Uveal Coloboma and True Klinefelter Syndrome

J. FRANÇOIS,* M. Th. MATTON-VAN LEUVEN, and Ph. GOMBAULT

The clinical features of 'Klinefelter' syndrome were first described by Klinefelter, Reifenstein, and Albright (1942). The true Klinefelter syndrome is chromatin-positive and is due to X chromosome polysomy, most frequently 47,XXY (Jacobs and Strong, 1959), but karyotypes with one or more X's or Y's additional to the XXY formula, such as 48,XXXXY, 49,XXXXXY, and mosaicisms of XXY with other stem-lines, are variants of the syndrome (Barr et al., 1959; Ford et al., 1959; Fraccaro and Lindsten, 1960; Muldal and Ockey, 1960; Ellis et al., 1961; Harnden and Jacobs, 1961). The somatic abnormalities of the syndrome are relatively minor, especially at an early age and mostly only observed at or after puberty. They are: hypogonadism, testicular underdevelopment and atrophy (hyalinization of seminiferous tubules), inconstant gynaecomastia, and hormonal deviations, such as increased excretion of gonadotrophins. The following extragenital manifestations are frequent: poorly developed musculature, osteoporosis, skeletal anomalies, cutaneous angioma, and mental retardation.

The clinical picture of XXY and other variants is similar to that of XXY subjects, though there seems to be a higher frequency of additional congenital abnormalities.

The purpose of this paper is to report the presence of bilateral uveal coloboma in a 46,XX/47,XXY chromatin-positive boy.

Case History

This boy (H. Franky) was referred to us at the age of 4 months; he was the son of healthy but consanguineous parents (Fig. 1), both aged 23 years, after a full-term uneventful pregnancy. The mother had had one x-ray of the abdominal region at the age of 15 years after an injury. The child had seizures on the 5th day, which lasted 20 minutes. The temperature and blood calcium levels were normal.

Intramuscular administration of phenobarbital (25 mg.) was helpful. Three days later, there was sudden high fever and his general condition became poor, due to a urinary infection (Esch. coli) which was treated with 'pentrexyl'. The EEG was disturbed and showed paroxysmal bisynchronous spike waves. After a week the patient was free of fever and urography was normal. The EEG returned to normal.

The patient's physical and psychological development continued satisfactorily and he could walk without help at 12 months. The genitalia were normally developed for his age: both testes had descended since birth (Fig. 2).

Ocular examination. This revealed bilateral coloboma of the iris (Fig. 3) and choroid, more pronounced in the right eye, where it included the optic nerve. In the left eye, the macular region and optic nerve have been spared. Both fundi had an albinoid aspect, normal for his age.

The child was last seen at the age of 16 months. He was alert and his mental status seemed entirely normal. Careful questioning of the parents and personal examination of several members of the proband's and of the parents' generation did not reveal the occurrence of a colobomatous lesion or equivalent.

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FIG. 1. Consanguinity of the proband's parents.
FIG. 2. Outer genitalia.

FIG. 3. Bilateral iris coloboma.

FIG. 4. Karyotype with 2n = 47,XXY (propositus).

Cytogenetic examination. This was performed in leucocytes, cultured following a micromethod seen in Professor Lejeune’s laboratory. A total of 75 cells was analysed numerically. In 5 cells, 2 or more chromosomes had been lost during the technical in vitro manipulations. In the remaining 70 cells, 2n was distributed as follows: 45: 8%, 46: 37%, 47: 49%, and 48: 6%. In each of these groups, karyotypes were analysed (28 in total). Of the cells with 2n=47, 11 karyotypes were prepared. They constantly were 47,XXY (Fig. 4). Of the cells with 2n=46, 12 karyotypes were analysed: 10 of them were 46,XX (Fig. 5) and 2 of them were 46,XY. Of the cells with 2n=45, 3 karyotypes were analysed: 2 of them had lost an autosome each in a different group and could be interpreted as 45,XX; the remaining one had an autosome missing in the C group and could be interpreted as 45,X. Of the cells with 2n=48, 2 karyotypes were prepared: one could be interpreted as 48,XXXXY and the other possibly as 48,XXYY.

