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GENETIC COUNSELLING IN X-LINKED EYE DISEASES

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SUMMARY

The fundamental principles of genetic counselling in X-linked heredity are reviewed. As many as 18 X-linked eye diseases are described and discussed. These include diseases of the eye-ball, lens, retina, choroid, optic nerve, ocular muscles, and pigmentation, as well as the ocular manifestations of systemic skin or metabolic diseases.

GENETIC COUNSELLING IN X-LINKED HEREDITY

The mean goal of genetic counselling is to advise parents or future parents on the risk of occurrence or recurrence in their offspring of a disease which may be genetically determined.

Accurate genetic counselling requires an extensive knowledge of the *family history*. Indeed, certain conditions, such as retinitis pigmentosa, can be inherited according to different modes of inheritance, so that a detailed genealogy is essential to know the mode of inheritance of the disease in a particular family.

Furthermore, *statistical evaluations* are often necessary to calculate the recurrence risk in further offspring. According to the magnitude of the probabilities for offspring to be affected, two main risk categories can be distinguished (Carter 1969):

(1) *Low risks*, which comprise:

(*a*) Risks, comparable to the random risk of any child in the population;

(*b*) Moderate risks, which are considerably greater than the random risk, but lower than 1 in 10 (10%), and for some diseases even lower than 1 in 20 (5%);

(2) *High risks* of 1 in 10 (10%) or higher.

This paper deals with X-linked diseases belonging to the high risk category.

As several affections may show similar clinical symptoms, but are in fact different, an exact *diagnosis* is of capital importance in genetic counselling.

It is clear that the functional *severity* of a disease, its *prognosis*, and the *therapeutic* possibilities, are also important counselling factors. Some hereditary diseases have no or little influence on a normal behaviour and are in no way a serious handicap in normal life, while others are.

Sex-linked diseases are caused by genes located on the sex chromosomes, the X-chromosome and the Y-chromosome (*sex-linked genes*). Three groups can be distinguished:

(1) Genes occurring at *homologous loci* on homologous parts of the X- and Y-chromosomes;

Rec. 5. II. 1973

Acta Genet. Med. Gemellol. (1973), 22: 51-74

(2) Genes occurring on the *nonhomologous part of the Y-chromosome* and for which there are no corresponding loci on the X-chromosome;

(3) Genes occurring on the *nonhomologous segment of the X-chromosome* and for which there are no corresponding loci on the Y-chromosome.

Practically, the term " sex-linked " or " X-linked disease " is used for a disease caused by genes of the third group, i.e., genes on the nonhomologous part of the X-chromosome.

Very little is known about the absolute *localization* of the different genes on either the long or the short arm of the X-chromosome, but for some genes the relative distance between them has been found.

A measure of the distance between two gene loci is the *recombination fraction*, i.e., the total number of recombinants (arising from reciprocal genetic recombinations via crossingover) divided by the total number of progeny individuals scored (Rieger et al. 1968).

The chance of recombination increases with increasing distance between the loci involved. The smaller the recombination fraction, the shorter the distance between the two loci. If two loci show more than 0.25 recombination, their linkage is not detectable and the distance between them is not measurable (Race and Sanger 1968).

Very important markers on the X-chromosome are the genes for the Xg blood group, the protan and deutan colour-blindness, the Xm serum group, and, in Mediterranean countries or Negro population, also for glucose-6-phosphate-dehydrogenase deficiency (G6PD).

It is accepted that the Xga gene must be situated at the end of the chromosome, and that the four other loci are fairly close to each other, forming a cluster. There are thus only two regions of the X-chromosome with good markers.

Of all the known X-linked loci, only a few are in the vicinity of these markers, the majority being far away from them.

The phenotypic expression of a gene depends on its dominance or recessiveness. It is not possible to draw a firm dividing line between dominance and recessiveness (François 1961). In medical genetics, the term, dominant gene, is used when its manifestation is usually seen in heterozygotes, and the term, recessive gene, when its manifestation is commonly seen in homozygotes (even if the heterozygote is detectable by some method or another). It is understandable that with increasing clinical investigations and biochemical techniques, an increasing proportion of heterozygotes will be identifiable.

A harmful visible gene-effect in heterozygotes can be designated as intermediate or partial dominance.

These concepts of dominance and recessiveness apply especially in autosomal inheritance. Practically all X-linked diseases are caused by recessive genes, whose phenotypic expressions is different in males and females and which is determined by another underlying mechanism.

Males have a small Y-chromosome and one X-chromosome which is much longer than the Y-chromosome. All the genes on the nonhomologous part of this X-chromosome are thus single unpaired hemizygous genes.

If a male carries a pathological recessive gene on this X-chromosomal segment, his phenotype is always abnormal, because this gene always expresses itself.

So, if a male is not affected, it is certain that he does not carry the pathological gene.

None of the children of a father affected by a recessive X-linked disease will manifest the

disease. Indeed, the sons receive the Y-chromosome of the father and one of the X-chromosomes of the mother, so that they cannot inherit the genes carried on their father's X-chromosome. On the other hand, the daughters receive an X-chromosome from their mother and also the father's X-chromosome which carries the abnormal gene. All the daughters will thus be heterozygous carriers of the gene, and will usually not manifest the disease. However in their turn, they will transmit the gene to 50% of their sons, who will manifest the disease, and to 50% of their daughters, who will only be heterozygous carriers.

Every male affected by an X-linked recessive disease must thus be the son of a heterozygous female carrier, unless he is a new mutant.

Normal *females* have two X-chromosomes and all the genes on these chromosomes are thus paired genes.

Until recent years it was generally accepted that the manifestation of a recessive X-linked gene occurred only in homozygous females and these are very rare. Nearly all females carrying a pathological X-linked gene are heterozygous and phenotypically normal. However, several examples have been observed of affected women, who have normal as well as affected sons and who are therefore certainly heterozygous. Most of these women show a mild form of the disease, but some of them also the complete manifestation, as seen in the hemizygous males.

