# GENETICS AND THE OPTOMETRIST

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April 1988

# ABSTRACT

There are many ocular conditions and anomalies which are inherited. These can range from eye color to severely vision debilitating and even lethal disorders. The optometrist may be the first health care professional that a patient consults, when a symptom of a genetic disorder arises, Optometrists may also play a role in the management of a genetic disorder through the use of low vision aids. Patients with genetic disorders or family members with genetic disorders may also inquire about odds and risks to their children or themselves.

Therefore, it is important for the optometrist to at least be familiar with some of the basic concepts involved in genetics. He or she should be familiar and able to recognize some of the more common genetic ocular disorders and know what is the best course of management for these patients. He or she should also know that genetic counseling is a complicated matter involving many factors and issues, It is dangerous for the optometrist to give "off the cuff' genetic advice. Consequently,the optometrist should know where and how the patient can get professional genetic counseling to seek the answer to his questions.

The purpose of this paper is to acquaint the reader with some basic genetic concepts, some genetic ocular disorders, and referral sources for genetic counseling.

There are many ways a trait or traits can be inherited. these are referred to as modes of transmission. The autosomal dominant and recessive modes involve a single gene carried on one of the somatic or non-sex chromosomes.

## AUTOSOMAL DOMINANT

The autosomal Dominant mode of inheritance is monogenic, meaning that only one mutant gene is required for the expression of a trait or traits. As a rule, most autosomal dominant genotypes are phenotypically expressed and transmitted directly from an affected parent to the offspring with the trait appearing in each generation.

Autosomal Dominant diseases tend to be milder than other modes of genetic disease. (e.g. inherited ptosis is autosomal dominant compared to Tay sachs, an autosomal recessive disease.) This is because defective autosomal dominant genes tend to produce structuraldevelopmental anomalies rather than inborn errors of metabolism. Therefore it is not feasible to use biochemical assay for finding defective enzymes in a carrier or a fetus, such as is done in amniocentesis.

As stated before, most autosomal dominant genotypes are phenotypically expressed. However, the phenotypes may be expressed in varying degrees . this variation is called expressivity and relates to the severity of the affected phenotype. Phenotypes that are not clinically shown even though the person carries an abnormal gene are said to be of reduced penetrance or forme fruste.

The following is a list of general rules associated with the autosomal dominant inheritance mode.

**1. Fifty percent of the offspring are at risk if there is one affected parent.[1].**

**2. Males and females are equally affected.**

**3. Unaffected persons will not transmit the defective gene to their offspring unless they have forme fruste. This may cause a trait to appear to skip a generation.**

**4. The affected individual has an affected parent.**

5. **Genotypes are revealed by phenotypes.**

6. **Expressivity may vary greatly**

7. **Relatively mild defects occur and mental retardation is not likely.**

The autosomal dominant inheritance mode diseases are documented more frequently than any other single gene (monogenic) mode. Approximately 25% of the 1,489 known autosomal dominant phenotypes have some kind of ocular manifestation.

Pleitropy, or multiple phenotypic effects may occur with the autosomal dominant mode. For example, Marfan'syndrome shows varying effects such subluxated lenses, arachnadactyally, weak aortic vessel walls, and elongated limbs and torso.

Some examples of autosomal dominant phenotypes are the following;

Marfan's syndrome (see above)

Best's macular dystrophy or vitelliform dystrophy is a dsystrophy of the retinal pigment epithelium. It is usually a bilateral condition that first manifests at the age of five as a yellowish discoid formation at the macula. The patient suffers from diminishing acuity that slowly progresses to 20/200 or worse. Later, the macula resembles an egg yolk as it has a yellow discoid center. The disc may appear to disintergrate or rupture at the onset of the next stage which is known as the scrambled egg stage. Ultimately, round areas of chorioretinal atrophy are seen at the macula. Besides the acuity loss, the patient may suffer from a color vision loss and central scotoma. The EOG is an important diagnostic tool, as it shows to be subnormal, even in carriers who are opthalmoscopically normal,

Familial drusen are found on the vitreal side of Bruch's membrane. They are hyaline accumulations secreted by the retinal pigment epithelium, and first appear as yellowish spots in the deep retinal layers of the posterior pole when the person is 20 to 30 years of age. Later the spots become whiter, more defined , and increase in number. They become arranged in a honeycomb pattern around the macula. Visual acuity is seldom affected before the age of 40, and then there is usually little decrease in acuity. Differntial diagnosis should be made to rule out degenerative drusen or the flecks that appear with other "flecked retina " syndromes.