The sex chromosomal configuration is thus distributed in the 28 karyotypes as follows: XX in 12 karyotypes (43%); XXY in 11 (39%); XY in 2 (7%); XXXY in 1 (3.5%); XXYY in 1 (3.5%); XO in 1 (in vitro loss?) (3.5%).

Structurally, the chromosomes were normal. In many karyotypes, however, the Y chromosome had long long arms. The mean Y/F index, i.e. the total length of the Y expressed as a ratio of the mean total length of the F chromosomes, was 0.96. The karyotypes were the result of three different blood cultures: the first time only XXY karyotypes were obtained. As the quality of the metaphases was not very good, a second blood culture revealed a high majority of cells with 46,XX. A third culture revealed a majority of cells with 47,XXY.

The sex chromatin was evaluated in buccal mucosa on three occasions by the same observer: the first time Barr bodies were seen in 12% of the cells (orcein stain), the
second time in 16% (orcein stain), the third time in 10% (Shorr stain). These results indicated the presence of two X chromosomes.

The drumstick evaluation revealed 0-4% polymorphs with a drumstick appendage. The lobulation of the polymorphs was extremely low.

Cytogenetic evaluation was also performed in the patient's parents. The karyotype of the mother was normal (46,XX), both numerically and structurally. The karyotype of the father was numerically normal (46,XY). Structurally, most karyotypes showed a long Y chromosome, the relative length of which was generally even longer than in the proband (Fig. 6). The mean Y/F index was 1.13.

Dermatoglyphic examination (Table I). This was carried out on the proband and his parents.

Total finger ridge count. Proband, not determined; ulnar loops on all fingers, except on right thumb on which a whorl was present. Father, 68; mother, 146.

Axial triradius and atd angle. Proband, distal displacement to position t', more pronounced on the left hand; atd right, 57°; atd left, 68°. Father, triradius in position t; atd right, 43°; atd left, 40°. Mother, distal displacement of axial triradius to position t'; atd right, 48°; atd left, 54°.

Digital triradii. Proband, left hand; triradius c absent. Father, all present; mother, all present.

a-b ridge count. Proband, right 32, left 40, summed 72. Father, right, not counted because of burn scars; left 40. Mother, right 37, left 37, summed 74.

TABLE I

<table>
<thead>
<tr>
<th>FORMULAE OF DERMATOGYPSH</th>
<th>Main Line Index</th>
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<tbody>
<tr>
<td>Proband</td>
<td></td>
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<tr>
<td>(Right)</td>
<td>11.9.7.5.13.r'.O.O.O.L.O</td>
</tr>
<tr>
<td>(Left)</td>
<td>11.9.0.5.13.r'.O.O.O.O.O</td>
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<tr>
<td>Father</td>
<td></td>
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<tr>
<td>(Right)</td>
<td>Not determined</td>
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<tr>
<td>(Left)</td>
<td>11.7.3.13.r.O.O.O.O.L</td>
</tr>
<tr>
<td>Mother</td>
<td></td>
</tr>
<tr>
<td>(Right)</td>
<td>9.9.5.5.13.r'.O.O.O.L.D</td>
</tr>
<tr>
<td>(Left)</td>
<td>11.9.7.5.13.r'.O.O.O.O.L.O</td>
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Discussion

A: Sex Chromosomal Anomalies

The sex chromatin values suggested the presence of two X chromosomes. The extremely low nuclear lobulation of the polymorphonuclear leucocytes, observed in our proband, has been reported as typical for Klinefelter syndrome (Mittwoch, 1964; Froland, 1969).

