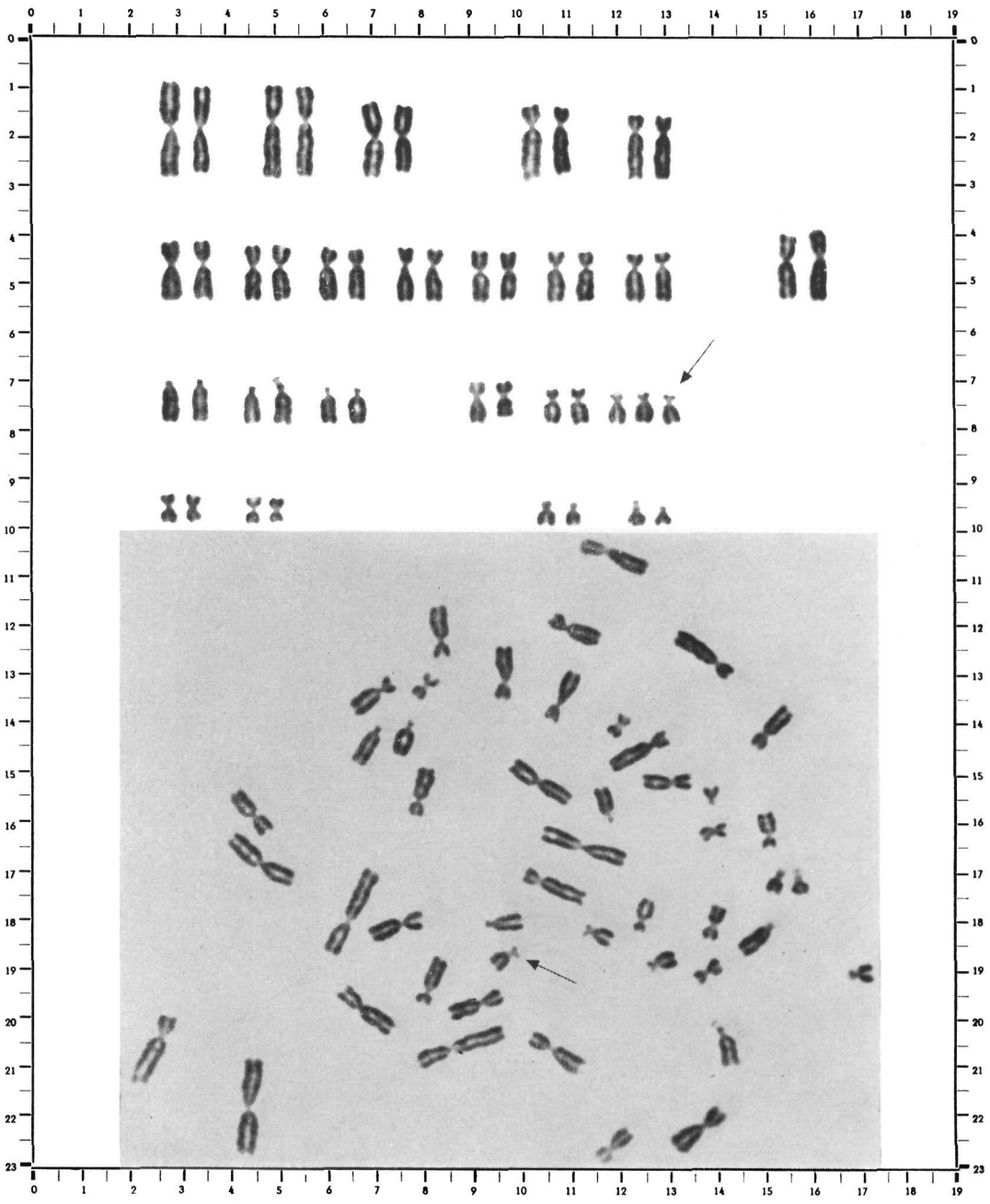

Fig. 9. 47,XX,E+

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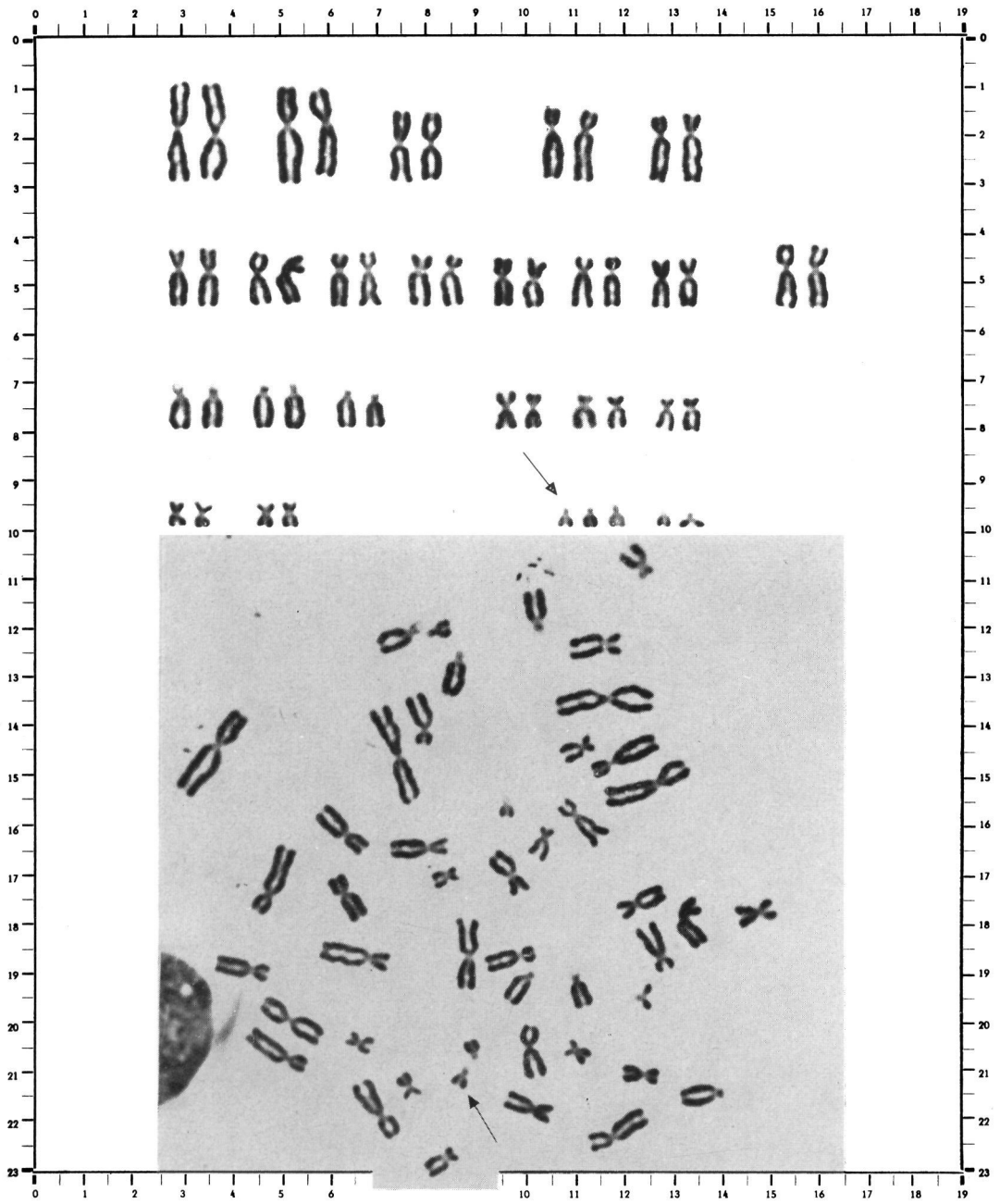

Fig. 10. 47,XX,G+

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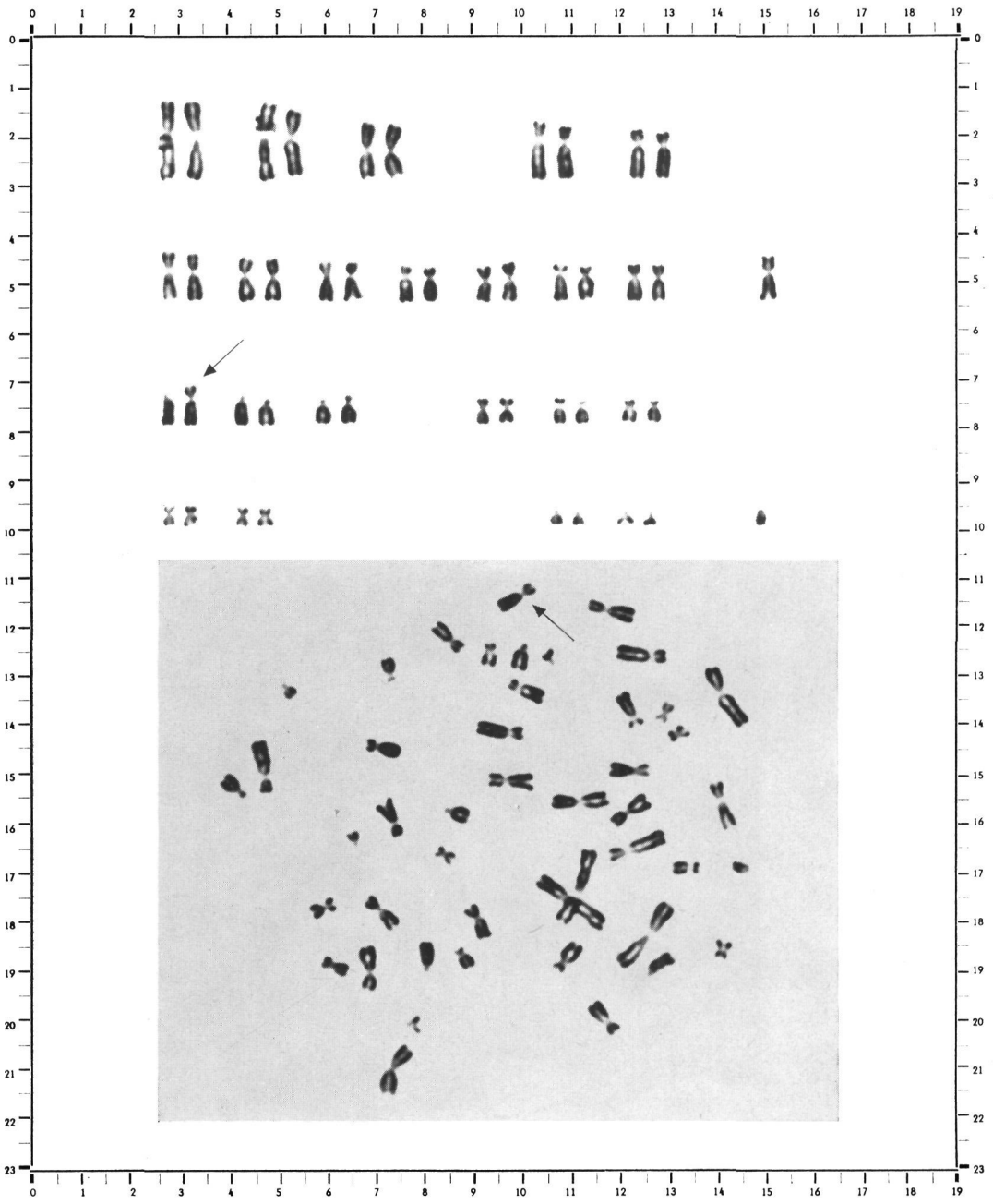