Several types of ptosis have been found to be autosomal dominant. These have been either congenital or non-congenital. these are not to be confused with the neurologically induced ptosis, which must be ruled out, but they are usually due to a structual deficiency in the striated fibers of the levator muscle. Management centers on the prevention of amblyopia and cosmesis. Sometimes a surgical correction is obtained.

Retinoblastomas are malignant tumors that arise most often from the inner nuclear layer of the retina. The tumor may be present at birth, but usually occurs at about 18 months. The incidence is 1: 23,000. It is usually inherited in the autosomal dominant manner, but may also arise due to chromosomal abberrations. The autosomal dominant form is usually bilateral and is more likely to involve secondary neoplasms in the body. Usually the diagnosis is made after the tumor has protruded forward into the vitreous and is visible in the eye as a grayish yellow reflex behind the lens. Because of poor vision, strabismus may ensue. Ophthalmoscopically, the tumor appears as a pale pink mass with newly formed blood vessels on its surface. When the case is unilateral, enucleation including as much of the optic nerve as possible is the preferred treatment. In a bilateral case, enucleation of the most involved eye and radiation and chemotherapy of the other eye is prefered. Prognosis depends on the number and size of the tumors involved, and whether metastasis has occurred. 80% of the deaths involving retinoblastoma are due to metatastic neoplasms, If an affected patient has either an affected sibling or parent, his offspring have a 40% chance of affliction. If a family has only one affected member, there is only a 1.1% chance of further offspring being affected.

Many of the corneal dystrophies are inherited in the autosomal dominant mode. The corneal dystrophies tend to progress with the age of the afflicted individual, Many do not seriously interfere with vision , but create interesting patterns on the normally clear cornea. Others can lead to serious vision loss. Meesmans corneal dystrophy involves dots, cysts, and swirls that appear on the epithelium in interesting patterns. Management in these cases is totally directed toward treating the symptoms. Serious loss to vision usually does not ensue. Lattice dystrophy becomes evident in young adults. Their anterior corneal stroma contains irregular lines and patterns made of amyloid that have become locally synthesized in the cornea. Painful epithelial erosions along with decreased acuity occur early in life. Early lamellar keratoplasty may be indicated.

# AUTOSOMAL RECESSIVE

The autosomal recessive mode of inheritance is also a single gene mode. Unlike the autosomal dominant mode, genotype is not necessarily expressed in the phenotype. Two defective allelesare needed for expression of an autosomal recessive trait or defect. In other words, a homozygous individual is required for expression.

Conditions associated with the autosomal recessive are severe, as they are usually due to inborn errors of metabolism. Expressivity usually does not vary as it does with the autosomal dominant mode. This may be due to the marked severity of many of the phenotypes. Of the 1,117 autosomal recessive phenotypes documented, 22% have associated ocular manifestations.

There is a high proportion of carriers in relation to afflicted because of the homozygous requirement for expression. There have been great advances made in the identification and detection of carriers via biochemical means of blood testing parents and amniocentesis of fetal cells to determine abnormal homozygous genotype. Because two carriers are required to produce an afflicted offspring, it is more likely that a relationship involving consanguinity produce an affected child.

The following is a list of general rules involving the autosomal dominant inheritance mode.

1. Parents of an affected child are usually clinically normal, but both parents are carriers.

2. Males and females are at equal risk.

3. Risk to offspring is 25% if both parents are carriers.

4. Transmission from an affected parent to offspring can only occur if the affected parent marries a carrier for the same defect. In this case 50% of the children are at risk for the disorder and the others will be carriers. If there two affected parents, 100% of the children will be affected.