The blood cultures revealed the presence of two main cell lines of about equal importance: 46,XX/47,XXY. The XX/XXY type of mosaicism has been reported a few times in the Klinefelter syndrome (Ford et al., 1959; Hayward, 1960; Rohde, 1963; Court Brown et al., 1964).
Three questions have to be answered:

(1) Do these two cell lines exist in vivo?
(2) If they exist in vivo, how did they arise and how are they distributed in the patient?
(3) Have the minor cell lines 45,X, 46,XY, 48,XXXY, and 48,XXYY originated in vitro through erroneous mitoses, or do they also exist in vivo?

Though the different ratios obtained in the three cultures might indicate the origin or the preferential growth of one of the cell lines in vitro, we feel that the two main cell lines exist in vitro and that the patient's karyotype is 46,XX/47,XXY. Indeed, our results were obtained from short-term blood cultures in which only one or two mitoses take place, and in which it is less likely than in long-term fibroblast cultures that selective forces for preferential growth for one or other cell line play an important role, or that a cell line with a karyotype other than the original one arises.

There are two ways in which the two main cell lines may have arisen in the patient.

(1) From an XY zygote. This hypothesis requires the occurrence of at least 2 successive mitotic errors: (a) mitotic nondisjunction of the X chromosome at the first division of the XY zygote, with production of XXY and YO cells and loss of the non-viable YO cell; (b) further early post-zygotic mitotic error, i.e. the loss of a Y chromosome at division of an XXY cell with production of XXY and XX cells.

(2) From an XXY zygote. This requires the subsequent occurrence of two different pathological conditions: an imbalanced gamete and erroneous somatic mitoses at or shortly after the first cleavage division.

(a) Imbalanced gamete. As the parents' karyotypes were normal, the possibility of a parental numerical chromosomal abnormality can be ruled out. The possibility of a gametogenetic error can neither be proved nor rejected. The hypothesis of meiotic nondisjunction could not be substantiated by data on the parents' ages which were normal (i.e. both 23 years), or by other cases of aneuploidy in the family, or by a history of a virus infection of the mother. The X-ray examination of the abdominal region at the age of 15 years can be rejected as responsible for an erroneous cell division taking place years later at ovulation.

The father had, however, an unusually long Y chromosome. The question whether such a Y can determine abnormal behaviour of the XY bivalent at meiosis with consecutive nondisjunction is not yet solved. More reports on the presence of long Y chromosomes in the families of aneuploid patients are needed to evaluate a possible causal relation.

In order to have an idea of the variation of the length of the Y chromosome in the Belgian population, we determined the Y/F index in the karyotypes of 120 males who were referred to our laboratory, either as patients or as normal relatives of affected subjects. This control series had a Y/F index = 0.87 ± 0.16.

Data from published reports on the Y/F value are as follows: 0.88 ± 0.11 in Asiatic Indians, 1.00 ± 0.15 in Japanese, 0.92 ± 0.09 in American Negroes, 0.94 ± 0.10 in Jews of eastern European extraction, and 0.86 ± 0.09 in non-Jews of Anglo Saxon origin (Cohen, Shaw, and MacCluer, 1966). In Japan, the Y/F was reported to vary between 0.78–0.93 in control patients with a normal Y, and between 1.07–1.56 in patients with a long Y (Makino et al., 1963; Tomonura and Ono, 1963; Makino and Takagi, 1965).

Though it is mostly accepted that a long Y chromosome is a variation of the normal karyotype, its presence in association with somatic and genital malformations, and also in association with other karyotypic anomalies, might indicate a possible adverse effect. Association of a long Y chromosome with sexual anomalies was reported by Van Wijck, Tijdink, and Stolte (1962), de la Chapelle and Hortling (1963), Gropp et al. (1963), Gustavson et al. (1964b), Makino et al. (1964), Makino and Takagi (1965), Kjessler (1966), Fraccaro et al. (1966), Nusso et al. (1967), Beer, Pfeiffer, and Dammmer (1967), and Dumars and Fisher (1968). Association of a long Y chromosome with other cytogenetic abnormalities was observed in trisomy 21 (de la Chapelle and Hortling, 1963; Jacobs and Harnden, cited by Penrose, 1961; Bishop, Blank, and Hunter, 1962; Gripenberg, 1964; Makino and Takagi, 1965). Familial occurrence of a long Y chromosome in families with a mongoloid proband was noted by Bishop et al. (1962), Dekaban, Bender, and Economos (1963), and Makino et al. (1963).