Mary Lyon has given an explanation for this phenomenon. According to her hypothesis (*inactivation* or *Lyon theory*), a large part of one X-chromosome becomes inactive around the 16th day of the foetal female life. A part of the short arm should not take part in this inactivation and should remain active. The inactivation occurs entirely at random: in some cells it is the paternal X-chromosome, in others the maternal one which is inactivated. Random inactivation implies that females have mostly an equal proportion of cells containing either an active maternal or an active paternal X-chromosome.

However, occasionally (perhaps in one out of 50 heterozygous females), all, or almost all, the cells contain an active paternal or, on the contrary, an active maternal X-chromosome. In fact, the proportion of cells, in which one or the other X-chromosome is inactivated, may vary in a continuous manner from one female to another.

In women, who are heterozygote carriers of an X-linked recessive gene, the phenotypic manifestation of the diesase will thus depend on the proportion of cells where the X-chromosome carrying the abnormal gene is active. In other words, a female, heterozygous for an X-linked trait, can present different phenotypes, i.e.:

(1) The perfectly healthy phenotype of the normal homozygote, when the X-chromosome carrying the pathologic gene is inactivated in the majority of the cells;

(2) The phenotype of the affected homozygote, when the normal X-chromosome is inactivated in the majority of the cells;

(3) An intermediate phenotype with frust signs or symptoms of the disease, when the X-chromosome with the pathologic gene is active in a certain proportion of the cells.

For genetic counselling in X-linked diseases it is often necessary to know whether a clinically normal female is a heterozygote carrier or a homozygous normal woman. One can only conclude that a female is a carrier in the following situations:

(1) If her father is affected;

(2) If she has two affected sons or if she has, besides an affected son, also an affected brother or any affected male relative in her mother's family;

(3) If she shows signs of minimal or partial manifestation. The presence of frust symptoms indicates that she carries the abnormal gene, but the lack of signs does not necessarily indicate that she is a normal homozygote. For some authors female carriers of X-linked retinitis pigmentosa, ocular albinism, and choroideremia, show some characteristic fundus abnormalities; for others not. This fact can be due to the varying skills of the observers, the variability of the minimal manifestations in females or a heterogeneity within the traits.

(4) Finally, a statistical evaluation can determine the probability for a female of being a carrier.

First, the *prior probability* is determined. This is an estimate of the probability of a parent to have a certain genotype, based on pedigree information, and his or her own phenotype, but having no information on his or her children. So, when a woman has affected brothers, her mother must be a carrier and she has a prior probability of one chance in two of being also a carrier.

Thereafter, the *posterior probability* is determined. This is the probability of a parent to have a specific genotype, estimated by taking into account the a priori expectation of having the specific genotype and also the condition of the children.

So, from the moment that the woman with the prior probability of one chance in two of being a carrier has one affected son, it becomes certain that she *is* a carrier, and all further sons will have one chance in two to be affected. When she has only normal sons, the probability of one in two of being a carrier diminishes with the increasing number of normal sons.

Genetic counselling in X-linked diseases is relatively easy, when the genotype of the mother is known with certainty.

The pedigree analysis is not easy, when the affected male is a sporadic case. He may be a *new mutant*, i.e., the first member of the family to receive a mutation, which arose *de novo* on the germ cells of his genotypically and phenotypically normal mother; or he may be a *segregant*, i.e., he has received the gene from his unaffected mother, who was however already heterozygous for the recessive gene. The sibs of a mutant are not at risk of receiving the pathologic gene. The sibs of a segregant, on the contrary, are at risk. So, whenever a sporadic affected boy is born, the risk for further children of the mother or for her daughters' children derives from the relative probability that he is a segregant or a mutant.

The *foetal sex* can now easily be determined in the amniotic fluid obtained by amniocentesis. Observation of the fluorescent Y-body spot in the amnion cells is a reliable and doubtless indication for the presence of a cytogenetic male foetus. The result of this method is known a few hours after amniocentesis (Matton et al. 1972). Determination of the foetal karyotype, which requires at least two or three weeks, can, when necessary, confirm the diagnosis.

It has to be kept in mind, however, that even when the presence of a male foetus is proven in a woman carrier of an X-linked recessive disease, the cytogenetic sex determination does not elucidate whether the boy is affected (50% chance) or is not (also 50% chance).

Prenatal diagnosis of a pathologic condition in the foetus is only possible when a chromo-

somal aberration or a specific metabolic defect can be demonstrated in the cultured amniotic fluid cells or in the supernatant fluid (Fabry's disease).

Sex-linked dominant inheritance seems to be extremely rare. Only a few conditions are known, where heterozygous females are invariably affected (vitamin D-resistant rickets or hypophosphataemia).

A man affected by such a sex-linked dominant disease does of course not transmit the gene to his sons, but will transmit it to all his daughters, who will be affected by the same disease and who will in their turn transmit it to 50% of their offspring, sons as well as daughters. A father affected by an X-linked dominant disease, married to an unaffected woman, will have none of his sons, but all his daughters affected.

X-LINKED EYE DISEASES

We know of at least 18 X-linked eye diseases, distributed in 8 groups as follows:

(1) Colobomatous defects of the eye-ball: microphthalmia;

(2) Anomalies of the lens: cataract;

(3) Functional abnormalities of the retina: essential hemeralopia, colour blindness;

(4) Chorioretinal heredo-degenerations: choroideremia, choroidal sclerosis, pigmentary retinopathy, sex-linked myopic chorioretinal heredo-degeneration, retinoschisis, Norrie's disease;

(5) Diseases of the optic nerve: optic atrophy;

(6) Anomalies of the ocular muscles: nystagmus, external congenital ophthalmoplegia with myopia;

(7) Anomalies of pigmentation: ocular albinism;

(8) Systemic diseases with ocular manifestations:

(8.1) Skin diseases: keratosis follicularis spinulosa cum ophiasi, congenital ectodermal anhydrotic dysplasia;

(8.2) Metabolic disease: Fabry's glycolipidosis, Lowe's oculo-cerebro-renal syndrome.

