Genetic Counseling in Retinitis Pigmentosa

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During his lifetime the practicing ophthalmologist will see more than a few retinitis pigmentosa cases. It is his responsibility not only to diagnose and prognosticate this eye disease, but also to set aside a little time in which to advise the patient and his family on its genetic aspects.

Retinitis pigmentosa has been established as a definite hereditary disorder. Therefore, the most important factor to consider for accurate counseling is the family history. Unfortunately, for one reason or another, this is not always available, and the investigator may need to rely on the nature and severity of the disease, examination of other members of the family, and the presence of other disorders. Pseudoretinitis pigmentosa caused by inflammation or drugs should be ruled out.

Family pedigrees of typical retinitis pigmentosa exist for nearly every known mode of genetic transmission. Over 90% of these pedigrees are concerned with an autosomal recessive gene, while 3% to 6% are related to an autosomal dominant gene. X-linked genes constitute 1% to 3% and may be recessive, intermediate, or dominant.

It is important to recognize the mode of transmission in individual cases. Unless this is done, no reliable eugenic advice can be forthcoming.

The autosomal recessive mode of inheritance is characterized by an unrevealing family history, although a history of consanguinity may be discovered (opinions vary, but this could be as high as 40%). This form of the disease is serious, with complete blindness by age fifty to sixty usually the rule. Parents of affected individuals are phenotypically normal.

Also characteristic of the recessive gene is the frequent association with other disorders. Such coexisting anomalies may offer a clue to the recessive nature of this gene when family history is lacking. The relationship of retinitis pigmentosa to any congenital anomaly is too great to be explained by mere coincidence. Most notable are afflictions of the aural, metabolic, genitourinary, musculoskeletal, and central nervous systems. Ten to 40% of retinitis pigmentosa is associated with sensorineural hearing defects alone, either congenital or acquired and with or without mutism. Deafness may be late or incomplete, and in such instances it is manifested initially by loss of the higher frequency sounds. Indeed, approximately 10% of all children with this type of hearing defect will later show signs of retinitis pigmentosa. The penetrance of the involved gene for hearing loss varies among the members of a pedigree of retinitis pigmentosa. Probably a single gene with pleiotropic action is responsible for this close association, and not a situation of polygenic heredity. Of particular interest is the fact that approximately 13% of heterozygotes demonstrate slight loss of hearing; thus an audiometric examination of non-affected members as well as affected members of a pedigree may prove valuable in determining recessiveness.

The CNS associations comprise mostly diencephalic-hypophyseal manifestations. Epilepsy may be present, as well as mental retardation, EEG abnormalities, and psychiatric disorders (most notably, recurrent depressive episodes, schizophrenia, and paranoia). Metabolic disorders are usually those of the lipidoses.

Many of these genetic combinations form very interesting and well-recognized syndromes:

Usher's Syndrome—retinitis pigmentosa deafmutism

Hallgren's Syndrome—retinitis pigmentosa, congenital deafness, vestibulo-cerebellar ataxia, schizophrenia-like symptoms, mental deficiency

Refsum's Syndrome—atypical retinitis pigmentosa, polyneuritis, spinocerebellar ataxia

Cockayne's Syndrome—retinitis pigmentosa, dwarfism, deafness

Bassen-Kornzweig Syndrome—atypical retinitis pigmentosa, acanthocytosis, Friedreich's ataxia

Spielmeyer-Vogt Syndrome—retinitis pigmentosa, multiple CNS manifestations
Kearns-Sayre Syndrome—retinitis pigmentosa, heart block, progressive ophthalmoplegia externa
Laurence-Moon-Bardet-Biedl Syndrome—retinitis pigmentosa, obesity, hypogenitalism, polydactyly, mental retardation
Hurler's Syndrome (and other mucopolysaccharidoses)—retinitis pigmentosa, corneal haze, gargoylism

The autosomal recessive form of retinitis pigmentosa is also associated with other eye disorders. Myopia of over two diopters is present in 30 to 40%. Keratoconus and glaucoma occur more frequently than in the normal population.

The autosomal dominant mode of transmission is usually more benign and much later in onset. Related congenital anomalies are not common; hearing loss is rare. Complicated cataracts are, however, more common than in the recessive form. At least three consecutive generations of affected individuals should be elicited from the family history to firmly establish this mode of inheritance. But this gene is not always regular; it may skip one or more generations, although such an occurrence is rare. According to most genetic investigators, mutations do not occur. This form of retinitis pigmentosa is apparently on the increase because of the gene's dominant nature and because "survival of the fittest" hardly holds true in today's society. Since one-half of an affected person's offspring (without regard to sex) will similarly be affected, prevention of such requires sterilization or abstinence from procreation. Proper thinking on the part of most should dictate their not bringing into the world others who inevitably would go blind. Counseling should be guided by this philosophy.

Pseudodominance refers to that situation where an affected individual (with recessive genes) mates with a heterozygous person, resulting in one-half of offspring affected. Such circumstances could easily fool the investigator into believing a dominant gene to be responsible. Consanguinity is almost always the rule in these cases.

The X-linked mode of inheritance is, as previously mentioned, of three types. Generally these modes are manifested by retinitis pigmentosa of the severest order. Of these, the X-linked recessive is the most frequent. In nearly 100% of such cases there is myopia of greater than two diopters. The X-linked dominant is very rare and typically abortive with little pigment. In this instance the female carrier is herself affected, usually at a later age. The X-linked intermediate form is equally rare. Of particular interest is the so-called "tapetoretinal reflex" in the female carrier, a brilliant silvery scintillation more pronounced in the macular area but covering the entire fundus in many cases. The affected males may have choroidal sclerosis in addition to the pigmentary degeneration. Female carriers should be made aware that half of their male offspring will be affected. Affected males should realize that all of their daughters will be carriers.

In offering genetic counseling, one would be wise to realize that patients and members of their families prefer that probability figures be expressed as "odds." Fraser Robert's yardstick, specifically that one of 40 random pregnancies will yield a child with one or more congenital anomalies, should suggest to the physician that absolute assurance might not be a sound policy. The autosomal dominant and X-linked modes of transmission are easily recognized in most instances, and the subsequent counseling is rather straightforward.

Most counseling will, of course, be concerned with the autosomal recessive gene. Here one would do well to remember an important statistic. The frequency of affected homozygous persons within the human population is one in twenty thousand. If "p" is the frequency of the normal gene and "q" the frequency of the defective gene, then $p + q = 1$. Squaring both sides gives $p^2 + 2pq + q^2 = 1$, which is the binominal equation of probability. Here, p^2 is the frequency of normal homozygotes, $2pq$ of normal heterozygotes, and q^2 of affected homozygotes. Since $q^2 = 1/20{,}000$, then $q = 1/141$, this being the frequency of the defective gene. The frequency of heterozygotes is thus $2pq = (2)(1 - 1/141)(1/141)$, or $1/71$. This means that the probability that an affected individual married to a normal person with no family history of the disease will give birth to an affected child is $(\frac{1}{2})(1/71)$, or one chance out of 142. The probability that a known heterozygote married to a normal person will have an affected child is $(\frac{1}{4})(1/71)$, or one chance out of 284. These odds are more than favorable, and the physician is not justified in recommending that such individuals should not rear children. Eugenically speaking, such needless advice would serve only to reduce very slightly the frequency of the defective gene, and at the sacrifice of the happiness derived from a new face in the home.

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