# Principles and Practice of Clinical Electrophysiology of Vision


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# PART XVI

# Diseases of the Outer and Midretina

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# Introduction to Carrier Detection

Richard G. Weleber

Molecular genetic studies hold the promise for unambiguous detection of the carrier state for autosomal and X-linked recessive disorders as well as the heterozygote state for those autosomal dominant disorders with incomplete penetrance. For the present, electrophysiological studies, especially the electroretinogram (ERG), are useful in refining the likelihood that a given women is the carrier of certain forms of X-linked retinal disease such as X-linked retinitis pigmentosa, blue cone monochromacy, and X-linked congenital stationary night blindness (CSNB). Yet all such carrier detection that is based upon electrophysiological tests is limited by the phenomenon of X chromosomal inactivation. This is the process by which one of the two X chromosomes in all cells of females (except for the ovarian germ line) becomes condensed and inactivated from a very early stage of embryogenesis to form the sex chromatin, or Barr body. Women are thus mosaics of cell lines that express the genetic information for either their paternally derived X chromosome or their maternally derived X chromosome, but not both.

This inactivation of one of the X chromosomes occurs as a random event for each cell. Once this decision is made for a given cell, all clonal descendants inactivate the same X chromosome. Thus, inactivation is both random and fixed. The precise time of inactivation has not been determined and may vary in different tissues. Gardner and Lyon[4] found that inactivation could not be demonstrated prior to the 4.5-day-old blastocyst stage. Deol and Whitten[3] suggest that it may take place as late as at the time of determination of tissue primordia. If inactivation occurs earlier than usual, the grain or patch size of mosaicism increases. Conversely, if inactivation occurs later than usual, the grain or patch size of mosaicism becomes finer.

Since lateralization occurs close to the time of inactivation, a large patch size of mosaicism combined with early inactivation could result in marked asymmetry of carrier manifestations. The cells destined to differentiate into one of the two eyes may contain large patches of cells that express the abnormal gene-containing X chromosome, whereas those cells destined to form the other eye may contain mostly cells expressing the normal chromosome. Thus, early inactivation occurring prior to lateralization might account for those carrier women who show striking asymmetry of carrier manifestations.

On average, women are roughly 50-50 mosaics for maternal and paternal X chromosome inactivation. However, the actual number of cells expressing the paternal X chromosome for a large sample of women, for example, follows a bell-shaped normal distribution, with some women expressing the paternal X chromosome in either fewer or greater numbers of cells. Thus, if a given woman happens to inactivate the X chromosome containing the abnormal gene in a high percentage of her cells (in other words, selectively expresses the normal gene-containing X chromosome), then detection of the carrier state by a functional test alone may be difficult if not impossible.

Most investigators agree that for a given individual, the most useful information that can be provided by abnormal electrophysiological function is positive evidence of the carrier state. A normal electrophysiological test result could result either because the woman did not inherit the abnormal X chromosome and was truly normal or because the abnormal gene-carrying X chromosome was inacti-

vated in the great majority of her cells. Bayesian probability calculations can be used to refine the actual likelihood of the carrier state, depending upon the sensitivity of the test for detection of large numbers of known obligate or demonstrated carriers.[6]

Several reports have suggested that the ERG and/or electro-oculogram (EOG) findings may be abnormal in the carrier state for autosomal recessive retinitis pigmentosa,[1] Usher's syndrome,[2] and renal-retinal dysplasia.[5, 7–10] In general, such findings have been reported as parts of case reports or in uncontrolled studies, and other causes of abnormal ERG findings or biased determinations have not been rigorously excluded. If these disorders are in truth autosomal recessive, then no functional defects should be demonstrable in carrier parents. However, if these disorders are the result of homozygosity for autosomal dominant genes that in the heterozygous state create no significant clinical disease or disability but may still affect the retina, then one could imagine that detection of the heterozygous state would be possible by such functional tests. Controlled studies are needed to settle this issue.

Additional information can be obtained on the following x-linked disorders in other chapters: retinitis pigmentosa (Chapter 102), choroideremia (Chapter 103), incomplete CSNB (Chapter 98), retinoschisis (Frumke effect) (Chapter 104), and blue cone monochromaticism (Chapter 105).

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