1. Colobomatous Defects of the Eye-Ball

1.1. *Microphthalmia*

Several authors (Sjögren and Larsson 1949, Lenz 1955, Cuendet 1961, Hoefnagel et al. 1963, Herrmann and Opitz 1969) reported families, in which a complicated microphthalmia with mental retardation and urogenital malformations, with or without skeletal anomalies, was inherited as a sex-linked trait. In the mothers of the probands, Lenz (1955) found abnormalities of the fingers, Herrmann and Opitz (1969) microcephaly and syndactyly.

2. Anomalies of the Lens

2.1. *Cataract*

Hereditary cataracts have mostly an autosomal dominant mode of inheritance (François 1961, Waardenburg et al. 1961). X-linked cataracts are exceptional.

Stieren (1907) reported a family with probable sex-linked congenital cataract. In three generations only males (17 out of 37) were affected. They were born blind and died in infancy. It remains an open question if the cataract was not secondary to an X-linked metabolic disease.

Halbertsma (1934) described a family, where 10 males were affected in four generations. The cataract was transmitted by heterozygous women: 5 out of 7 carriers were normal, but 2 had a cataract.

Fraccaro et al. (1967) reported a pedigree of five generations. Nine men showed a total nuclear cataract with severe visual impairment and 1 man showed a bilateral stationary punctiform anterior polar cataract with normal sight. There were 8 female carriers with posterior Y-sutural cataracts and 1 with additional bilateral polar cataracts. Two female carriers showed progressive opacification of the lens in one or both eyes. The evidence for linkage with Xg is quite hopeful: the recombination fraction in this family was 0.17 (Race and Sanger 1968).

Krill et al. (1969) described a pedigree of three generations: of 8 affected men, 2 were first seen with sutural opacities only. Eight female carriers showed posterior Y sutural lens opacities.

Cataract and microcornea. Gragg (1971) described a family of 4 generations where cataract and microcornea were inherited as an X-linked recessive trait.

The affected men showed a microcornea and a congenital zonular cataract which rapidly increased in size shortly after birth. The posterior segment was of doubtful normal size.

Heterozygous females showed an opacity of the posterior lens sutures, but the corneas were of normal or slightly subnormal size.

Cataract and microphthalmia. Cataract associated with microphthalmia may be inherited as an autosomal dominant or as an X-linked trait.

Hussels (1971), Goldberg et al. (1971) described a family where 2 successive sons showed a congenital cataract. The first had also microcornea. Both developed bilateral microphthalmia. The mother had an extensive suture cataract and a slight microcornea (10 mm).

3. Functional Abnormalities of the Retina

3.1. *Essential Hemeralopia*

There are four groups of essential congenital hemeralopia. One of these is the Bornschein and Schubert type (1952, 1954), which may be associated with myopia (Varelmann 1925) and is recessive, either autosomal or sex-linked.

The dark adaptation curve is monophasic and high. The ERG shows no scotopic component, the photopic component being normal or slightly subnormal. The EOG is pathologic (subnormal base value, only slight variations in dark or light adaptation).

The visual field may be normal and the visual acuity is often reduced.

The eventual myopia is of a variable degree (6-10 δ) and is often associated with astigmatism The choroidosis is more or less pronounced. Pigmentation is frequently observed at the retinal periphery (Franceschetti et al. 1959).

In a sex-linked case, François and De Rouck (1963) found a *female carrier*, aged 4 years, who showed a mosaic retinal pigmentation and a clear posterior pole.

In our opinion sex-linked hemeralopia with myopia and sex-linked myopic chorioretinal degeneration (see p. 61) are the same disease.

3.2. *Colour Blindness*

Colour vision is trichromatic: the mixture of three primary colours normally allows to reproduce all the coloured sensations (Wald 1966).

Anomalous trichromats mix these three fundamental colours, but the proportions are different from these of normal subjects: protanomals use an excess of red, deuteranomals an excess of green and tritanomals an excess of blue (Krill 1968).

Dichromats use only two colours to reproduce their coloured sensations: blue and yellow for protanopes and deuteranopes, red and green for tritanopes. Only the anomaloscope enables a clear-cut diagnosis between protans and deutans.

Monochromats have only luminosity sensations.

Deutan and protan defects are inherited as X-linked traits. Tritanopy is probably inherited as an irregular autosomal dominant trait, while the inheritance of tritanomaly is still not known. Complete achromatopsia, or typical monochromatism, is inherited as an autosomal recessive, while atypical monochromatism, or blue mono-cone monochromacy, is inherited as a Y-linked recessive trait.

Protan and deutan defects. These defects are found in 8 % of the European male population. There are two series of multiple alleles situated on different loci, but close to each other.

Linkage studies reveal a recombination fraction of 0.095 between the loci for protan and deutan (Arias and Rodriguez 1972). A close linkage also exists between deutan and Xm (recombination fraction of 0.07). The data for protan and Xm are too limited to be conclusive (Berg 1969). The haemophilia-A locus, the deutan and protan loci, are very closely linked, the recombination fraction being between 0.06 and 0.12 (Whittaker et al. 1962). The locus for G6PD is also very close to both colour defects loci (Race and Sanger 1968). One may conclude that the loci for deutan and protan defects, G6PD, Xm, and haemophilia-A, really form a cluster.

Heterozygous females for genes of the protan series show an abnormal spectral luminosity curve, the maximum being displaced halfway between the normal position and the typical position for protan phenotypes (Schmidt 1934 and 1955, Walls and Mathews 1952, Crone 1959). Crone (1959) found a similar phenomenon in deutan heterozygotes.

At the anomaloscope some heterozygous females may show a pathologic scatter, the equation being more dispersed (François et al. 1973).

Finally, some heterozygous females have dyschromatopsia (François et al. 1973).

Tritanomaly. Although Kalmus (1965) thinks that this defect is sex-linked recessive, its inheritance is still doubtful (Waardenburg et al. 1963). Some authors even do not accept the existence of tritanomaly (Krill 1968, Schmidt 1970).