5. Afflictions are severe

6. Biochemical assay is useful in the detection of carriers and affected individuals.

An example of an Autosomal recessive defect that is important to the eyecare professional is general albinism, in which there is An absolute defiency of the enzyme tyrosinase, causing a lack of melanin production. In these patients, the maculae are poorly developed and corrected acuities are significantly reduced (20/100). In addition, there is usually the presence of high myopia, marked astigmatism extreme photobia and rapid nystagmus. Low vision aids along with antiglare devices are important to the management of these individuals.

Achromatopsiais another autosomal recessive disorder. This is a rare disorder in which the affected person has no color perception as we know it. The patient is usually photophobic, has nystagmus and reduced distance acuities of 20/200 to 20/600. The acuity deficit remains stable throughout life. In addition, the patient may have mydriatic but responsive pupils, central scotoma, astigmatism and optic disc pallor. These patients may also be managed with the use of low vision aids and anti-glare devices.

Stargardt's Macular Dystrophy or juvenile type macular dystrophy is usually autosomal recessive. It is characterized by normal acuity during childhood followed by rapid bilateral acuity loss in the second decade of life, progressing to around 20/200. Macular changes may at first be unnoticeable, but later the maculae take on a granulate appearance and yellow flecks may appear in the posterior pole. This is similar to Fundus Flavimaculatus ,which is also autosomal recessive. Again, low vision aids are useful with these patients.

Although most of the corneal dystrophies are autosomal dominant in nature, Macular corneal dystrophy is autosomal recessive. Studies suggest that there is a primary defect in the metabolism of the keratocytes in which there is a genetically determined local enzyme defiency leading to mucopolysaccharide storage. The manifestations first appear between age 5 to 9 and start as diffuse clouding in the superficial parts of the central cornea. The clouding increases throughout the second decade of life and involves the full thickness of the stroma. Nodular opacities appear in the third decade of life along with surface and thickness irregularities . By age 40, the patient is essentially blind.

Tay Sachs is a serious neurological, autosomal recessive disorder that is caused by an inborn meatobolic error involving an enzymatic defect and a build up of lipid storage in the glial

cells of the nerves leading to demyelinization. It is found to occur primarily Jews of east European descent. Life expectancy is seldom beyond two years. The affected child will have nystagmus,strabismus and poor vision that will lead to total blindness due to optic nerve atrophy. A cherry-red spot at the macula is the classic sign of the disease. Along with loss of vision, the child will suffer from mental retardation, convulsions, and progressive spasticity.

## THE SEX-LINKED PATTERNS

The previously discussed hereditary patterns have been controled by loci located on one of the 22 pairs of autosomes, The sex-linked patterns are governed by genes on the X or Y chromosomes.

More information is available about genetic loci on the X chromosome than any other chromosome in the chromosomal complement. This is because, in the male XY condition all loci on the X chromosome, whether dominant or recessive are phenotypically expressed. The reason being that the small Y chromosome has very few if any loci in common with the X chromosome, thereby giving the male only one dose of the genes on the X chromosome.

Males cannot be heterzygous or homozygous at these loci, but instead, are hemizygous which literally means half zygotes. Loci found only on the X chromosome are specifically referred to as X-linked and are always expressed in the hemizygous male.

## X-LINKED RECESSIVE

The X-linked recessive inheritance mode of transmission is also monogenic. It involves defective gene loci carried on the X chromosome. The X chromosome is the site of many genes effecting ocular abnormalities. This,combined with the fact that this transmission mode follows recessive guidelines is the reason that many of the genetic ocular disorders are X-linked recessive and makes understanding of the mode important to the eyecare practioner. In fact, of the 205 X-linked recessive phenotypes, 33% show ocular manifestations.

The following is a list of general guidelines regarding the X-linked recessive pattern.

1. Males are predominantly affected, practically all abnormal phenotypes in a pedigree are male. and both parents are non-affected.

2. A female carrier will theoretically transmit the defect to half of her male offspring.

3. An affected male will not transmit the disease to his male offspring, but all daughters of an affected male will be carriers.

