GENETIC COUNSELING IN X-CHROMOSOMAL-LINKED NEUROOPHTHALMOLOGICAL DISEASES

Status of the Female Heterozygote. Linkage and Crossingover with Xg Blood Group

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Among X-linked neuroophthalmological ailments, congenital nystagmus is particularly interesting because of the affected female heterozygote.
Linkage and crossingover with Xg blood group suggest that the locus of the nystagmic gene is on the long arm of the X chromosome.
A draft of genetic counseling is given according to the various possible family situations.

1. INTRODUCTION

X-linked neuroophthalmological illnesses are numerous: Leber's hereditary optical atrophy; Fabry's disease or diffused angiokeratosis; dyschromatopsia; Duchenne's muscular dystrophy; certain dysfunctions of the metabolism of the mucopolysaccarides, such as Hunter's or Morquio's diseases; Lowe's oculorenal syndrome; congenital nystagmus etc.

Among all these ailments, congenital nystagmus is particularly interesting. The affliction is frequently total in the heterozygote female. It is therefore a dominant sex-linked ailment. Nevertheless this penetrance is far from complete. Furthermore the expressivity is so variable that only the biomicroscope allows detection of certain affected subjects.

2. PERSONAL OBSERVATIONS[1]

We have observed a nystagmus family of 140, comprising 5 generations, 30 members are afflicted (Figure). The visual acuity of the latter is generally very diminished, not only from the ocular movement, but also from amblyopia and strong astigmatism. These serious handicaps justified a number of genetic counseling sessions.

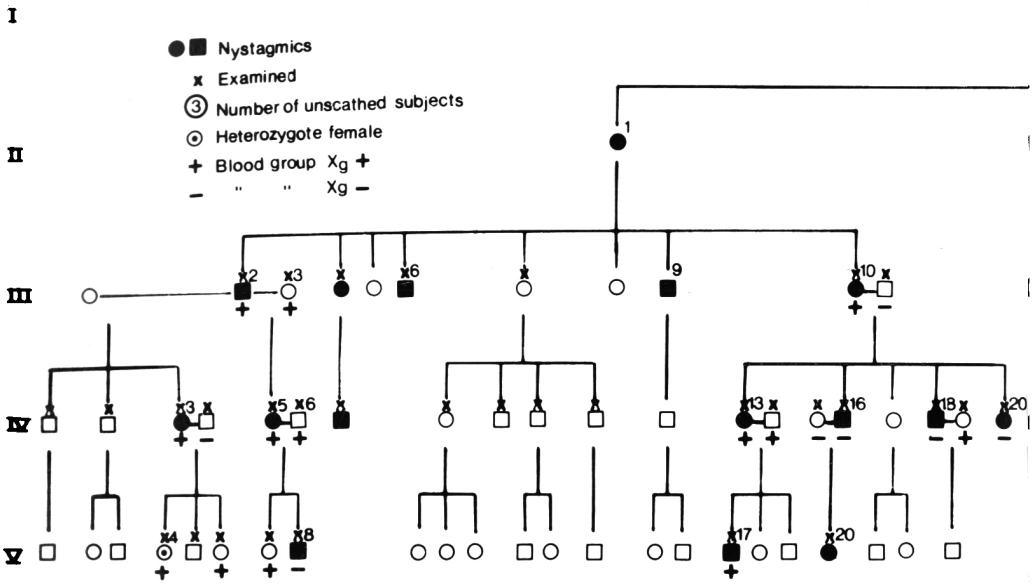
No other particular ocular malformation was observed; the macula was not affected, no retinal degeneration, no albinism, no coloboma or aniridia, no dyschromatopsia.

The absence of father-to-son transmission proves the existence of the link between the nystagmus gene and the X chromosome. The afflicted males had in all 7 sons, all unscathed. This is statistically significant ($0.990 < P < 0.995$).

The dominant character of the ailment is demonstrated by its presence in women. Here, howewer,

[1] Ophthalmological details concerning this family are published by Cuendet et al. (1973).