Fig. 11. 46,XY,D–,t(DqGq)+

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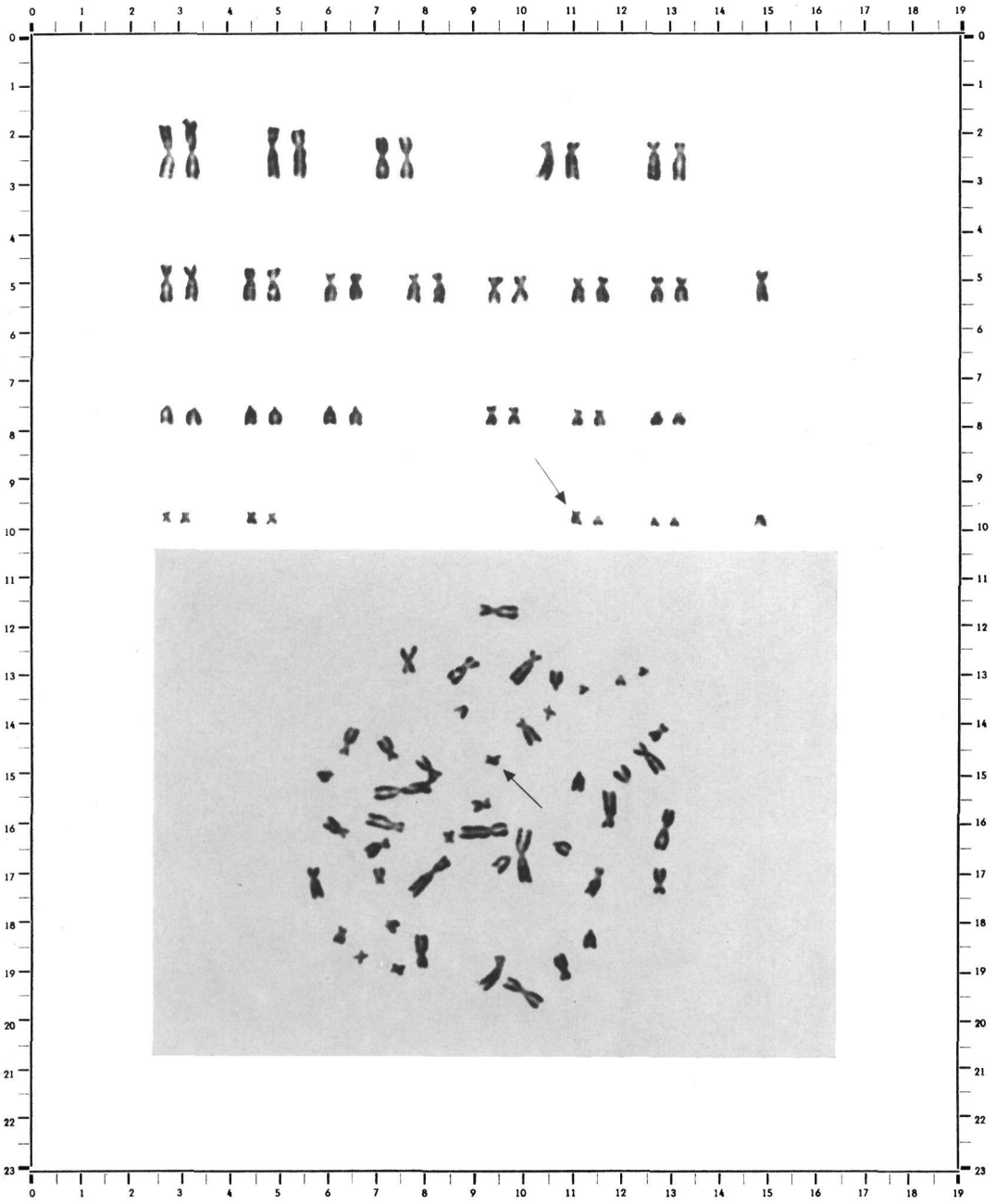

Fig. 12. 46,XY,G–,t(GqGq)+

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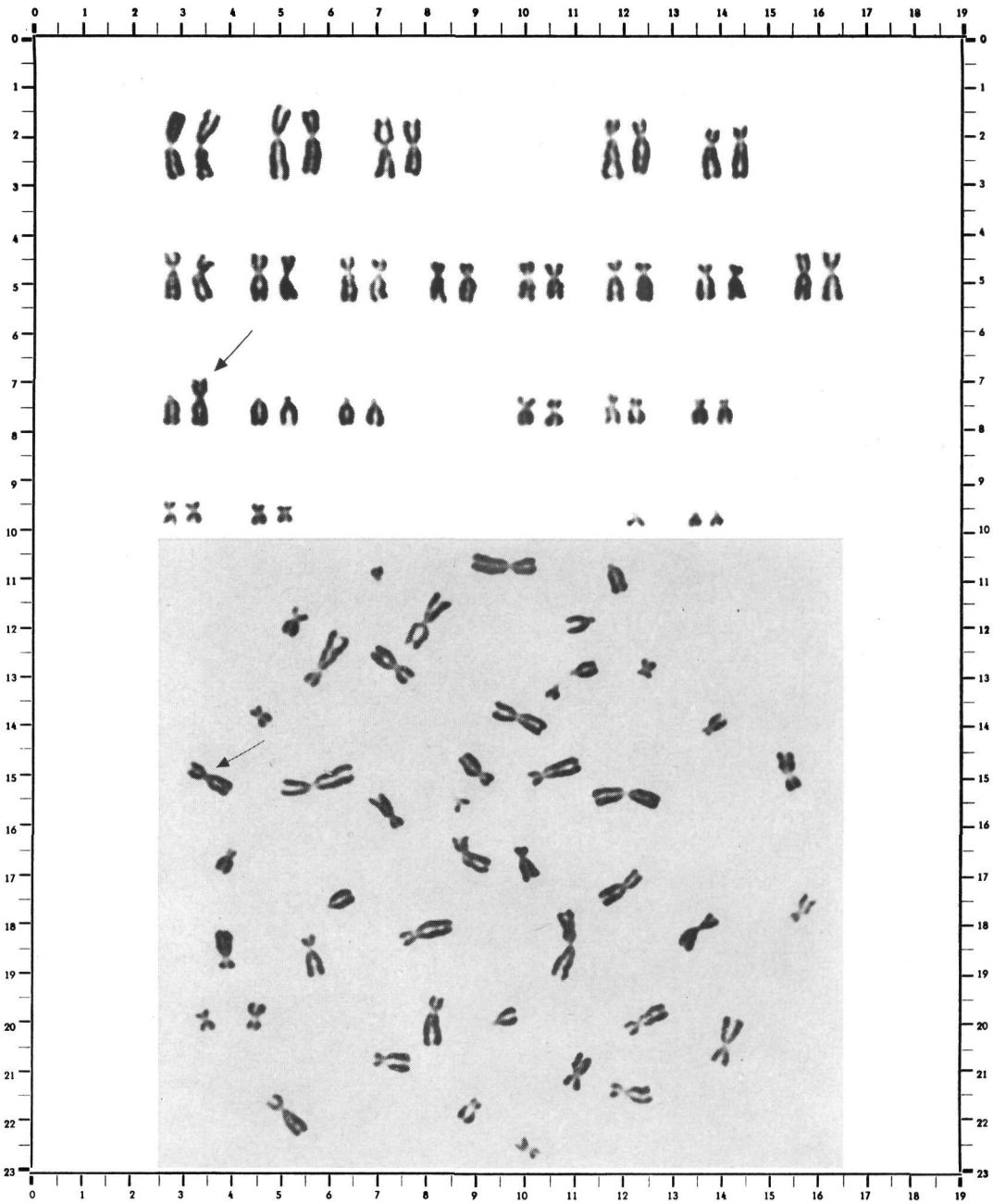