A mosaic karyotype similar to the one found in our patient, 46,XX/47,XXX, where the Y chromosome was long, was reported by Burgio, Severi, and Biscatti (1965) in a patient with a right endo-abdominal testis and left gonadic agenesis.

Comparison of the Y/F index of our proband (0.96) and of his father (1.13) with, on the one hand the data from published reports, and on the other hand the values in the Belgian controls, shows that the father certainly has a longer Y chromosome than normal, but that the proband, though at the upper limit, is still within the normal variation. This is a
puzzling fact. However, in the karyotypes which showed 5 chromosomes in the G group, the 5th chromosome was interpreted as a Y. Indeed, if there were an autosomal anomaly, the child would be expected to be mentally retarded, which is not the case in our proband. The child is well developed both physiologically and psychologically and is by no means mentally retarded.

(b) Mitotic error in the 47,XYY foetus, early post-zygotic after the first cleavage division, such as the following:

(i) Somatic non-disjunction of 47,XY cells with production of either 48,XXXXY and 46,XY cells or 46,XX and 48,XXYY cells. This is not very likely in view of the percentages obtained for the different cell lines.

(ii) Direct loss of a Y chromosome giving rise to 47,XXY and 46,XX cells, which is more likely to have occurred.

The percentages suggest that whether the karyotype of the zygote was 46,XY or 47,XXY, a divisional error (including loss of a Y chromosome) must have occurred very early, resulting in the production of 46,XX and 47,XXY cell lines in about the same quantity.

Mitotic errors may have occurred occasionally in the XXY cells, with production of the minor cell lines, 45,X, 46,XY, 48,XXXXY, and 48,XXYY, either very late in embryonic life or in vitro during culture. In view of the extremely low frequency of these cell lines, it was impossible to judge whether they represented true mosaicism or accidental deviations. The 46,XY configuration was indeed found only in two and the 48,XXXXY, 48,XXYY, and 45,X configurations, respectively, only in one karyotype, whereas the 47,XXY and 46,XX cells represented the great majority of cells.

It was impossible to perform a skin or fascia biopsy so that the frequency of the different cell lines in tissue other than blood could not be studied. In any case, blood mosaicism indicates that the error must have occurred at or before the gastrula stage, i.e. around or shortly after the 14th day.

The clinical picture of mosaic patients is probably less dependent on the number of cell lines than on the relative frequency of the cells in each cell line. This frequency depends on the stage of embryonic development at which the non-disjunction which causes the mosaicism takes place. The earlier mosaicism originates in embryonic life, the more severe probably is the influence on the phenotype. The relative influence of the different cell lines will only become evident at puberty. Repeated cultures are sometimes necessary in order to reveal the existence of mosaicism. A mosaic pattern can indeed be overlooked if an inadequate number of cells is counted. We can compare in this respect our patient with the patient reported by Hecht et al. (1966) who was originally described as a 46,XX patient without Y chromosomes, in whom, when further investigations were carried out, a mosaic cell line (1%) was detected.

B: Coloboma

Coloboma results from abnormal closure of the foetal cup cleft soon after gastrulation at the end of the first or the beginning of the second foetal month, when the optic vesicle is in an active stage of differentiation (Duke–Elder, 1940; Mann, 1957). This faulty development of the ectodermal eye structures can be caused by chromosomal, Mendelian, and environmental intrauterine teratogenous factors.