Monochromatism. Atypical achromatopsia or blue mono-cone monochromacy has been functionally individualized by Blackwell and Blackwell (1957). A recombination fraction of 50% has been found between the Xg^a blood-group and the monochromatism locus, indicating that both loci are not close together (Spivey 1965).

The *affected men* show a congenital achromatopsia associated with myopia (Spivey et al. 1964, Spivey 1965, Earll et al. 1966, François et al. 1966). They may have some degree of slight colour perception (Earll et al. 1966).

Heterozygous women have completely normal colour vision, but, according to Spivey (1965), they show a delay of the dark adaptation curve and a reduction of the *a*-wave of the ERG. These signs were not found by other authors (François et al. 1966).

4. Chorioretinal Heredodegenerations

4.1. *Choroideremia or Progressive Chorioretinal Degeneration*

Choroideremia is a progressive atrophy of the choroid and secondarily of the retina. It is transmitted by intermediate sex-linked heredity. Klein et al. (1967*a*), Other (1968), Bell and McCulloch (1971), found a loose linkage between the choroideremia gene and the Xg loci. The combined data for the three family studies gave 6 recombinants out of 13 individuals, which indicates that the recombination fraction is probably high (50%).

In *affected men*, the disease begins very early with minimal lesions in the form of atypical peripheral pigmentary retinopathy or as a chorioretinopathy of the "salt and pepper" type. In the second stage there is atrophy of the pigment epithelium and of the choroidal vessels. In the third stage there is atrophy and progressive disappearance of the choroidal vessels from the periphery to the center, the macular region being spared the longest. In the final stage, usually after the age of 40 years, we see a complete atrophy of the retina. The fundus becomes uniformly yellowish-white with a pearly luster and only the macular region sometimes remains more or less pink. Disseminated pigment clumps, irregular or rounded, may be seen. Curiously enough, the retinal vessels and the disk remain normal. The fluoroangiography shows the choroidal and pigment epithelium alterations.

The visual functions are seriously affected and progressively so as the disease develops. Useful visual acuity may persist even in advanced cases. Total blindness is not found until the terminal stage, after the age of 50. The photopic visual field shows a ring scotoma or a concentric constriction that is sometimes extreme. Hemeralopia is a constant symptom. The dark adaptation curve becomes high and monophasic. The chromatic sense may be intact as long as the macula is spared, but very early the blue-green differentiation is affected. Finally, the patient becomes colour-blind. At first, the photopic components of the ERG

may be intact, but in most cases of late choroideremia the ERG response is completely extinguished.

The *heterozygous women* may be recognized by their fundus anomalies (François 1958, 1971). Most frequently, there is pigmentation, irregularly grouped, covering a varying width of the periphery, situated deep in the retina and often associated with zones of depigmentation. In other cases a chorioretinopathy of the " pepper and salt " type has been noted. In yet other patients, there may be changes in the macular region (deep pigmentation or white areas). None of these lesions progress and all the visual functions are and remain normal — and this is a point of great importance.

Occasionally, a partial or complete choroideremia has been observed in heterozygous females (Kurstjens 1965, Krill 1967, Fraser and Friedmann 1968, Harris and Miller 1968).

Van den Bosch (1959) described a family where choroideremia was associated with (1) mental deficiency, (2) acrokeratosis verruciformis, (3) anhidrosis and (4) skeletal deformities.

4.2. *Choroidal Sclerosis*

Choroidal sclerosis may show an autosomal transmission, sometimes dominant, sometimes recessive. A few pedigrees indicate however a sex-linked heredity (Thompson 1901, Wilmer 1934, Sorsby and Savory 1956, François 1958, Stankovic 1958, Jacobson and Stephens 1962).

In *affected men* the fundus shows a more or less extensive sclerosis, which becomes generalized and is accompanied by disseminated pigment in the later stages. There is a progressively increasing central scotoma with constriction of the visual field. The ERG is firstly diminished and later extinguished.

In *heterozygous women* there are pigmented and depigmented spots at the periphery of the retina, but the visual functions and the ERG are normal.

Female carriers may sometimes show a complete manifestation (François 1958).

4.3. *Pigmentary Retinopathy*

Pigmentary retinopathy (retinitis pigmentosa) shows mostly an autosomal inheritance. Sex-linked pigmentary retinopathy is rare and the number of families concerned hardly exceeds thirty.

The locus for retinitis pigmentosa is not close to that for the Xg blood-group. The two loci are more than 10 map-units apart (Hussels 1967). The combined data of two pedigree studies gave 3 combinants out of 6 individuals (Klein et al. 1967*a*, Grützner et al. 1972). The locus for sex-linked pigmentary retinopathy should also be far away from the locus for colour-vision deficiency, as Grützner et al. (1972) found 2 recombinants out of 4 individuals.

The *affected men* show typical pigmentary retinopathy accompanied by osteoblastic pigments, more or less generalized choroidal sclerosis, narrow retinal vessels and optic atrophy. The functional symptoms (hemeralopia, visual field defect, progressive deterioration of central vision) are identical with those found in the classical autosomal recessive form. The ERG response is extinguished.

In *heterozygous women* the fundus shows a brilliant scintillating golden tapetoretinal reflex, most pronounced at the posterior pole (Frost 1902, Falls and Cotterman 1948, Sorsby 1951, Weiner and Falls 1955, François 1962, Ricci et al. 1963, Heck 1963, Goodman et al. 1965, Krill 1967, Klein et al. 1967*b*, Warburg and Simonsen 1968, François 1971). The visual functions are normal.

The female carrier may exhibit, however, a wide range of pathologic expressivity, as it is illustrated by the following family studies:

(1) In McKenzie's family tree (1951), which is sometimes quoted as an example of dominant sex-linked heredity, we find that among 12 female carriers, 4 show pigmentary retinopathy, but the functional prognosis in this family is clearly better for females than for males.

(2) In Roberts' family (1959), 8 female carriers showed only the tapetal reflex, but 3 had the full disease, which in 2 was as severe as in the males.