4. Fifty percent of a female carrier's brotherswould theoretically be affected. therefore careful history of maternal uncles is valuable in pedigree analysis

5. Biochemical assay is sometimes used for detection of defective genes.

6. Sometimes, female carriers may express some subtle abnormalities which may allow for their identification.

7. Purported fatherhood should be questioned if an X-linked recessive is expressed in a daughter of a male not affected by a trait. (This follows a general rule that fatherhood should be scrutinized in genetic counseling.)

The mutant gene for color vision deficiencies is carried on the X chromosome. The congenital color deficiencies are divided into three types; 1. protan (red weak) 2. duetan (green weak) 3.tritan (blue weak). All three types are X-linked recessive. The prevalence for white males is 8.0%. for females it is 0.4% Occupational counseling rather than genetic counseling takes importance for these patients.

Leber's optic atrophy is thought by many to be x-linked recessive, although other means of transmittance have been proposed.. It is most often found in males, and is characterized by a rapid severe acuity loss in the second or third decade. Later, there is stabilization and sometimes slight improvement. In the acute stage,the disc appears hyperemic, swollen, and has telangiectatic capillaries extending from it, which characteristically do not leak fluorescein. The nerve fiber layer is swolen and opacified and the internal limiting membrane appears wrinkled. as the swelling of the disc recedes, a flat , pale disc remains. Visual fields show dense

central scotoma including the blind spot. The degree of symmetry and the failure to reactivate help to distinguish

Leber's from the retrobulbar neuritis of multiple sclerosis. Treatment with massive doses of hydroxycobalamin and steroids is controversial.

Retinitis pigmentosa is actually a group of several diseases, each with the triad of night blindness, constricted visual fields and typical fundus appearance. Purely ocular RP can be inherited in the autosomal dominant, autosomal recessive, and X-linked recessive modes. The X-linked recessive mode is usually the most severe. The disease primarily affects the retinal rods. It typically begins in adolescence with night blindness and peripheral field loss which is so insidious, that it is not noticed until there is extreme constriction of the field. Photophobia and glare are important secondary symptoms of the condition. The earliest internal changes are seen at the equatorial retinaas areas of atrophy and retinal pigment epithelium hypertrophy which give a dappled appearance. the disk appears waxy with pallor and there is attenuation of the retinal arterioles. Advanced cases have intraretinal bony corpuscular pigmentation in the retina and atrophy at the disk. As the condition progresses, the visual fields become more and more constricted , leading to tunnel vision. The macular area is usually spared until very late in the progression of the disease. These patients may benefit by the use of tinted lenses to reduce glare , mobiltiy training for adaption to the field constriction, and also, fromlow vision devices that expand visual field. Vitamin A treatments has been a controversial treatment used to try to slow down progression of the disease.

Retinitis Pigmentosa is also associated with many well known syndromes, such as Usher,s syndrome, Laurence-Moon syndrome, and Leber,s amaurosis.

<u>Ocular albinism</u> is inherited as an x-linked trait and is manifested only in males. These patients have nystagmus, and hypopigmentation of the iris and retina, Distance acuity is ususlly reduced, but acuity at near may be near normal. Extreme photophobia and strabismus are common with the trait.the effects are liimited to the retinal pigment epithelium and the uveal tract. There are no other cutaneous signs of albinism. Female carriers of the trait may have irides that show transillumination.

# X-LINKED DOMINANT

The X-linked dominant transmission mode is a single gene inheritance mode. The x-linked modes involve gene loci ocurringon the X chromosome.

Although there are many genes on the X chromosome that cause ocular anomalies, the recessive rather than the dominant defective genes are always involved. As such, the diseases and syndromes which fall under the X-linked dominant transmission do not involve major ocular defects. therefore, this mode of transmission is of lesser importance to the eye care practioner.

The following is a list of the general rules involving the X-linked dominant inheritance mode.

1. because of the dominant effect, thegenotype shows the phenotype. Thus, there are no carriers.