(i) Chromosomal anomalies. Coloboma and other eye defects have been found in anomalies of all the autosomal groups and are not specific for any particular chromosomal abnormality: A group (Lele, Dent, and Delhanty, 1965; El Massri and Riad, 1965), B group (Hirschhorn and Cooper, 1961; Hirschhorn, Cooper, and Firschein, 1965; Gustavson et al., 1964b; Shaw, Cohen, and Hildebrandt, 1965; Wolf et al., 1965; D. Jesberg, personal communication, 1966), C group (Salonius and Opitz, 1964), D group (Patau et al., 1960), and E group (François et al., 1965; D. Jesberg, personal communication, 1966).

Colobomatous lesions of the eye ball have not been found in trisomy 21.

A t(B/G) translocation trisomy was found in a child with multiple anomalies among which were blepharophimosis and colobomata of the irides (Gustavson et al., 1964a). Uveal colobomata are part of the oculo–anal syndrome, which is caused by an extra small submedian chromosome in girls with mongoloid slant of the eyelids, hypertelorism, microphthalmia, anarasia, recto-vaginal fistulas, pre-auricular fistulae, renal malformations, and mental retardation (Schachennmann et al., 1965; Cagianut, 1968).

Colobomata were also found associated with oligophrenia, various congenital abnormalities, exotropia, myopia, and the presence of a small extrametacentric chromosome in a sex chromatin-negative boy (Heimann, Jaeger, and Dollmann, 1968).

The importance of a chromosome aberration as a causal factor should not be overstressed.

(i) In the case of autosomal aberrations, the coloboma is only part of the general pathological condition.
(ii) Chromosomal aberrations are usually absent in cases of isolated coloboma with an otherwise normal phenotype.

(iii) When a coloboma is found in association with a chromosomal peculiarity, but when the latter is also present in one of the phenotypically normal parents (Lele et al., 1965), the causal relation between the coloboma and the chromosomal peculiarity becomes doubtful.

(iv) There exist several reports of coloboma patients with associated multiple congenital malformations, who had a normal karyotype (Edwards, Young, and Finley, 1961; Angelman, 1961).

In sex chromosomal aberrations, ocular anomalies are infrequent and uveal coloboma is exceptional.

In the Klinefelter syndrome the eyes are usually normal. Other severe somatic malformations are also extremely infrequent. A possible explanation is that the major part of the extra X chromosome is genetically inactivated. Out of the impressive bibliography on Klinefelter syndrome, including review studies on large series (Court Brown et al., 1964; Froland, 1969), on smaller series, and the numerous individual case reports (Nowakowski, 1961; de la Chapelle and Hortling, 1963; Prader, Mürset, and Hauschrecke, 1964, etc.), totaling 400–500 karyotyped or sex chromatin typed Klinefelter patients, the following ocular morphological features were noted.


48,XXYY karyotype. Severe myopia (Ferguson-Smith, Johnston, and Handmaker, 1960).

49,XXXXY karyotype. Esotropia and myopia (−18D) (Anders et al., 1960), hypertelorism (Fraccaro, Klinger, and Schutt, 1962; Barr et al., 1962), hypertelorism, epicanthus, strabismus internus concomitans, myopia (−3D) (Pfeiffer, 1962), alternating esotropia and hypertropia caused by obvious overaction of the inferior obliques (Atkins and Connelly, 1963), conspicuous epicanthus (Farquhar and Walker, 1964), hypertelorism, palpebral fissures, slanting downwards and medially (Joseph, Anders, and Taylor, 1964), strabismus (Fraser et al., 1961), divergent strabismus and hypertelorism (Barr et al., 1962), strabismus, bilateral coloboma of iris and optic nerve (Joannides and Tsenki, 1968), pronounced epicanthus (Froland, 1969, case 47), pronounced epicanthus, slight hypertelorism, alternating external strabismus, high myopia (−20D), and myopic fundus degeneration (Freeland, 1969, case 48).