(3) In Kobayashi's family (1960), which was published as an example of dominant sex-linked heredity, in addition to 12 affected males, 17 female carriers were affected. While all the males showed typical pigmentary retinopathy, among the 17 females there were 5 with the classical form, 9 with a paucipigmentary form, and 3 with an abortive form. It is to be regretted that no information is given concerning visual functions in these cases.

(4) In Hussels' family (1967), 14 affected men and 11 female carriers are found. One carrier had hemeralopia (*forme fruste* of pigmentary retinopathy). Another showed a retinopathy localized in an inferior sector and a reversible tapetal reflex (attenuated form of pigmentary retinopathy). A third carrier had hemeralopia, a decreased vision of the right eye, a constricted visual field with relative central scotoma of the same eye, a subnormal adaptation curve; there was a typical pigmentary retinopathy of the right eye and a paucipigmentary retinopathy of the left eye; there was also a reversible tapetal reflex (inverse Mizuo phenomenon). The other carriers showed only this phenomenon.

Although Warburg (1971*a*) concludes from linkage studies for choroideremia and sex-linked " dominant " retinitis pigmentosa that these two diseases are different clinical entities, we think that sex-linked choroidal sclerosis and sex-linked pigmentary retinopathy may both develop into a chorioretinal degeneration of the choroideremia type. The latter, moreover, begins with fundus changes that are difficult to distinguish from those seen in choroidal sclerosis or in pigmentary retinopathy.

Furthermore, there are families with the intermediate sex-linked form of chorioretinal degeneration, in which different numbers may show pigmentary retinopathy, choroidal sclerosis, or choroideremia (Sorsby and Savory 1956, François 1962).

On the other hand, it is a matter of fact that the female carriers may show a wide range of fundus manifestations. In Sorsby and Savory's family a heterozygous woman showed a myopic albinotic fundus with scintillating white spots in the macular region. These shining spots are possibly an abortive form of tapetal reflex. Kurstjens (1965) found a tapetal reflex in a female carrier of the gene of choroideremia.

To summarize, progressive chorioretinal degeneration, choroidal sclerosis and sex-linked pigmentary retinopathy are so closely related that it is impossible to separate them, since the three forms terminate in the same total chorioretinal atrophy. They constitute different

stages of the same disease and may depend on a single gene, the differences that may be observed from one family to another being probably due to interfamilial variability.

4.4. *Sex-linked myopic chorioretinal heredodegeneration*

In 1963 François and De Rouck described two families with myopia and chorioretinal degeneration, which, in one of them, was combined with hemeralopia. In this family, *one female carrier* showed a mosaic retinal pigmentation, the posterior pole being clearer than the periphery. In the other, female carriers showed only a slight myopia without chorioidosis or functional disturbances.

In *men*, ophthalmoscopy showed a myopic choroidosis, a diffuse chorioretinal atrophy, an incipient choroidal sclerosis of the posterior pole, and pigment displacement. The visual field showed ring scotomas or could even be tubular with a temporal islet. The dark adaptation curve was pathologic. The ERG was abolished. When using a very strong light stimulus, an *a*-wave without positive component might be seen.

In 1964 Forsius and Eriksson (1964*a*,*b*) described analogous cases (Äland eye disease). Their family was reevaluated by Eriksson et al. (1969*a*), Waardenburg et al. (1969), Waardenburg (1970) and Van Vliet et al. (1972).

The loci for this disease and the Xg blood-group seem to lie close to each other, the recombination fraction being only 0.12. As the recombination fraction for ocular albinism and Xg blood-group is 0.175 (Fialkow et al. 1967), the loci for myopic chorioretinal degeneration and ocular albinism might well be adjacent (Eriksson et al. 1969*a*).

The affected men in Forsius and Eriksson's family had an axial myopia (— 2 to — 20 δ) with astigmatism, a horizontal and oscillating nystagmus, and a tapetal pigment deficiency, especially in the central part. This pigment deficiency was not similar to classical ocular albinism, but was only characterized by irregularly scattered albinoid-like areas and foveal hypoplasia. The iris was normal and not diaphanous. The vision was bad (0.05-0.4). The dark adaptation as well as the ERG revealed defective scotopic and photopic retinal function.

Of the 9 investigated *female carriers*, 2 showed only nystagmus.

4.5. *Vitreoretinal Degeneration* (*Retinoschisis*)

There exist three main forms of vitreoretinal degeneration: an autosomal recessive hyaloidotapetoretinal degeneration (Goldmann-Favre's disease), an autosomal dominant hyaloidoretinal degeneration (Wagner's disease and Favre's disease), and a sex-linked recessive idiopathic retinoschisis.

Sex-linked recessive vitreoretinal degeneration or retinoschisis is a rare disease. Its locus could be within measurable distance from the Xg locus (recombination fraction = 0.28 in one family), but far from the deutan locus (Eriksson et al. 1967 and 1969*b*, Vainio-Mattila et al. 1969, Forsius et al. 1971).

Forsius et al. (1971) found a combination of congenital dyschromatopsia of the deutan type and X-chromosomal retinoschisis in three families. In all these families, recombination

of crossingovers had taken place between the deutan and the retinoschisis loci. In two families, however, the exact number of recombinants could not be determined, because the phase of the mother was not known. In the second family, 3 recombinants out of 6 individuals were found.

Retinoschisis occurs mostly in young *men*, between 15 to 30 years of age. It is nearly always bilateral. It divides the retina into two layers, the cleavage being localized in the nerve fiber layer (Yanoff et al. 1968).

At the retinoschisis site, the retina is translucent. The vessels of the anterior, detached layer project their shadows onto the underlying layer. The margins of the retinoshisis are often marked either by slightly pigmented lines or by scalloped, whitish lines. The retinoschisis, which is usually localized in the inferior portion of the retina, may lead to rupture and after retraction of the internal layer, may form arches that project into the vitreous. A cystoid degeneration of the macula is a sign of great importance. The pathological process is sometimes limited to the macula (Krause et al. 1970). Vitreous veils or nonvascularized vitreous structures and whitish cords can be observed in the vitreous. These are implanted at the margin of the retinoschisis and form a network with wide meshes.