Fig. 13. 45,XX,D–,G–,t(DqGq)+

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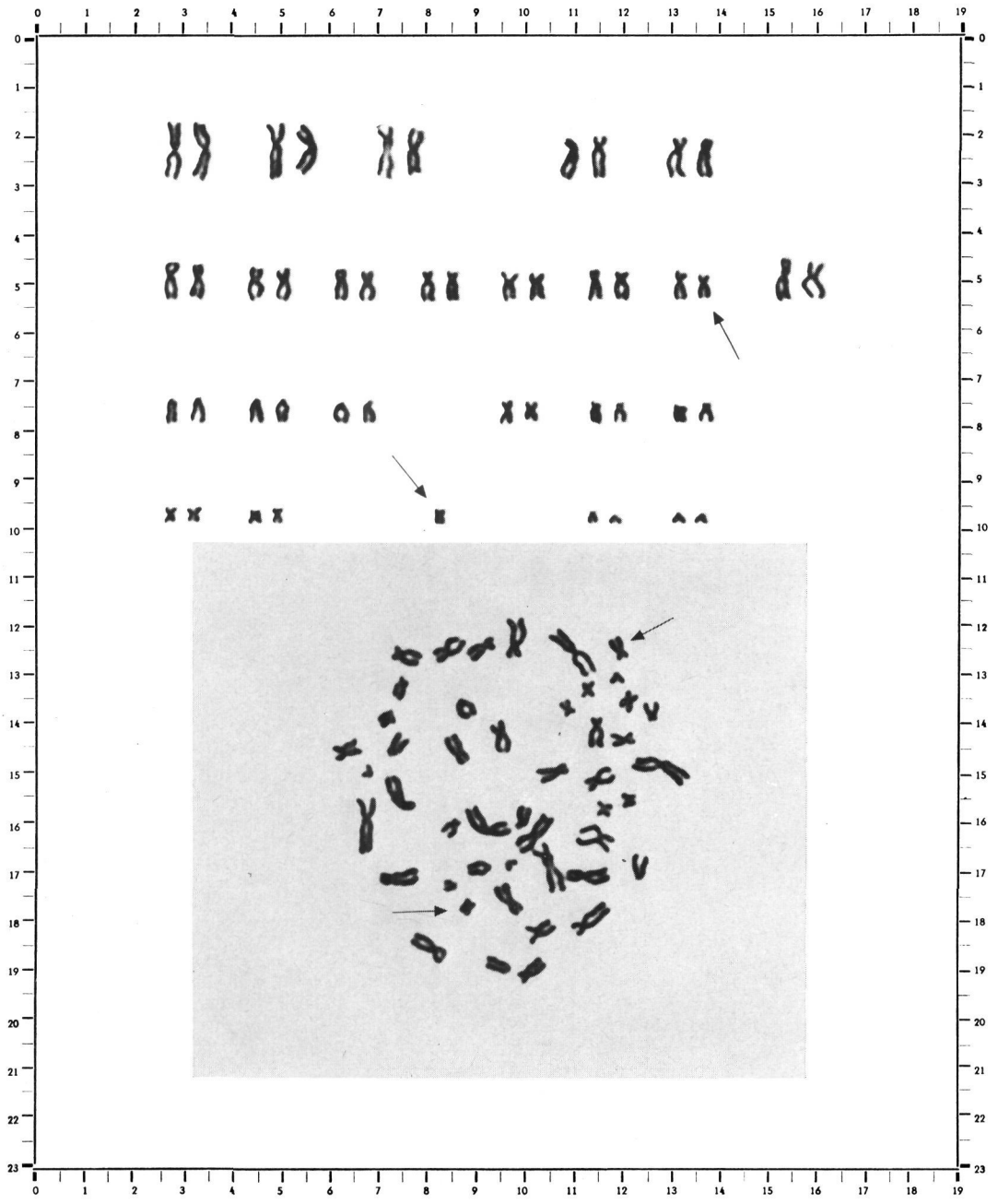

Fig. 14. 47,XX,Cq−,t(GqCq−)+

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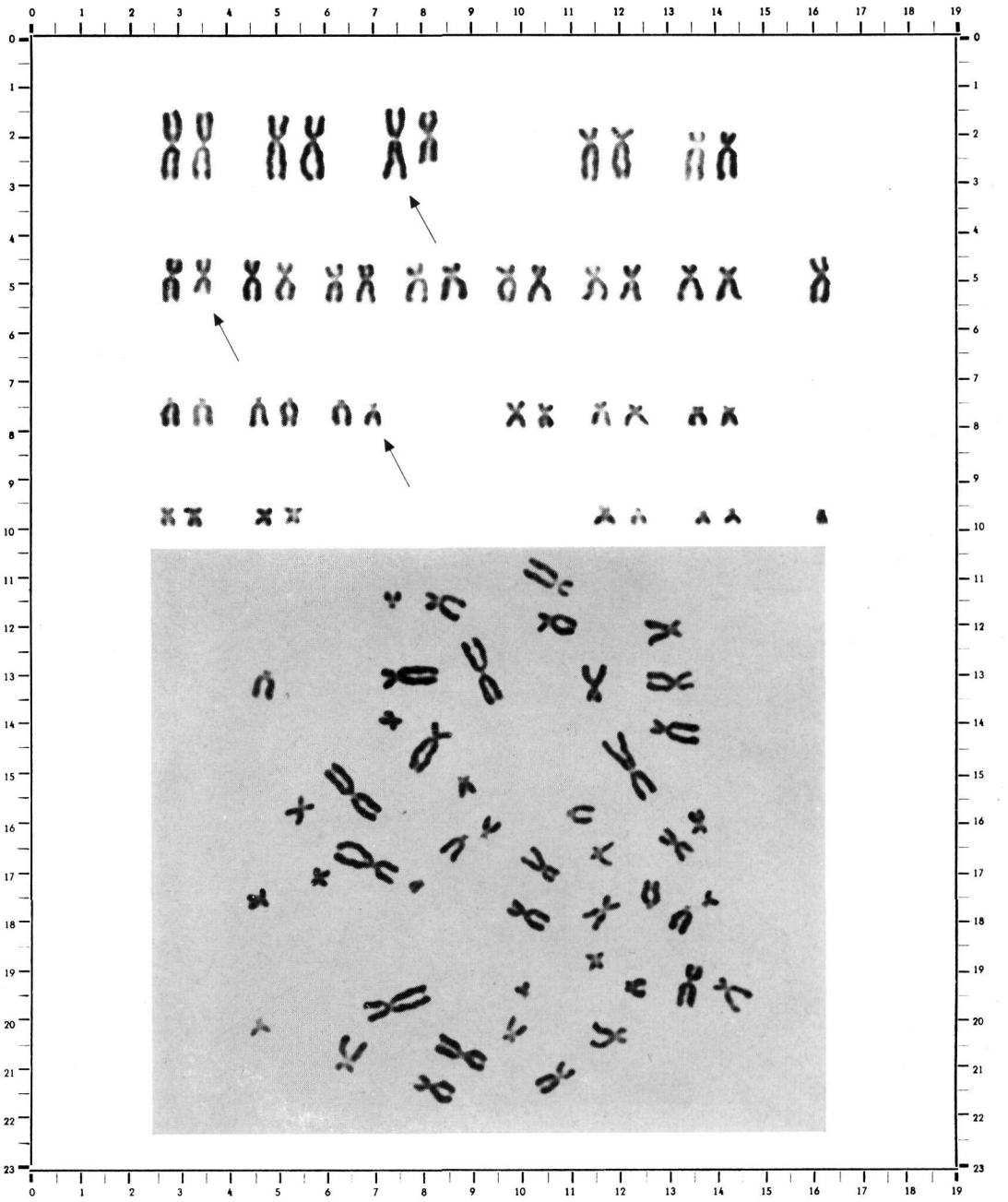

Fig. 15. 46,XY,3p+q+,Cq−,Dq−

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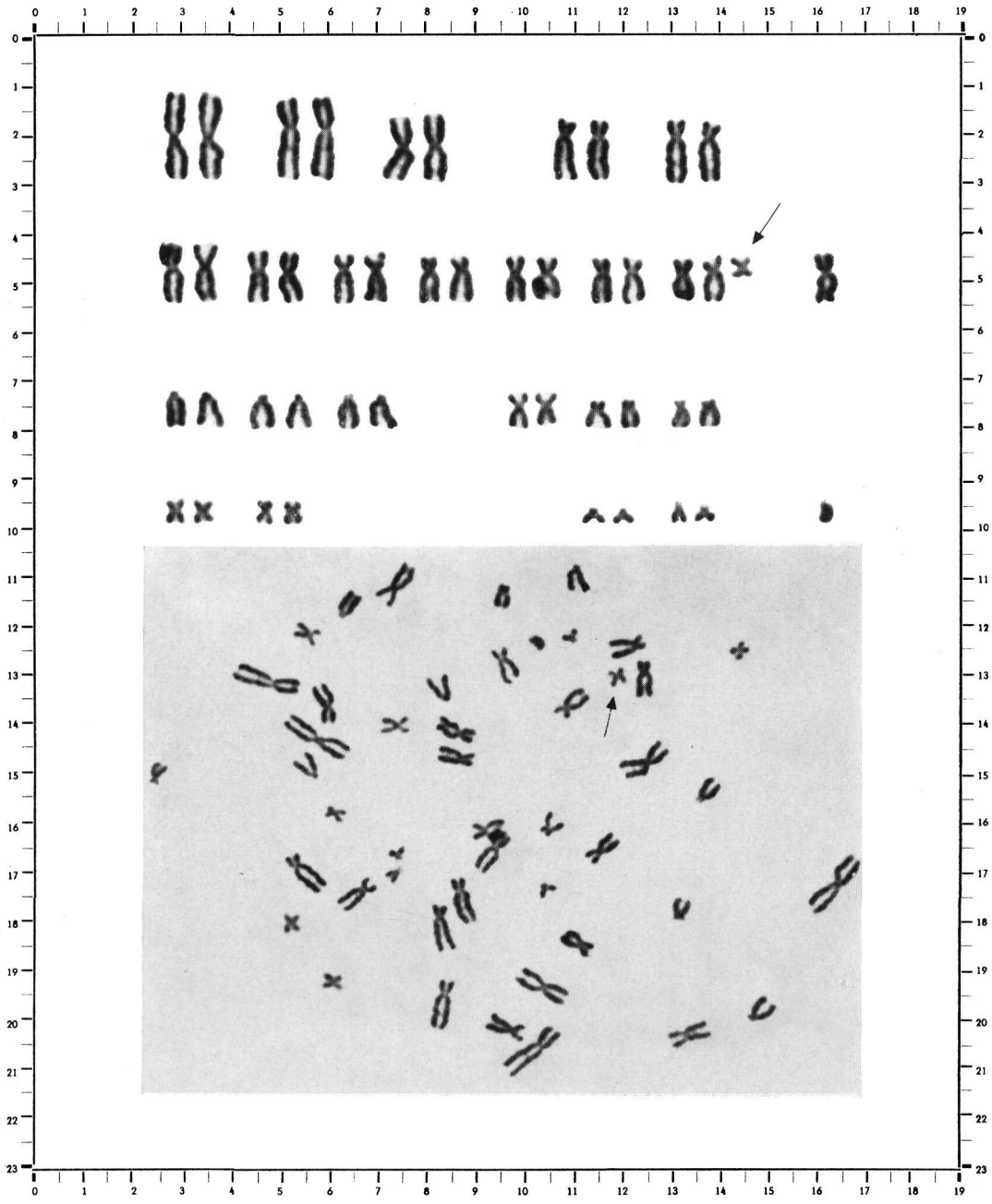