48,XXYY karyotype. Cataract, strabismus, high myopia, and choroidal atrophy (Laurence, Ishmael, and Davies, 1963), epicanthus (Miroouze et al., 1964), myopia (Herbeuval et al., 1965), iris aplasia (Warburg, 1968), prominent supra-orbital ridges (Ellis et al., 1961). In a case of Amalaric et al. (1966) there was an uveal dystrophy: iris atrophy and atrophic insertion of this iris root. The iris atrophy was more pronounced in the periphery. The sphincter zone was yellow. The zone of the dilator muscle fibres was grey. This bicolour iris atrophy reminded one of the atrophies found in genetic mesodermal syndromes. Atrophy in the chamber angle was especially pronounced between 4 and 6 o’clock. The iris root continued there only in a thin grey-yellow strip, attaching itself very high up. This atrophic iris insertion masked all the underlying structures.

Mosaic karyotypes

48,XXYY/49,XXXXY: epicanthus, right iris coloboma, and bilateral choroidal colobomata adjacent to the papilla in a 48,XXYY/71,XXXXY infant with peculiar facies, syndactyly, and multiple minor malformations (Schmid and Vischer, 1967).


47,XXYY/48,XXYY: Prominent supra-orbital ridges and myopia (Spencer, Eyles, and Mason, 1969), prominent supra-orbital ridges and optic atrophy (Spencer et al., 1969).

48,XXXXY/49,XXXXY/50,XXXXXY: high myopia (−18D) and convergent strabismus (Anders et al., 1960).

Long Y: coloboma, developmental errors of the brain and the heart, cleft scrotum, small penis, in a child in whom ‘preliminary investigations pointed to some chromosome abnormality’ (Angelman, 1961): the boy had 46 chromosomes, but had a larger Y than normal (H. Angleman, personal communication, 1969).

47,XXYY + chromosome resembling a no. 15: myopic astigmatism (Nowakowski, 1961: Case 9), myopia (Nowakowski, 1961: Case 11).

This review shows that the association of coloboma with Klinefelter syndrome has been reported only three times (Appelmans et al., 1965; Schmid and Vischer, 1967; Joannides and Tsenki, 1968). To our knowledge, our proband is the fourth case.

In this connexion it is interesting to note that the peculiar iris observed by Amalaric et al. (1966) in the 48,XXYY Klinefelter patient and in the 47,XXY Klinefelter/achondroplasic patient, was most pronounced at the lower half of the angle, i.e. at the localization of the foetal cleft. The lesions found
in the anterior chamber were classified by these authors as belonging to the malformative group of cleavage of the anterior chamber together with other pathological conditions, such as persistence of mesenchymatous tissue, posterior embryotoxon, hyaline corneal membrane, posterior marginal dysplasia of Streiff, and mesodermic dysgenesis of Rieger (Amalric et al., 1966).

The small number of reported ocular anomalies in the Klinefelter syndrome might be due to incomplete examination of the patient, omitting an ophthalmological examination, or to the fact that the ocular functions are not always disturbed, so that the patient does not complain and is not referred to an ophthalmological department. The frequent associated mental retardation also makes complete ophthalmic examination difficult. Coloboma of the iris, being an easily seen congenital anomaly, is however not likely to be overlooked, or to be omitted in a report when it is present in a patient.

We examined extensively the eyes of 3 adult Klinefelter patients, including evaluation of the refraction, mobility, fundus, and anterior chamber angle: these patients were karyotyped in our laboratory and all were 47,XXY, and we did not notice any ocular abnormality (Table II).

The results of different sex chromatin surveys in newborn males, normal adult males, males with mental retardation, and other institutionalized patients, indicated that an additional X chromosome was present in some or all of the cells of 2.07 per 1000 newborn male babies and of 1.96-2.18 per 1000 adult males (Prader et al., 1958; Moore, 1959; Berlemann, 1961; Maclean, Harnsen, and Court Brown, 1961; Maclean et al., 1964; Paulsen et al., 1964; Maclean, 1966; Taylor and Moors, 1967; Maclean et al., 1968; Frøland, 1969).