Functionally, there is a decrease in central vision, a visual field defect, corresponding to the region of the retinoschisis, a normal dark adaptation curve, and a normal colour vision. The ERG shows a normal *a*-wave, but a subnormal scotopic *b*-wave. In severe cases and in patients over 40 years of age, when there is a dysfunction of the bipolar cells, the ERG response may even disappear. The EOG remains normal, except in patients over 40 years with no recordable ERG.

Lesions have been described in *female carriers.*

In the case of Rieger (1944, case 2) the question can be raised as to whether the familial condition should not be classified under the group of hyaloidoretinal degeneration of Wagner with dominant transmission.

In the case of Forsius et al. (1962) the affected woman is homozygous, being the child of the marriage between two first cousins (father affected, mother heterozygous).

In the family reported by Gieser and Falls (1961) a girl aged 13, showed a macular cyst on the left with bilateral central scotoma and this may be regarded as a heterozygous manifestation, the more so as the father is affected as well.

Sabates (1966) described the classical senile type of retinoschisis in 2 females, aged 41 and 42 years, and belonging to a family in which there were 4 cases of juvenile retinoschisis.

Stepanik (1969) found a slight unilateral retinoschisis in the retinal periphery of one female carrier. Other lesions have been described in heterozygous women: peripheral retinal degeneration of the senile type (Eriksson et al. 1969*b*, Ewing and Ives 1969, Vainio-Mattila et al. 1969, Deutman 1971), high myopia (Guyot-Sionnest 1969) and a black pigment clump in the posterior pole (Carr and Siegel 1970).

4.6. *Congenital Hyaloido-Retinal Dysplasia* (*Norrie's Disease*)

Norrie's disease is a peculiar type of pseudoglioma, which causes bilateral blindness at birth or during the first few months of life.

The X-linked inheritance of this disease has been stressed by many authors (Norrie 1927,

Stephens 1947, Andersen and Warburg 1961, Warburg 1961, Franceschetti et al. 1963, Forrester 1963, Capella et al. 1963, Warburg 1966, Hansen 1968, Ricci 1969, Hamburg 1970, Ashton 1971, Holmes 1971, Warburg 1971*b*, Brini et al. 1972).

Analyzing 35 Scandinavian cases, Warburg at al. (1965) found no close linkage between the locus of Norrie's disease and the Xg locus. Nance et al. (1969) made the same statement, but found a loose linkage between Norrie's disease and G6PD.

In *male children*, a bilateral white vascularized retrolental membrane is seen initially at the age of three to eight months. At the sides of the mass elongated ciliary processes are often noted. During infancy the cornea becomes opaque, anterior synechiae build up and cataract develops. Later the eyes shrink and become atrophic. Progressive mental retardation, dementia, and hearing loss, appear frequently in childhood or middle life.

Chromosomes were found to be normal by Warburg (1966) and Holmes (1971). Brini et al. (1972) described a family in which 7 males were affected in three generations. There was a slight and nonspecific alteration of the karyotype, both in the child whose eyes were examined and in his mother (carrier): a translocation on the chromosome D (46,XY Dp+ in the patient, 46,XX Dp+ in his mother).

The *heterozygous females* show neither ocular defects nor other abnormalities.

5. Diseases of the Optic Nerve

5.1. *Optic Atrophy*

De Vries-De Mol et al. (1972) reported an X-linked optic atrophy in a 9-years-old proband and 8 other members of his family. Four of the 9 patients also present neurological and psychological troubles. The loci for X-linked optic atrophy and Xg were far away from each other: 4 nonrecombinants and 3 recombinants were found out of 7 informative individuals.

Bruyn and Went (1964) described a degenerative disorder of the central nervous system (spastic paraplegia), associated with optic atrophy. This syndrome was present in at least 18 members of one family. Only one of these was female, but the diagnosis in this case was doubtful.

We do not speak of Leber's optic atrophy, because this disease is in fact not sex-linked. Although its mode of inheritance is still not known with certainty, it is probably cytoplasmic.

6. Anomalies of the Ocular Muscles

6.1. *Nystagmus*

Nystagmus may be due to a disease of the eyes, the visual pathways, or the central nervous system. It also may be an isolated phenomenon which is often genetically determined.

Isolated, primary or idiopathic congenital nystagmus, occurring in normal eyes, is apparently due to a developmental anomaly in the central nervous system. It is usually reduced in amplitude when the eyes are converging, so that near vision is better than distance vision (6/36 or less).

There are two types of hereditary nystagmus:

(1) The congenital jerky nystagmus with a fast and a slow component;

(2) The idiopathic pendular nystagmus with an equal speed in both directions.

Nystagmus shows exceptionally an autosomal dominant or recessive inheritance. Sex-linked recessive transmission is frequent (François 1961), but sex-linked dominant inheritance is the most common. As there is a variability of penetrance which ranges from 5.6 to 78% (Hemmes 1924), or from 3 to 62% (Cuendet and Della Porta 1950), the normal gene may predominate over its abnormal allele, so that one third or one half of the female carriers may be normal (François 1961, Harcourt 1970, Forssman and Ringner 1971). A reduced penetrance may also be found in men (Forssman and Ringner 1971), as well as a variable expressivity with micromanifestations.

6.2. *External Congenital Ophthalmoplegia with Myopia*

The transmission is sex-linked recessive.

In *men*, there is a complete or incomplete external ophthalmoplegia with myopia, pupillary ectopia, dyscoria or anisocoria, patellar and achillean areflexia. There may be other abnormalities, such as degenerative changes in the retina, spina bifida, flat-foot, enuresis, cardiopathy, hernia, dental and thoracic malformations.

In *heterozygous women*, there is an absence of the rotular and Achilles reflexes, but no ocular lesions (Salleras and De Zarate 1950, De Zarate 1966).

7. Anomalies of Pigmentation

7.1. *Ocular Albinism*

Ocular albinism is a pigment deficiency limited to the eye. Skin and hair pigmentation are nearly normal.