2. All daughters of an affected male show the trait.

3. An affected male will not transmit the trait to his sons

4. When the female is the affected partner, 50% of the male and 50% of the female offspring are at risk of having the defective gene.

5. Since the male does not have a normal gene on the Y chromosome to balance the defective gene on his X chromosome the male hemizygote (having XY chromosome pairing) may show more clinical manifestations than the female heterozygote , (XX) and is occassional lethal.

6. Theoretically, there are twice as many females as males affected .

# COMPLEX INHERITANCE PATTERNS

The complex heredity patterns include multiple inheritance patterns, chromosomal abnormalities, and polygenic or multifactorial disorders. These inheritance patterns do not follow the rules governing the monogenic transmission modes. This combined with the fact that they are more unpredictable than the monogenic modes, makes pedigree analysis of a defect or trait very difficult.

## Multiple Inheritance Patterns or Genetic Heterogeneity

These are genetic disorders which can be inherited in more than one manner. The clinical manifestations of the disease however are very similar even though the disorder is due to different types of genetic transmission. Strictly speaking, if there are three modes of inheritance possible , there three different diseases, no matter how similar they may seem. One example of this is Retinitis Pigmentosa. This is most commonly observed as an X-linked recessive disorder. However, families representing autosomal dominant and autosomal recessive modes of transmission have been reported. R.P. can also be associated with other systemic disorders and syndromes, such as Hurlers syndrome.

Another example of genetic heterogeneity is genetically caused retinoblastoma, which can be either autosomal dominant or a chromosomal defect. Likewise, general albinism can be either autosomal recessive or autosomal dominant.

## Chromosomal Abberations

These are defects involving some mutation to the chromosome itself. Most Chromosomal errors involving autosomes are either lethal or severely debilitating, and mental retardation is frequent in survivors. The mutations involving the sex chromosomes are usually not as severe. Biochemical analysis is not feasible for detection of a defect, but rather, karyotyping or chromosomal analysis is of primary importance. There are several subdivisions of chromosomal abberations.

## ANEUPLOIDY

One subdivision is aneuploidy. It is an abnormality in the number of chromosomes present. It may occur during cell division of either the autosomes or the sex chromosomes ( mitosis or meiosis ) . such abnormalities occur during early mitotic divisions of the fertilized ovum and are termed nondisjunction.

The normal chromosomal count in diploids (2n) is 46 an example of an aneuploidic cell is one containing 2n + 1 chromosomes, for a total of 47. This condition is termed trisomy. In contrast,a monosomy is the absence of one chromosome from one normally paired group, resulting in a hypodiploid state for a total of 45 chromosomes (2n - 1).

Polyploidy is also a condition involving abnormal chromosomal count. Exact multiples of the normal diploid (2n) number; e.g. 3n (69) , 4n (92).

One example of aneuploidy is Down's syndrome or Trisomy$^{21}$ Syndrome. This disorder is usually due to an extra number 21 chromosome. the most common ocular findings are epicanthal folds, esotropia, high refractive errors, Brushfield's spots, ( transient yellow spots on the irides), cataracts (occuring in 50% of cases), and kerataconus in some cases. The ocualr signs are accompanied by moderate mental retardation, dwarfism, and a mongoloid-type facial appearance. Pregnant women over the age of 35 have an increased risk of bearing a Down's child. Karyotyping after the first trimester can determine the diagnosis.

## TRANSLOCATION

This is a structural alteration of chromosomal material in which

part of the genetic material from one chromosomal pair is exchanged for that of another nonhomologous pair. It may be initiated during an abnormal break of a chromosomal arm during

cell division.

One example of translocation is Down's Syndrome in which genetic material from another chromosome appears on the number 21 chromosome in the cells of the affected individual. Clinically this is the has the same affects as trisomy 21 Down's syndrome.

## DELETION

Deletion invloves the loss of part of a chrosome during the process of cell division. The cause is unknown , but the exposure to certain toxins, radiation, and disease during pregnancy have been implicated. When the first child is affected it is useful to determine if the chromosomes of both parents are normal. If they are,there is little chance of a second child being affected.