Fig. 16. 47,XY,t(Cq−)+

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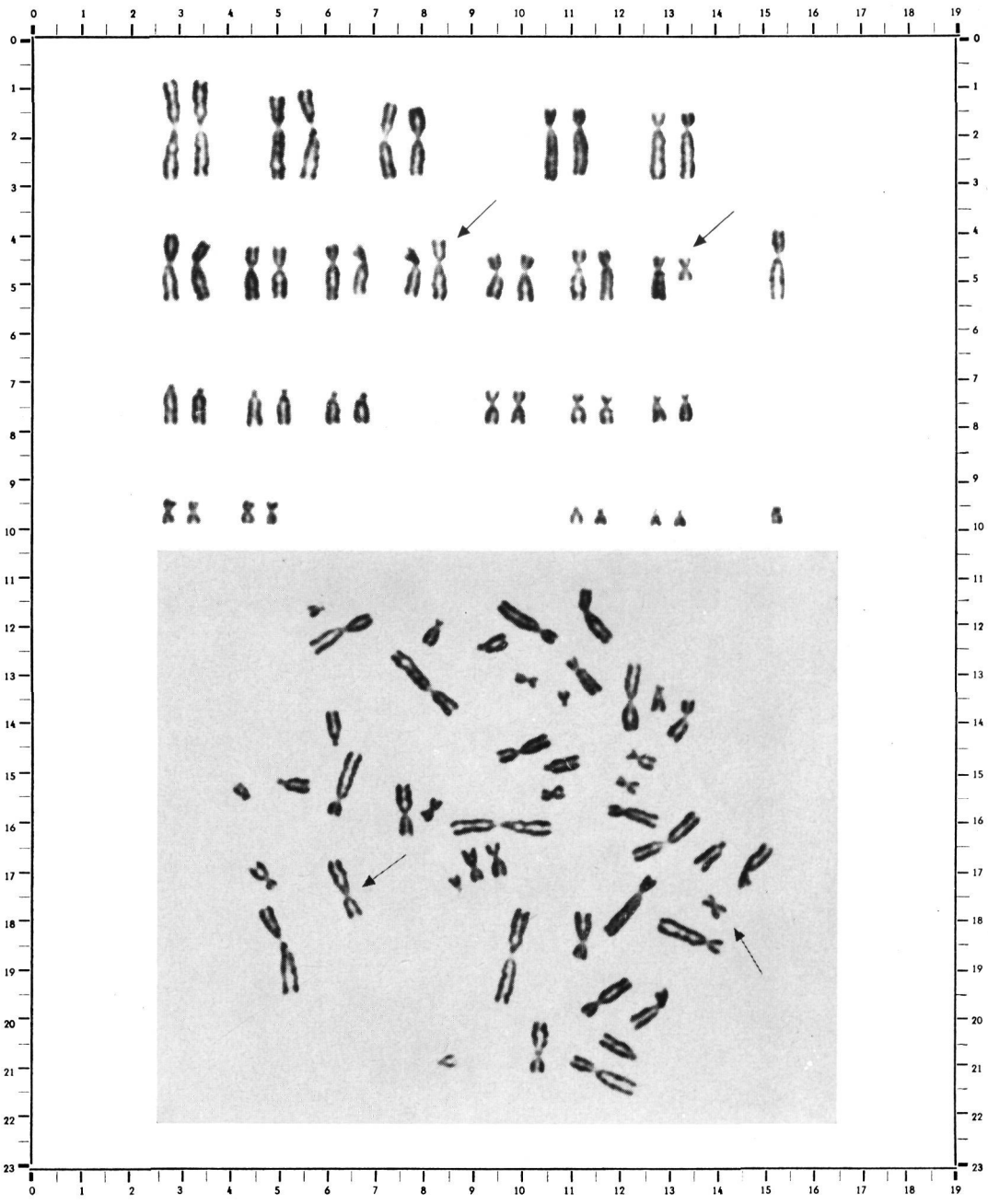

Fig. 17. 46,XY,C–,C–,t(9q12q)+,t(9p12p)+

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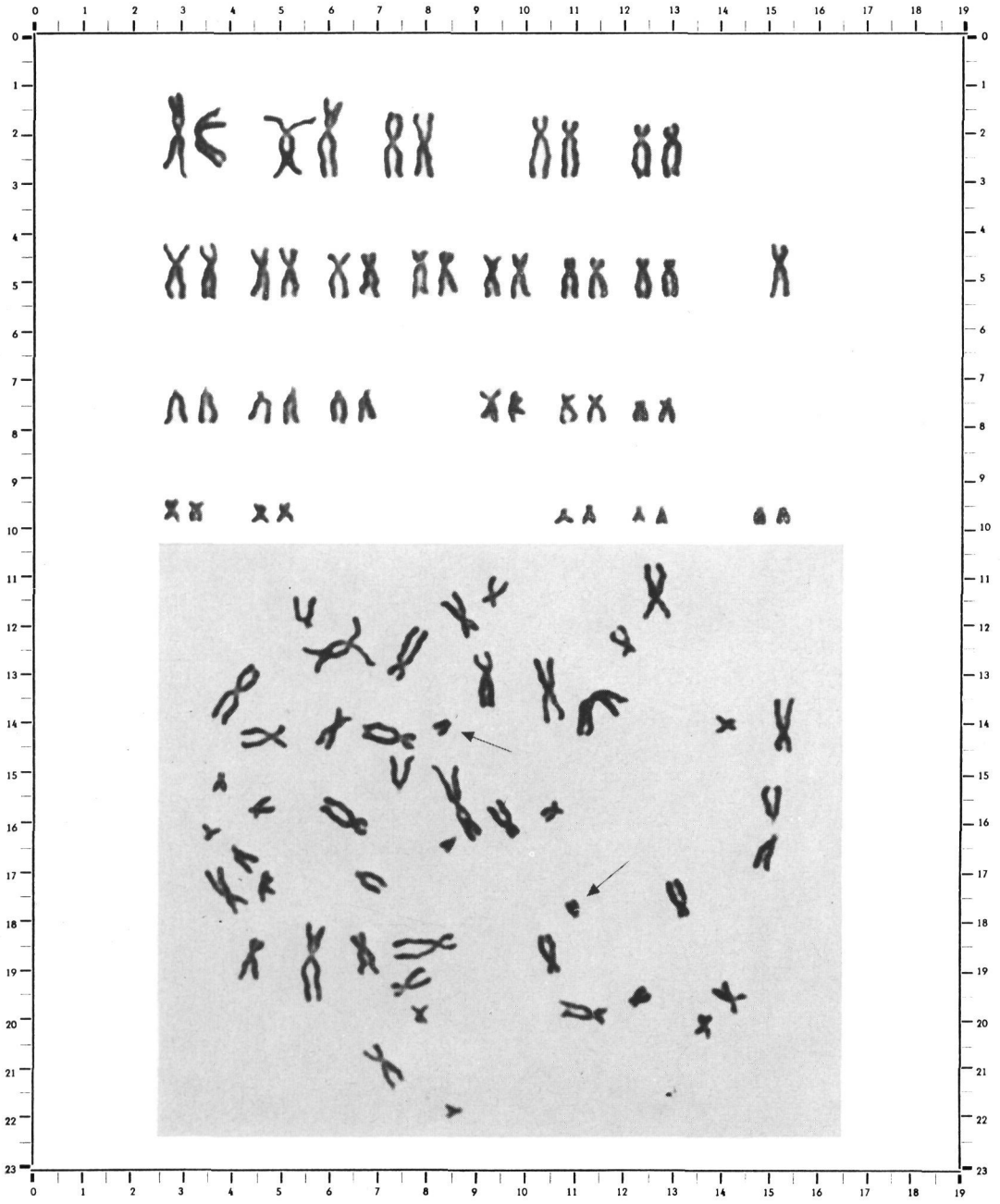

Fig. 18. 47,XYY

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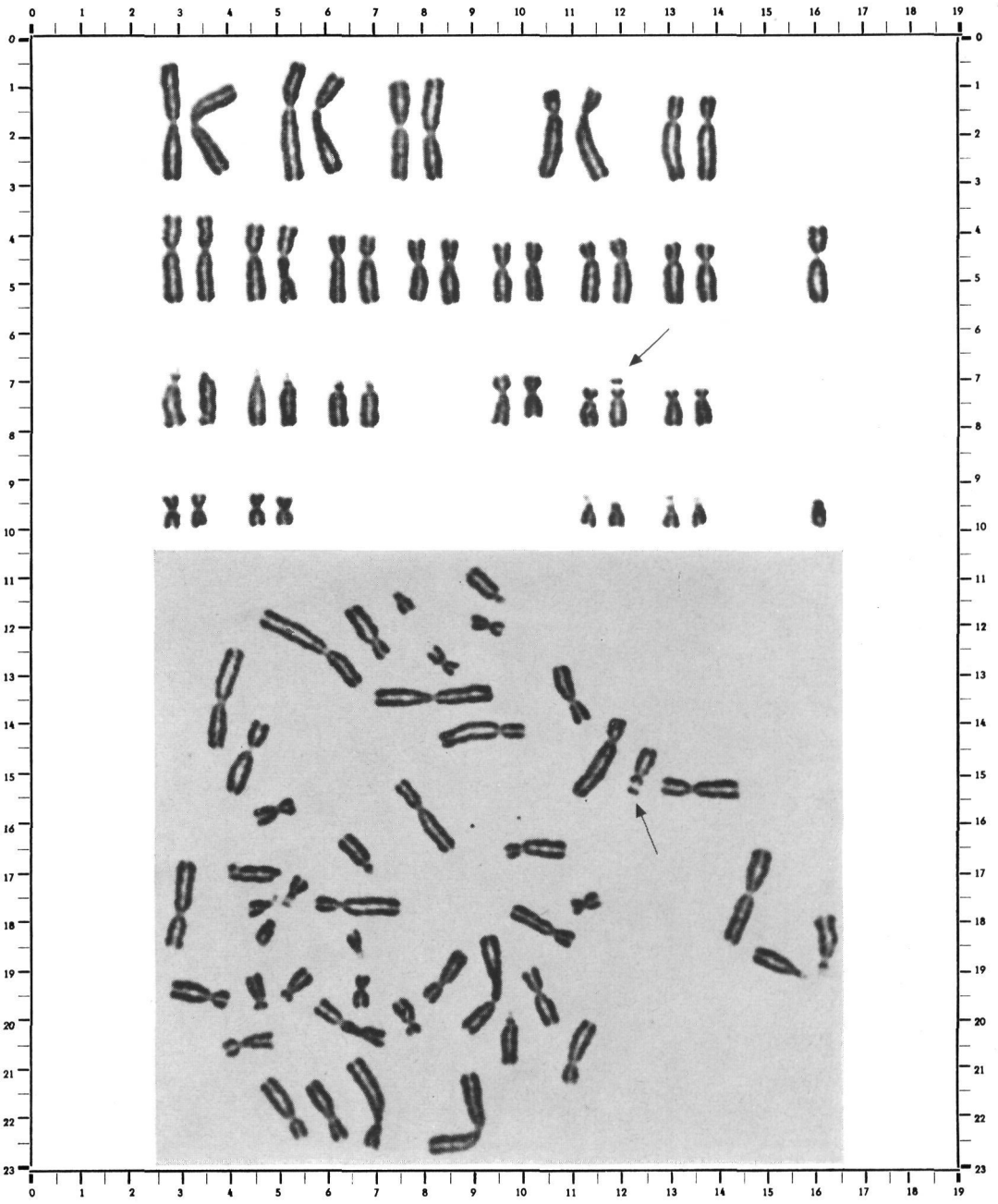