The responsible gene is X-linked recessive. The distance between the locus for ocular albinism and for the Xg^a blood-group is probably measurable, the recombination fraction being around 0.175 (Fialkow et al. 1967, Pearce et al. 1968, Renwick 1968, Hoefnagel et al. 1969).

The manifestation in *men* is complete and characterized by the following signs (François 1972):

(1) Slightly pigmented, grey-blue and diaphanous iris;

(2) Characteristically red pupil reflex, caused by the lack of pigment in the eye, which allows light to pass through the iris and sclera so readily as to give the reflected light the red glow of the choroidal blood;

(3) Depigmented fundus with clearly visible choroidal vessels and hypoplasia of the fovea (absence of foveal reflex);

(4) Frequently nystagmus and head-nodding;

(5) Greatly diminished visual acuity (0.1-0.3);

(6) Visual fields, colour vision, dark adaptation and ERG are normal (Krill and Lee 1963, pers. obs.).

Heterozygous women, who are often pale with blond hair, most frequently show a partial manifestation (intermediate sex-linked heredity), which is characterized by morphologic signs without functional disturbances (Vogt 1942, Falls 1951, François and Deweer 1953, Gedda and Magistretti 1956, Ohrt 1956, Klein et al. 1958, Gillespie 1961, Gillespie and Covelli 1963, Goodman et al. 1965). The following signs are seen:

(1) Iris translucency: transscleral illumination shows the iris to be diaphanous, the pigmented layer being hypoplastic, even when the mesodermal layer is well pigmented;

(2) The retinal periphery may show a powdering of pigment of the « salt and pepper » type, a chocolate-brown pigmentation, a blackish-brown pigment dust heaped into small clumps, irregularly distributed and standing out against a light background where the choroidal vessels are visible, a polymorphous greyish-brown pigmentation or blackish-brown pigment granules irregularly distributed, forming a true mosaic of spots and resembling drops of oil on the surface of water;

(3) Functional disturbances are absent and the vision is good.

Occasionally, heterozygous women may show a complete manifestation of the gene. In this case, the morphologic and functional signs are the same as in affected men (Waardenburg and Van den Bosch 1956, Johnson et al. 1971, Pearce et al. 1972)[1].

8. Systemic Diseases with Ocular Manifestations

8.1. *Skin Diseases*

8.1.1. Keratosis Follicularis Spinulosa cum Ophiasi

This disease may be transmitted as an autosomal dominant, but also as a sex-linked recessive (Siemens 1925, Thelen 1940, Holthuis 1943, Jonkers 1950, Franceschetti and Thier 1961, Snyder and Klunker 1966, Kuokkanen 1971).

The locus for X-linked keratosis follicularis is probably not close to the Xg locus. In one family of three generations, 2 nonrecombinants and 3 recombinants out of 5 individuals were found (Race and Sanger 1958).

In the families with sex-linked transmission, the *men* show a pilary keratosis of the scalp, the beard, the eyebrows, and the eyelashes, with loss of hairs and follicular keratosis of the eyelids, the nape of the neck, the ears, the vertebral groove, and the limbs, more particularly of the palms and the foot soles. There is a thickening of the eyelids with blepharitis and ectropion, as well as degenerative lesions of the cornea characterized by diffuse punctate epithelial change and peripheral superficial vascularization in arches, by photophobia and lacrimation.

Heterozygous women have only discrete follicular keratosis of the extremities and sometimes slight changes in the corneal epithelium with recurrent erosions (Lameris 1905, Rochat 1906, Siemens 1925, Holthuis 1943, Jonkers 1950 and 1958, Franceschetti and Thier 1961).

[1] Johnson et al. and Pearce et al. discuss the same patient.

8.1.2. Congenital Ectodermal Anhydrotic Dysplasia

It is transmitted as an autosomal dominant or as an X-linked recessive disease.

The locus for X-linked ectodermal anhydrotic dysplasia must be far away from the Xg locus. In three families of three generations, 5 recombinants out of 5 individuals were found (Race and Sanger 1968).

The affected *men* show hypo- or anodontia, more or less generalized hypotrichosis, lanuginous hair, absence of sweat and sebaceous glands with anhydrosis, ozena, and sometimes absence of lacrimal glands and eyelashes.

Heterozygous women show only a malformation of the teeth and hair which may be rarefied (Olinsky and Thomson 1970, Katz and Penneys 1971), mammary anomalies such as athelia or absence of nipples (Grant and Falls 1944) and a patchy absence of sweat glands (Reed et al. 1970).

When the skin of these women is covered with a starch iodine mixture and exposed to heat, the mixture turns blue in the sweating areas.

A severe form of the disease was seen in a 27-year-old Indian woman (Singh et al. 1962). Whether this was a homozygous or a heterozygous female is uncertain: no information on the father and on two possibly affected brothers was available.

8.2. *Metabolic Diseases*

There exist a number of rare genetic diseases, caused by an error of metabolism, which is either an enzymatic deficiency or the synthesis of an abnormal protein.

Some of these diseases can be diagnosed prenatally. Some of them can be treated medically and some surgically (cataract extraction).

A conjunctival biopsy is often helpful in the diagnosis of some storage diseases. Only a few of these are dominant. Most of them are recessive, and some sex-linked or sex-influenced, such as hyperamonemia type 2, Fabry's disease, Lowe's syndrome, Hunter's disease (MPS II), G6PD deficiency, Albright's hereditary osteodystrophy and metachromatic leukodystrophy.

8.2.1. Fabry's Disease

Fabry's disease or glycolipidosis is a recessive sex-linked metabolic disorder, which begins early in life. It is caused by a congenital disorder in the metabolism of the glycolipids and belongs to the sphingolipidoses. The glycolipids are deposited especially in the endothelium and in the smooth muscle cells of the vessels, but may be found also in all organs and tissues. The affected glycolipid is a ceramide-trihexoside and its accumulation is due to a ceramide-trihexosidase deficiency.

No causal links could be shown between the chromosomal pattern and the disease (Eberle and Denden 1969, Denden and Eberle 1970).