Proc. 4th Int. Congr. Neurogenet. Neuroophthalmol. (1973)
Acta Genet. Med. Gemellol. (*Roma*), 23: 211-215



the penetrance is not complete. This penetrance can be calculated in three ways: through the study of the descendants of nystagmic fathers; through that of nystagmic mothers; by the sex ratio.

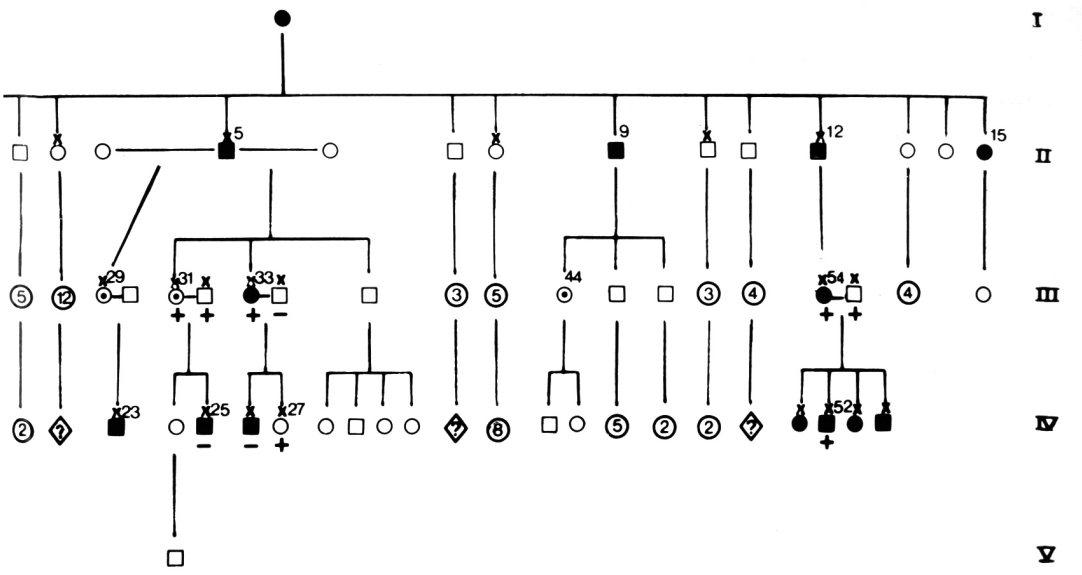
In the family which we observed, the arithmetic average of these three calculations gives $P = 0.55$.

3. Xg BLOOD GROUP

Among the known physiological hereditary properties related to sex, there are the Xm factor of the serum proteins and the Xg(a) blood group of the red blood cells. It is difficult to determine the Xm property of the serum proteins because of the rareness of the reactives necessary for its investigation. Therefore, actually, the Xg blood group, discovered in 1962, is today the sole physiological property known in connection with erythrocyte conditioned by a gene related to the sex. The determination of the Xg blood group, although delicate, is technically not difficult. It was particularly interesting to determine the Xg group in a family affected by another dominant X-linked gene. It should be noted that there are only two phenotypes, Xg(a+) and Xg(a—). In males, the genotype corresponds with phenotype. In females, on the other hand, the presence of Xg(a+) phenotype can be due either to a homozygotic (a+/a+) or to a heterozygotic (a+/a—) genotype.

The pedigree in the Figure shows the results of 30 determinations. The examinations were carried out with the help of two anti-Xg(a) sera of different sources and the activity of these sera was verified on known Xg(a +) and Xg(a —) red blood cells. If our Xg(a) results were correct, we may draw the following conclusions:

Subject IV/5 manifests a crossingover. She inherited from her father the nystagmus gene and the a+ on the same X. From her mother, she inherited a—. She could only have a nystagmic and a— son as a result of a crossingover between her two Xs during gametogenesis.