Fig. 19. 46,XY,E satellited

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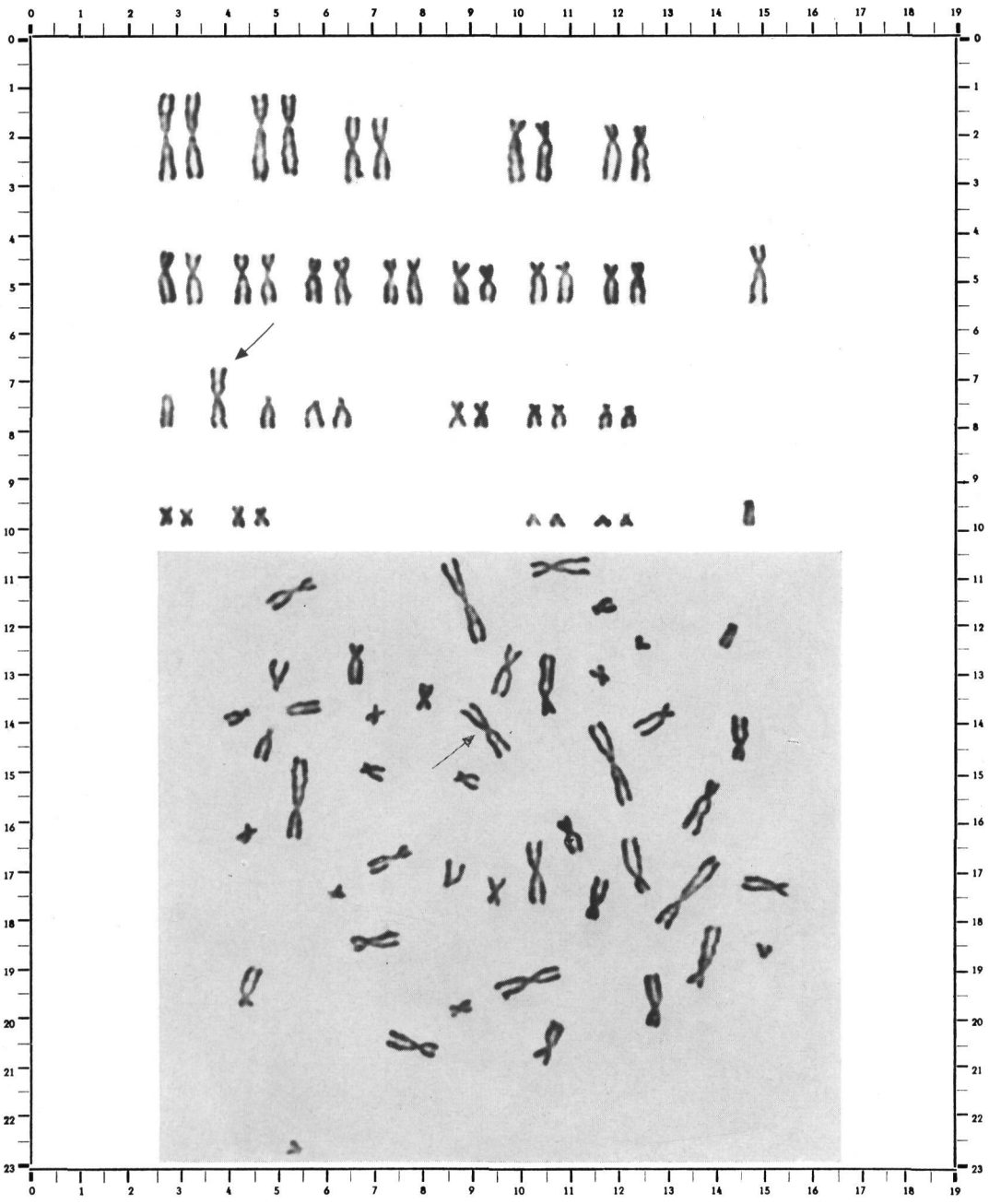

Fig. 20. 45,XY,D–,D–,t(DqDq)+,Yq+

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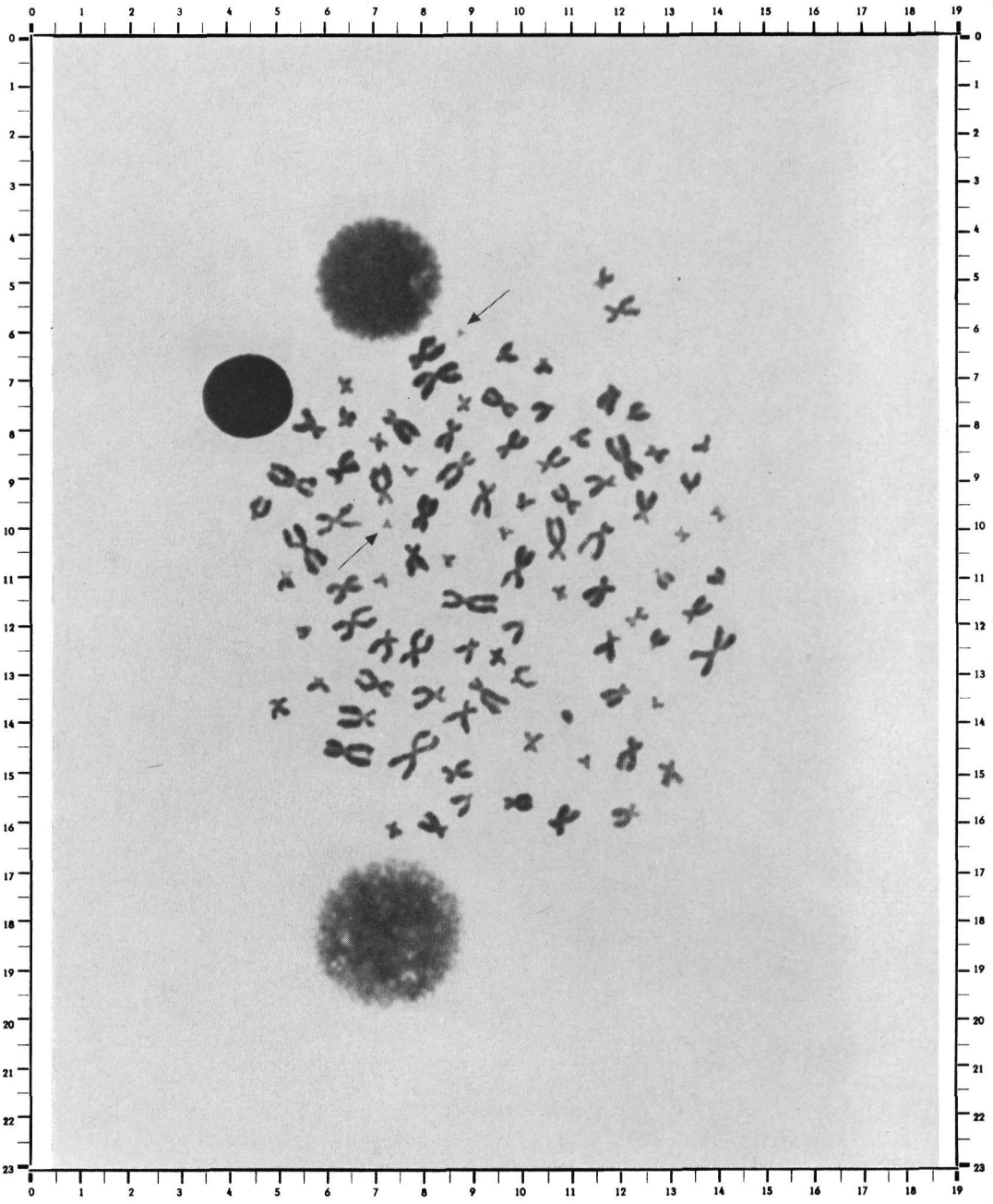

Fig. 21. Tetraploid mitosis. Ph chromosome indicated by arrows.