Coloboma of the iris is judged to have an incidence of about 1:6000 (Duke–Elder, 1940), i.e. 1:12,000 males. Knowing that the frequency of Klinefelter syndrome is 2:1000 males, it can be calculated that there is a probability of about 1 in 6 million that the two conditions would occur in the same individual by chance alone.

The fact that in the published reports of 400-500 karyotyped or sex chromatin–typed Klinefelter patients, coloboma was found 4 times (±1%), can indicate that coloboma may possibly be part of the phenotypic expression of Klinefelter syndrome, though the causal mechanism remains entirely obscure.

The idea has gained ground that the human sex chromosomes act in two different ways (Commoner, 1964).

(a) The euchromatic X chromosome exerts its influence via sex-linked Mendelian genes and control biochemical specificity. (b) The second heterochromatic X chromosome would act as an agent of nucleotide sequestration and regulate metabolic processes, which result in quantitative differences. The difference between the sexes would be of a quantitative rather than of a qualitative nature, and would not be correlated with any biochemical specificity. In this respect, Klinefelter patients can be considered as males having a quantitatively altered production of sex hormones. According to Ohno (1967) and Mittwoch (1967), the metabolic pathway of steroid sex hormone synthesis is such that 'the functional difference between androgen-producing interstitial cells and estrogen-producing follicular cells is not qualitative, but quantitative. The former inhibits further conversion of androstenedione, while the latter does not permit the accumulation of androstenedione, but converts it further to estrone.'

(II) Mendelian heredity. Though uveal coloboma occurs most frequently as a sporadic condition, it can be familial and is then usually transmitted as an irregular dominant trait. On rare occasions, however, recessive transmission has been reported (Waardenburg, 1934; Gesell and Blake, 1936; McLain and Dekaban, 1963). Consanguinity of the parents was reported by Waardenburg (1932).

We have observed an occurrence of coloboma of the uvea, which can best be explained by recessive transmission rather than by dominant transmission (François, 1966): a father and a daughter are affected, but the mother also has a nephew who suffers from it. Therefore, a marriage between a homozygote and a heterozygote giving rise to the manifestation in the daughter (pseudo-dominance) could be postulated.

Isolated cases of Klinefelter syndrome have been associated with other Mendelian diseases, such as Ehlers–Danlos syndrome (Hsu, Geller, and Nemanhauser, 1966), achondroplasia (Sendrail et al., 1967),* familial spino–cerebellar degeneration,† (Indemini and Ammann, 1961), and thyroid hypofunction (Herbeuval et al., 1968). In the present case family data were entirely negative. So, though the parents were consanguineous, the chance exists that the coloboma in our proband is not due to Mendelian heredity.

(III) Disturbed embryogenesis. As possible adverse influences on the closing of the optic cup the following have been suggested: inflammation

* The frequency of achondroplasia is estimated to be around 0.1 per 1000; it is inherited either in a dominant or a recessive mode.
† In a sibship of 3, Klinefelter syndrome was associated with a neurological syndrome including ocular manifestations; 3 sibs had a paresis of an external ocular muscle; 2 had Fuch's heterochromia.
(Mann, 1957), vascular defect (Stroeva, 1961), germinal defect in the epiblast (Von Szily, 1924), and defect in the mesoblastic tissue surrounding the optic cup (Von Hippel, 1903).

C: Dermatoglyphs

Developmental disturbances taking place during the third and fourth months of foetal life affect the arrangements of the dermal ridges. Contrary to the specific dermatoglyphs, discernible on first view, which are found in autosomal trisomies, the peculiarities in Klinefelter syndrome are mainly quantitative, and consist of a tendency to fingertip patterns with a low ridge count. Many loops have so few ridges that they constitute a transition to arches. The frequency of true arches is also increased. The mean total finger ridge count (TFRC) of Klinefelters (117.8) was found to be about 30 ridges lower than the mean of control males, and about 9 ridges lower than the mean of control females. As in all races, normal females have more arches, fewer whorls, and lower ridge counts; this finding has been interpreted as suggestive for sex reversal (Forbes, 1964).