Note that the genetic constitution of the father (IV/6), which was a+, could play no role in these phenomena.

This crossingover suggests an important distance separating the two genes. It suggests that the locus of the nystagmus would be on the long arm of the X.

Among the affected females, 8 are a+ and 1 is a—. This proportion corresponds well with the Xg(a) blood group frequency in the Swiss population. This is 89% females a+ against 11% a—.

Among afflicted males, 3 are a+ and 5 are a—, whereas the frequency of the Xg(a) blood group in the Swiss male population is 67% a+ against 33% a—. This suggests a correlation between nystagmus and Xg(a—) in males. Howewer, the number of cases is too limited to draw any valid conclusions.

On the other hand, if in a given family the affected males have different Xg(a) blood group, this can only be due to repeated crossingovers, for initially the nystagmus gene must have been linked with either an a+ or an a—.

4. STUDY OF PUBLISHED PEDIGREES ON CONGENITAL NYSTAGMUS

Autosomal transmission is very rare. The great majority of published observations shows sex-linked transmissions with variable penetrance. As we did for our personal pedigree, we calculated the gene's penetrance through three differents methods.

All the intermediate values are so observed between dominance with penetrance as high as 73% and complete recessivity, that is, penetrance = 0. This proves the relativity of classic Mendelian concepts of dominance and recessivity. Far from be opposed, those two notions

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Author	Mean penetrance (%)
Hemmes 1924 (MM)	73
Waardenburg 1932 (Hemmes BB)	67
Waardenburg 1932 (Hemmes CC)	56
Cuendet et al. 1973	55
Clarke 1903	50
Hanhart 1953 and Semadeni 1939	47
Dubois 1913 (Hemmes Z)	43
Rucker 1949	38
Hemmes 1924 (HH)	36
Cox 1936	36
v. Kibort 1910 (Hemmes R2)	25
MacGillivray 1895 (Hemmes F)	10
Basu 1956	4
Engelhard 1915 (Hemmes AA)	3
Hemmes 1924 T	0

are simply the two extremes of the same inheritance that could move from one to the other end but usually stays in between. This position is as a rule the same in a given family for a definite gene.

5. STATUS OF THE FEMALE HETEROZYGOTE

The majority of affected females presents a severe nystagmus, serious amblyopia, and astigmatism, just as the affected males.

Nevertheless, some females like IV/13, IV/20 present only light syndrome with almost normal visual acuity. Furthermore, subject III/31, who was considered as nonaffected, shows very slight nystagmic eye movements only visible with magnification of the biomicroscope. Finally, subject III/29, genetically heterozygote, is completely normal.

In conclusion, the female heterozygote shows all the intermediate degrees between complete syndrome and normality. In one sibship (III/29, III/31, III/33) we observed three various phenotypes. Therefore we can ascertain that the gene nystagmus has an incomplete penetrance as well as a variable expressivity.

6. GENETIC COUNSELING

The severe amblyopia required several sessions of genetic counseling. We can summarize them as follows:

Father unscathed	R (risk) = 0
Father affected	R for boys = 0 R for girls = 1.0; P (penetrance) = 0.55
Mother affected or certainly heterozygote	R for boys = 0.5 R for girls = 0.5; P = 0.275

Mother possibly heterozygote, that is, descending of a nystagmic patient through filiation without any unscathed male. For instance, subject III/7 had a risk of 0.5 to be heterozygote. Now, she was phenotypically unscathed. According to the cases with lack of penetrance the risk of being heterozygote is $R = \frac{1 - P}{2}$.

For subject IV/8, $R = \left(\frac{1 - P}{2}\right)^2$

For subject V/9, $R = \left(\frac{1 - P}{2}\right)^3$

Generally, $R = \left(\frac{1 - P}{2}\right)^n$

n = number of unscathed generations after the affected patient.

This draft of genetic counseling is applicable not only for congenital nystagmus but also for the other sex-linked ailments with the necessary modifications due to the variability of the status in female heterozygotes.

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