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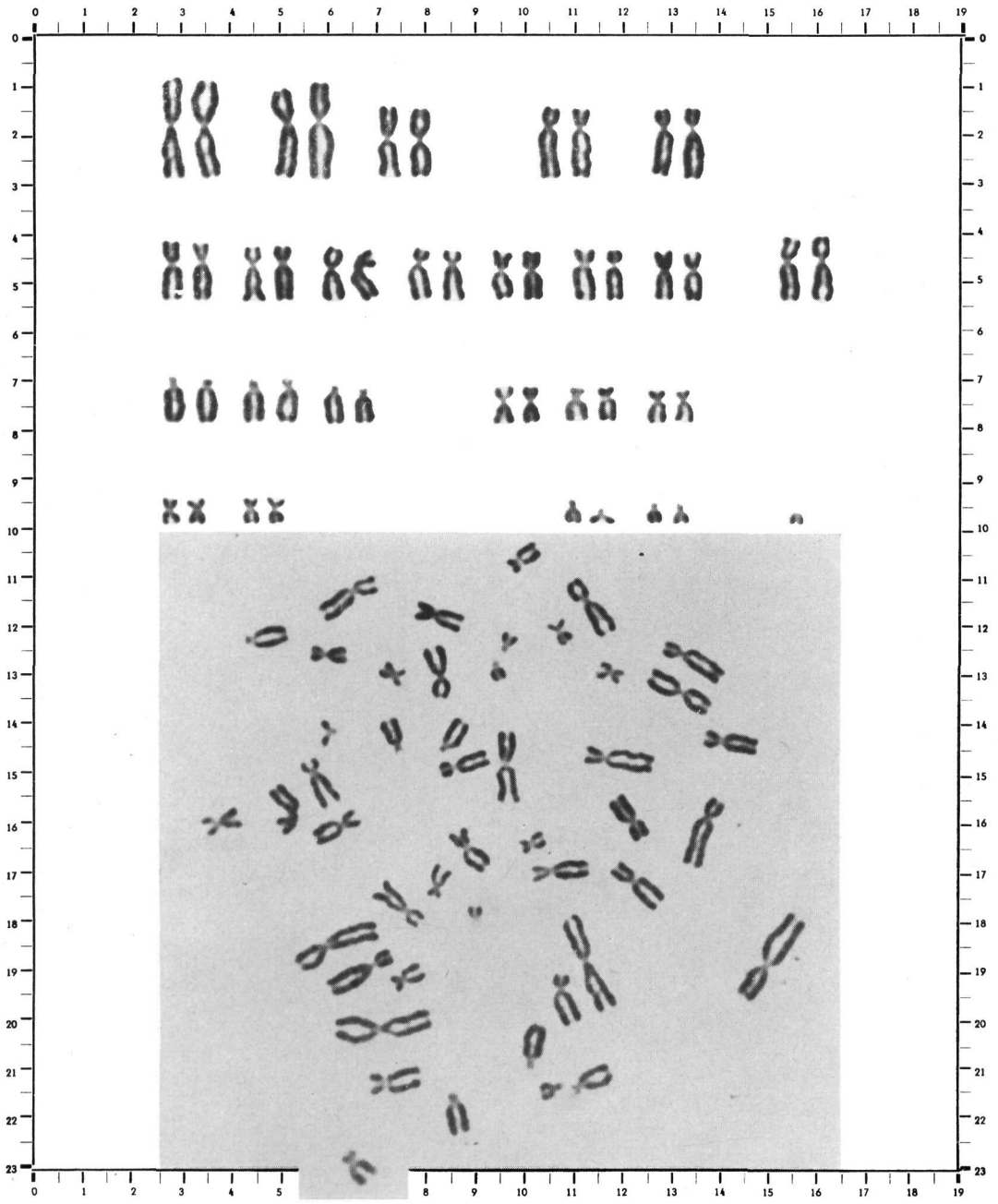

Fig. 22. 47,XXY

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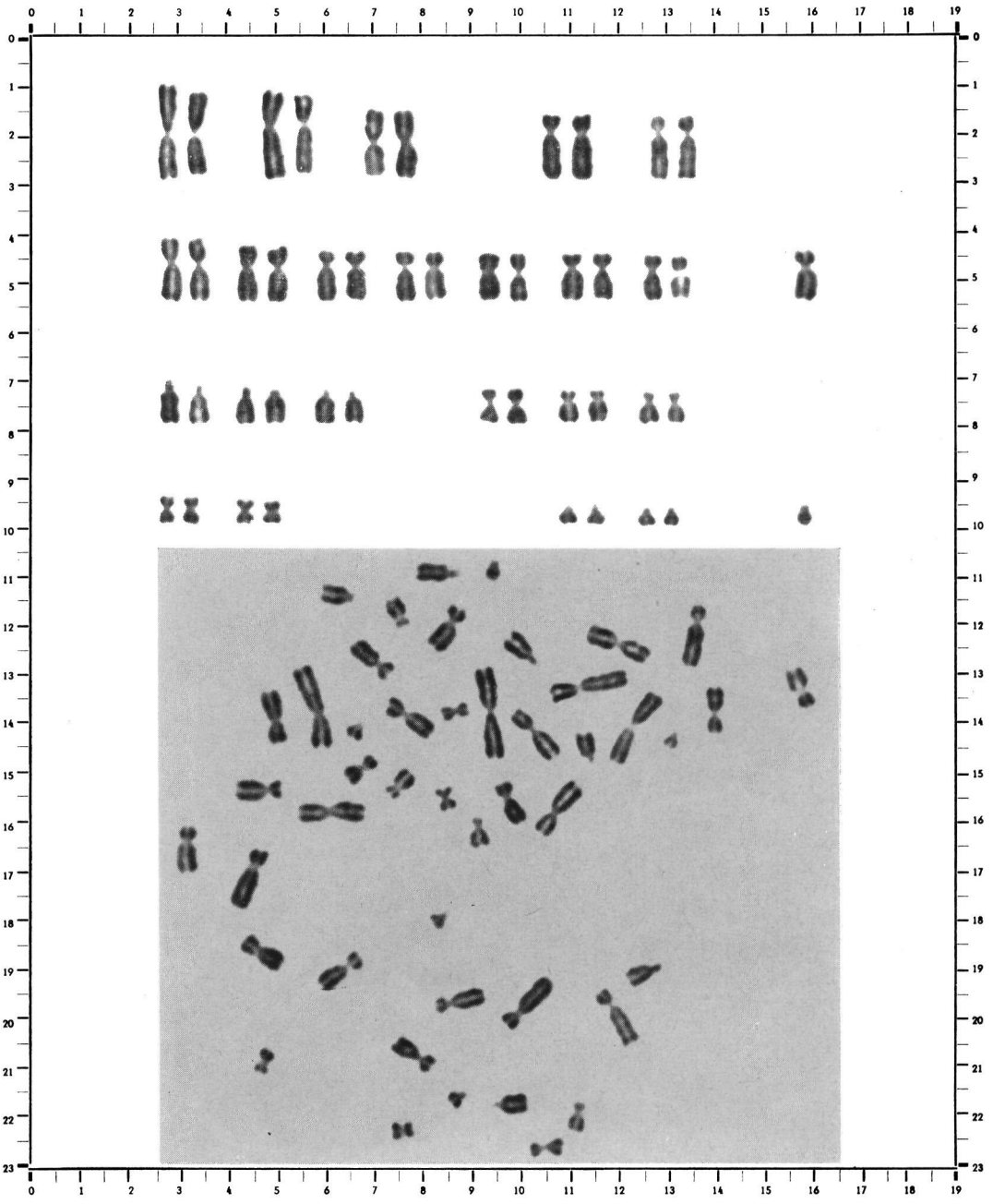

Fig. 23. 46,XY/47,XXY/48,XXXY mosaicism: 46,XY

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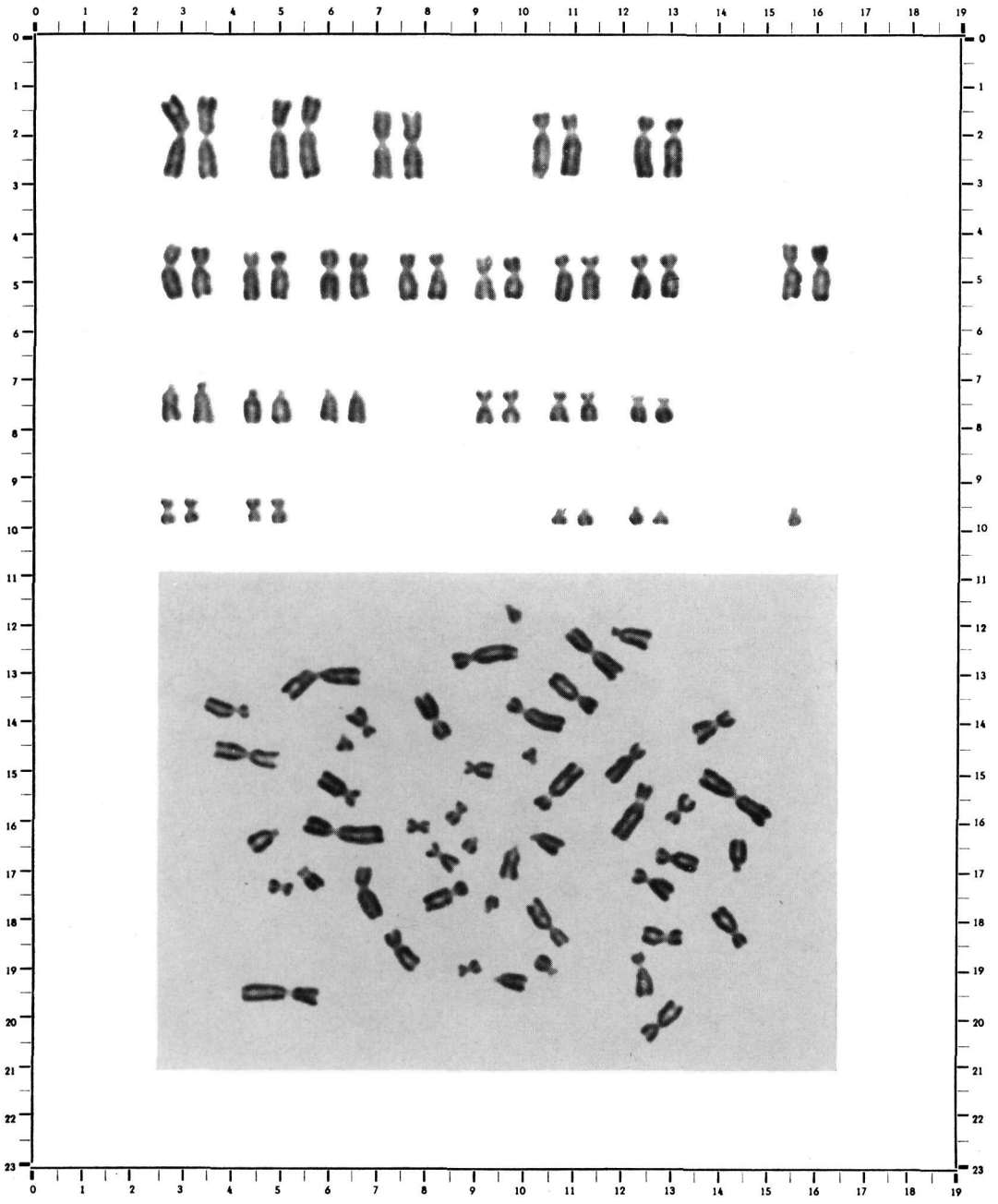