Our proband could not be tested for fingertip counting. His father had a very low TFRC (68), whereas his mother had a high TFRC (146).

The axial triradius tends to be situated low in the palm in Klinefelter patients (Holt, 1968), corresponding with a normal maximum atd angle. Surprisingly, our proband’s axial triradius is displaced distally, a phenomenon that is not typical of Klinefelter syndrome.

According to Holt (1968), genetic as well as environmental factors must play a role in the determination of the position of the axial triradius. In this respect it must be mentioned that the atd angles of the father were normal, i.e. less than 45° (corresponding with position t of the axial triradius), but that the atd angles of the mother were intermediate (49° and 54°) corresponding with position t' of the axial triradius. This makes it difficult to judge whether the distal displacement of the axial triradius in the proband is inherited from the mother or whether it reveals an intrauterine disturbance during the third or fourth month.

The fact that the triradius c was absent needs to be stressed. An absent triradius c on both palms, d being sited nearer to the radial border of each palm than normal, was reported by Jancar (1964) in a 49XXXXXY patient. Vague et al. (1968) reported Klinefelter syndrome in monozygotic twins, in one of whom triradius c was absent on the left hand. In our own series, the triradius c was absent in the proband and in another patient on the left hand (Table II, V. C. Eric). It has to be remembered, however, that even in a normal population in some palms one of the digital triradii, most commonly c, is absent. More data on dermatoglyphs in Klinefelter patients are needed in order to interpret this finding.

In Klinefelter syndrome the distance between triradii a and b tends to be shortened as compared with the distance in the general population, where the range of ab counts summed for both hands lies between 47 and 122 ridges. The ab ridge count is genetically controlled, though environmental factors exert a greater effect on the ab ridge count in early prenatal life than they do on the finger ridge count (Holt, 1968). The ab ridge count of our family did not allow any conclusion regarding a possible diminution of the a-b distance in the proband.

As can be seen from the palmar formulae, the direction of the main lines is normal, and no special patterns were present in the thenar or hypothenar areas. The main line indices were also within normal range, as compared with the mean main line index of the population: 16.38 (Holt, 1968).

Conclusions

The proband presents the association of three pathological conditions which may have arisen at different embryonic stages.

1. Sex chromosomal aneuploidy and mosaicism 47,XXY/46,XX around or shortly after the 14th day.
2. Uveal colobomata at the end of the first or the beginning of the second foetal month.
3. Abnormal dermatoglyphs during the third or fourth months.

Whether the three conditions are causally linked can neither be proved nor rejected. Published data indicate however that coloboma may be part of the
phenotypic expression of the Klinefelter syndrome. Except for the consanguinity of the parents, no familial data indicate a possible Mendelian origin of the coloboma, so that it can also be the result of disturbed embryogenesis.

The major cell lines, 46,XX and 47,XXX, are assumed to be present in the proband and not to have arisen in vivo. The minor cell lines, 48,XXXXY and 48,XXYY, could be present in the patient, but might well have arisen in vivo. The mosaicism can as well have arisen from an XY zygote as from an XXXY zygote. In the latter case the father’s long Y chromosome may have played a causal role in nondisjunction. In both cases a divisional error including the loss of a Y chromosome must have occurred early in the postzygotic stage.

The effect of the mosaicism on the clinical (sexual) phenotype of the patient will only become evident at puberty. The abnormal dermatoglyphs are not typical for Klinefelter syndrome, and can be the result of a disturbed embryogenesis. The displaced axial triradius may however also be inherited from the mother.

References


Uveal Coloboma and True Klinefelter Syndrome


Uveal coloboma and true Klinefelter syndrome.

J François, M T Leuven and P Gombault

doi: 10.1136/jmg.7.3.213

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