The linkage between Fabry's disease and Xg loci may be measurable: the recombination fraction was estimated to be around 0.27 (Opitz et al. 1965, Johnston et al. 1969). Fabry's-disease locus and deutan locus are probably close: the recombination fraction was 0.17 in the family studied by Johnston et al. (1969).

The males show angiokeratomas generally in the bathing-suit area, progressive renal insufficiency and other systemic signs (heart, lung, or brain involvement). There are ocular manifestations in at least 90% of cases. The most characteristic ocular sign is a whirl-like dystrophy of the corneal epithelium (cornea verticillata). There are also dilated and sausage-shaped vessels in the conjunctiva, a condensation of the anterior and posterior sutures of the lens cortex or sometimes a cataract, tortuous veins and arteries of the retina.

The *heterozygous women* show a vortex corneal dystrophy or cornea verticillata (Wise et al. 1962, Rahman 1963, De Groot 1963 and 1964, Von Gemmingen et al. 1965, Opitz et al. 1965, François 1966 and 1967, François et al. 1968).

Christensen Lou et al. (1970) found signs of the disorder in 11 individuals of the same family (7 females and 4 males). Five women presented skin lesions, 5 a pronounced corneal dystrophy. In one woman, abnormalities could be demonstrated in the conjunctival vessels, and in another woman, in the retinal vessels.

Brady et al. (1967) found a low ceramide-trihexosidase activity in an intestinal biopsy from the mother of a patient with Fabry's disease. In 4 females of two families and who were presumed to be carriers, Kint (1970) found a reduced alpha-galactosidase activity in the leucocytes.

8.2.2. Lowe's Oculo-Cerebro-Renal Syndrome

The inheritance appears to be sex-linked recessive (Streiff et al. 1958, Wilson et al. 1963, Abassi et al. 1968), as only boys are affected. Warburg (1972) notes, however, that the affected individuals die before puberty; so there is no offspring to verify sex linkage.

According to Berg (1969), the locus for Lowe's syndrome should not be close to the locus of the Xm group. He tested a family of three generations, in which 2 children were recombinants and 1 was a nonrecombinant.

In *men*, this syndrome, described by Lowe et al. (1952), is characterized by a renal tubulopathy with generalized aminoaciduria, a systemic acidosis, a vitamin-D-resistant renal ricketts, a generalized hypotonicity, a mental, psychomotor and growth retardation, and ocular abnormalities. The three main ocular abnormalities are bilateral congenital cataract, which is seen in nearly all cases (95%), bilateral glaucoma, which is found in 50% of cases and is always associated with cataract, and miosis.

Sporadic cases have, however, been described in *girls*.

Scholten (1960) described a girl with hypotonia, areflexia, aminoaciduria, slight proteinuria, and glucosuria, who did not have cataracts, but who had corneal opacities.

Svorc et al. (1967) observed a 2-year-old girl with bilateral congenital cataract, mental retardation, and proteinuria.

In *heterozygous women*, the following symptoms were noted: lens opacities or cataract (Wilson et al. 1963, Richards et al. 1965, Chutorian and Rowland 1966, Pallisgaard and Goldschmidt 1971), aminoaciduria after loading with ornithine (Chutorian and Rowland 1966).

After a search for lens opacities and oral ornithine loading tests in parents of children with Lowe's syndrome, Holmes et al. (1969) concluded that the female carriers cannot be detected:

no aminoaciduria was produced in either parent by the ornithine lodaing test and lens opacities were only found in both parents of one child. These lens opacities were similar to those found in 18 of 100 normal adult controls.

CONCLUSIONS

From the description of the X-linked eye diseases, it appears that there are only a few diseases, where the visual handicap is so great or the general condition so bad, that prenatal genetic counselling can be considered. These diseases are choroideremia, pigmentary retinopathy, myopic chorioretinal heredodegeneration, Norrie's disease, Fabry's disease, and Lowe's disease.

Ocular albinism, retinoschisis, microphthalmia, keratosis follicularis spinulosa decalvans, congenital anhydrotic dysplasia, cataract, external congenital ophthalmoplegia with myopia, essential hemeralopia with myopia, colourblindness, and nystagmus, are, in our opinion, conditions which can allow a more or less normal life.

From the eugenic standpoint, one might object the systematic, repetitive, and exclusive prevention of the birth of males possibly or certainly affected by a sex-linked disease, while allowing female possible carriers to be born. However, in view of the fact that in X-linked recessive heredity, the ratio mutants to segregants is rather high, this practice will not significantly change the gene frequency in the population. If applied systematically and on a large scale it might bring about an increase in the population's female to male sex-ratio. Female carriers, who obtain a therapeutic abortion for a male foetus possibly or certainly affected by a sex-linked disease, should be given complete information about the risks for their daughters' progeniture.

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RIASSUNTO

Sono passati in rassegna i principi fondamentali della consulenza genetica nelle malattie legate al cromosoma X. Vengono quindi descritte e discusse 18 malattie oculari legate al cromosoma X, riguardanti bulbo oculare, cristallino, coroide, nervo ottico, muscoli e pigmentazione, nonché manifestazioni oculari di malattie sistemiche della pelle o metaboliche.

RÉSUMÉ

Les principes fondamentaux du conseil génétique dans les affections liées au sexe sont exposés. Dixhuit maladies oculaires liées au sexe sont décrites et discutées. Elles concernent le globe oculaire, le cristallin, la choroïde, le nerf optique, les muscles oculaires, la pigmentation, ainsi que les manifestations oculaires des maladies de la peau ou des maladies métaboliques.

ZUSAMMENFASSUNG

Überblick über die Richtlinien für die Erbberatung bei den ans X-Chromosom gebundenen Krankheiten. Beschreibung und Erörterung von 18 ans X-Chromosom gebundenen Augenkrankheiten, die Augapfel, Linse, Aderhaut, Sehnerven, Augelmuskeln und Pigmentierung sowie die Augensymptome der Krankheiten des Haut-oder Stoffwechselsystems betreffen.

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