Fig. 24. 46,XY/47,XXY/48,XXXY mosaicism: 47,XXY

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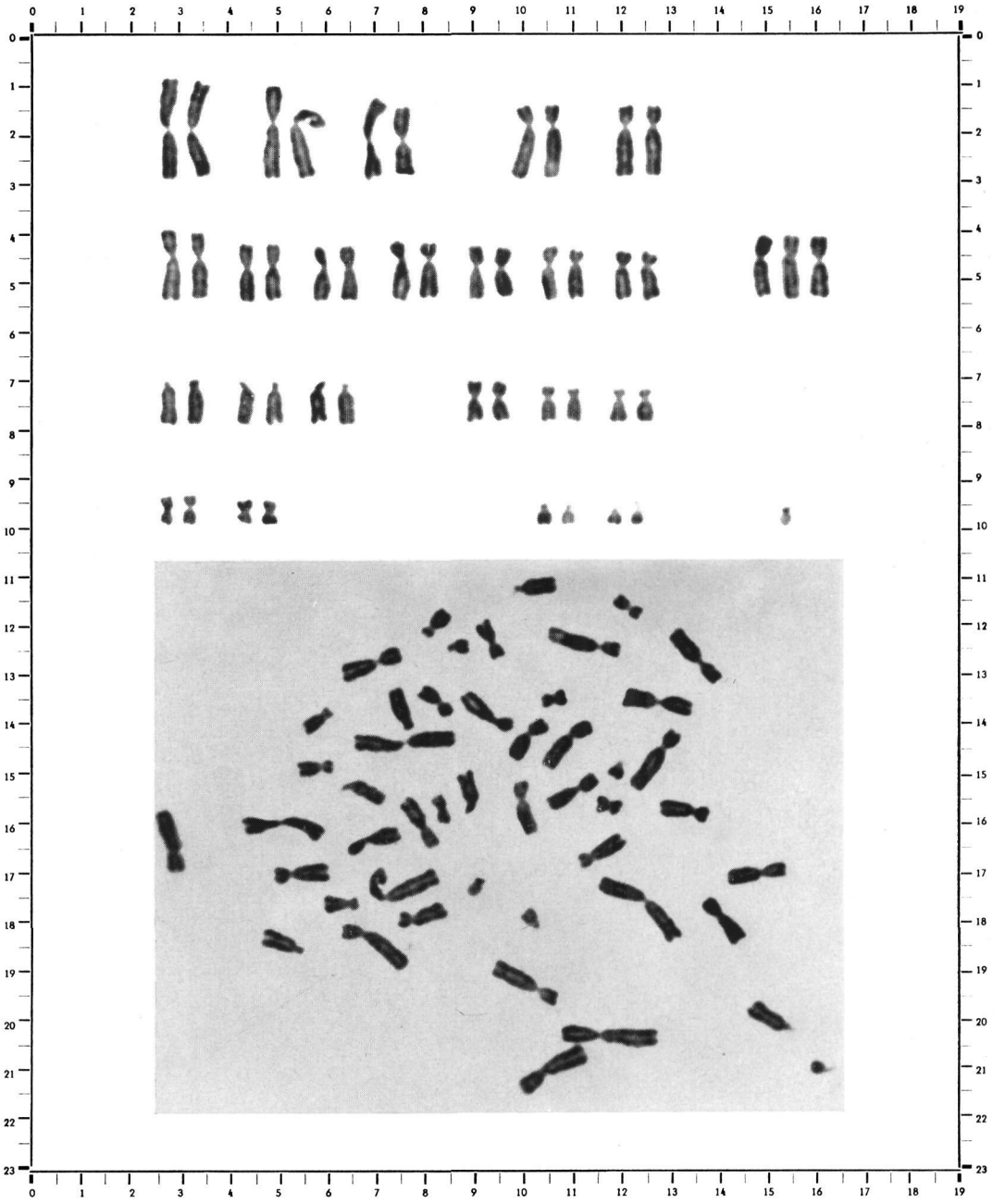

Fig. 25. 46,XY/47,XXY/48,XXXY mosaicism: 48,XXXY

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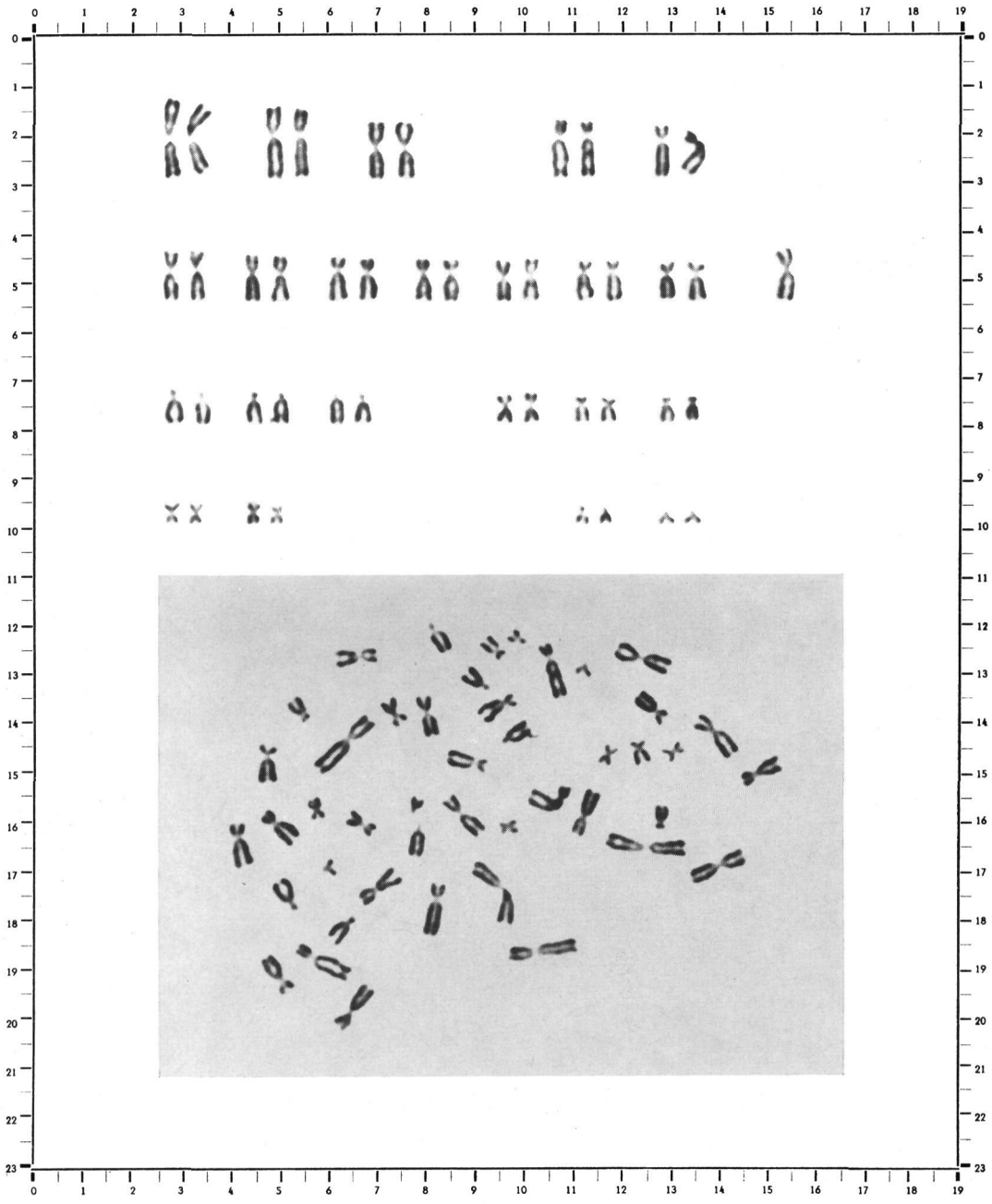

Fig. 26. 45,XO

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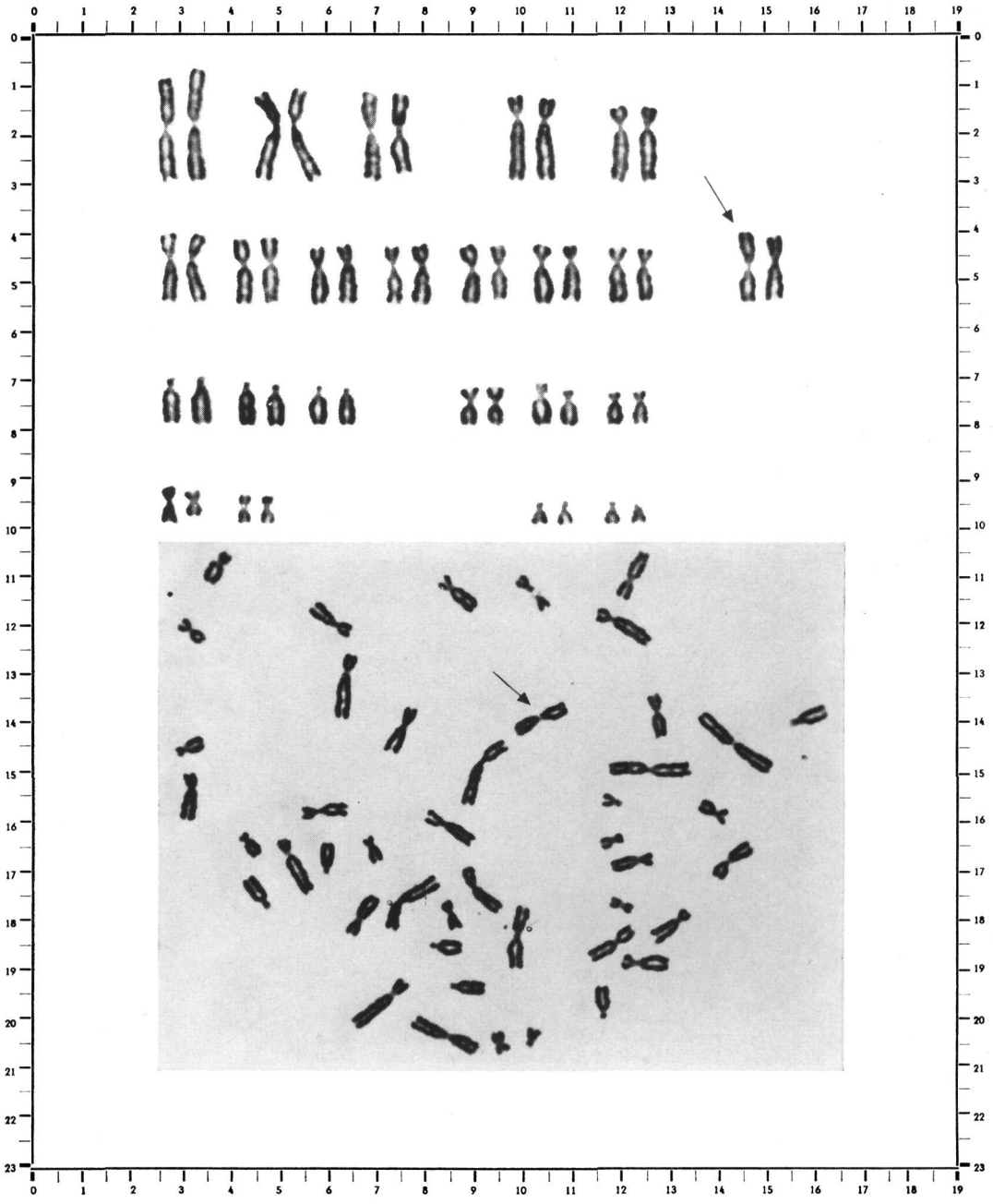

Fig. 27. 46,XX$_i$

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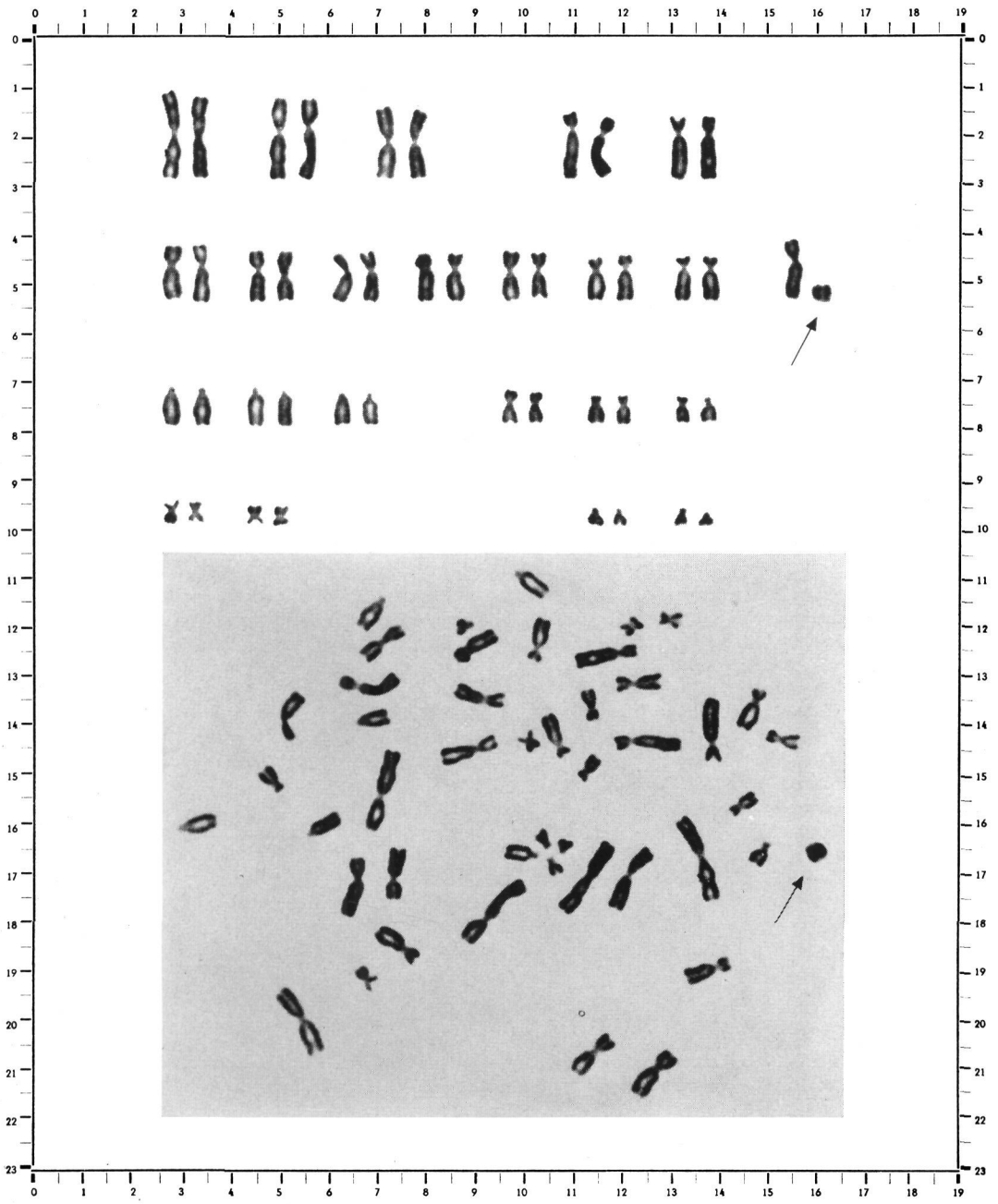

Fig. 28. 46,XX$_r$

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RIASSUNTO

Fin dal 1966 gli autori stanno conducendo un'indagine sulle anomalie cromosomiche. Fra i 1.551 soggetti finora esaminati sono stati individuati: 2 casi di traslocazione C/C, 1 di traslocazione D/C, 5 di traslocazione D/D, 9 di traslocazione D/G; 2 casi di sindrome di Patau con trisomia D; 5 casi di sindrome di Edwards; 176 casi di sindrome di Down, di cui 163 con trisomia G, 4 con mosaicismo, 7 con traslocazione D/G, 1 con traslocazione G/G e 1 con traslocazione C/G; 10 casi con cariotipo 47,XXY; 1 caso con mosaicismo 46,XY/47, XXY/48,XXXY; 4 casi con cariotipo 45,XO; 3 mosaici 45,XO/46,XX; 1 mosaico 45,XO/46,XY; 2 mosaici 45,XO/46,XX_r; 1 mosaico 45,XO/46,XX_i; 2 casi con cariotipo 47,XYY; 2 casi di sindrome di Morris; 5 casi di leucemia mieloide cronica con cromosoma Ph.

Inoltre, sono stati osservati diversi tipi di "normal variants", come: costrizione secondaria accentuata del cromosoma 9, "enlarged short arm" dei cromosomi D o G, eteromorfismo del 16, polimorfismo dell'Y, cromosoma E con satelliti.

RÉSUMÉ

Une recherche sur les anomalies chromosomiques a été conduite par les auteurs dès 1966. Chez les 1.551 sujets examinés on a relevé: 2 cas de translocation C/C, 1 de translocation D/C, 5 de translocation D/D, 9 de translocation D/G; 2 cas de syndrome de Patau avec trisomie D; 5 cas de syndrome de Edwards; 176 cas de syndrome de Down, desquels 163 avec trisomie G, 4 avec mosaïcisme, 7 avec translocation D/G, 1 avec translocation G/G et 1 avec translocation C/G; 10 cas avec caryotype 47,XXY; 1 cas avec mosaïcisme 46,XY/47,XXY/48,XXXY; 4 cas avec caryotype 45,XO; 3 mosaïques 45,XO/46,XX; 1 mosaïque 45,XO/46,XY; 2 mosaïques 45,XO/46,XX_r; 1 mosaïque 45,XO/46,XX_i; 2 cas avec caryotype 47,XYY; 2 cas de syndrome de Morris; 5 cas de leucémie myéloïde chronique avec chromosome Ph.

Des types différents de "normal variants" ont été observés, tels que: constriction secondaire accentuée du chromosome 9, "enlarged short arm" des chromosomes D ou G, hétéromorphisme du chromosome 16, polymorphisme du chromosome Y, chromosome E avec satellites.

ZUSAMMENFASSUNG

Verf. beschäftigen sich seit 1966 mit den Chromosomenanomalien in Italien. Bisher wurden 1551 Personen untersucht und dabei folgendes beobachtet: 2 Fälle von C/C-Translokation, 1 Fall von D/C-Translokation, 5 Fälle von D/D-Translokation, 9 Fälle von D/G-Translokation; 2 Fälle von Patau-Syndrom mit D-Trisomie; 5 Fälle von Edwards-Syndrom; 176 Fälle von Down'schem Syndrom (163 mit G-Trisomie, 4 mit Mosaizismus, 7 mit D/G-Translokation, 1 mit G/G-Translokation und 1 mit C/G-Translokation); 10 Fälle mit Karyotyp 47,XXY; 1 Fall mit Mosaizismus 46,XY/47,XXY/48,XXXY; 4 Fälle mit Karyotyp 45,XO; 3 Mosaike 45,XO/46,XX; 1 Mosaik 45,XO/46,XY; 2 Mosaike 45,XO/46,XX_r; 1 Mosaik 45,XO/46,XX_i; 2 Fälle mit Karyotyp 47,XYY; 2 Fälle von Morris-Syndrom; 5 Fälle von chronischer myeloischer Leukämie mit Ph-Chromosom.

Ausserdem wurden verschiedene Typen von "normal variants" beobachtet: betonte sekundäre Konstriktion des Chromosoms 9, "enlarged short arm" der Chromosomen D oder G, Heteromorphismus des Chromosoms 16, Polymorphismus des Chromosoms Y, E-Chromosom mit Satelliten.

Prof. E. BATTAGLIA, Direttore Istituto di Botanica dell'Università, Roma, Italy.