One example of deletion is Wolf's Syndrome, in which there has been a deletion of genetic material from chromosome number 4. The results of this are low birth weight, mental retardation, strabismus , broad bridge of the nose, abnormal ears and ocular colobomas.

Another example is Cri du chat or Cat Cry in which genetic material from chromosome number 5 has been deleted. This syndrome is named so because a child with this condition sounds like a cat mewing when he cries. In addition the child is mentally retarded, microcephalic,hyperteloric, and has pecularities of the hands and feet. Ocular manifestations include micropthalmia, lid coloboma, cataract, optic atrophy, and high refractive error.

Retinoblastoma can be caused by a deletion of chromosome number 13. It is much rarer than retinoblastoma which follows the autosomal dominant mode, but it has the same clinical manifestions.

## Multifactorial or Polygenic Transmission

Disorders in this category are inherited only when a variety of genes combine with each other, with or without environmental influences. The number of multifactorial traits is greater than for any other mode of inheritance. These are traits that are said to run in families. However, expressivity varies greatly with these phenotypes, and it can depend on the proportions of environmental and genetic influence. Risk of inheritance is correlated with the closeness of relationship ,and is estimated on data of past family history . It decreases sharply with remoteness of relationship. However predictions are precarious since so many influences play a part.

Two major ocular anomalies that have been reported to follow this mode are refractive error and strabismus. Diabetes mellitus in adults is a multifactorial disease that can be aggravated by environmental influences such as poor nutrition. Hypertension is another multifactorial disorder that can have ocular associa1tions and can have vast environmental influences.

# GENETIC COUNSELING

As can be gathered from the information given so far, human genetics is a very involved subject. Therefore, genetic counseling should never be done without a completely accurate diagnosis. In most cases, the primary eye care practioner will refer the patient to a medical as well as genetic specialist.

Genetic counseling is a specialized branch of modern medicine and traditionally is done in large medical institutions. Such indications for referral to genetic counseling centers include:

1) Genetic or congenital anomaly in a family member;
2) Abnormal somatic or behavioral development in a child:
3) Mental retardation of unknown etiology in a previous child;
4) Pregnancy in a woman older than 35 years of age
5) Specific ethnic background that may suggest a high rate of genetic abnormality;
6) Drug use or chronic exposure to possible teratogens or mutagens;
7) Three or more spontaneous abortions and/or early infant deaths
8) Infertility.

According to the book, Genetics, Law, and Social Policy, the most widely used definition of genetic counseling now emphasizes communication as its critical element. The book defines genetic counseling as a communication process which deals with the human problems associated with the occurance, or risk of occurance of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to achieve the following goals;

1) Comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management;

2) Appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives;

3) Understand the alternatives for dealing with the risk of recurrence;

4) Choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and to act in accordance with that decision;

5) To make the best possible adjustment to the disorder in affected family member and /or to the risk of recurrence of that disorder.

While achieving the above mentioned goals, certain criteria should be maintained by the counselor. He must make sure the consultee feels at ease to be honest and open on all the issues raised in a session. He must ascertain that the consultee understands what has been discussed, by stating the mechanics of inheritance in the simplest terms and use layman's vocabulary where possible. Also, the sessions should remain confidential.

After the impact of the diagnosis has been made on a consultee, the counselor may help guide the consultee through three common psychological stages described in the literature. Stage one involves shock and disorgnaization. The second is rationalization denial and blame casting, where relatives blame each others side of the family for being the cause of a defect. The third stage is equalization where the parents or consultee are able to act realistically and function effectively to deal with the genetic condition.

The Department of Health and Human Services publishes a comprehensive national directory of clinical genetic service centers as a resource guide for administrators and health profressionals who deal with individuals and families affected by or concerned with genetic disorders. It identifies names, addresses and contact persons of clinical genetic service centers throughout the United States. This guide can be obtained through the Public Health Service , Health Resources and Services administration, or it can be found in the government documents section of the public library. The directory identified several counseling services in the state of Michigan, including locations in Detroit, East Lansing, Ann Arbor, Grand Rapids, Flint , Kalamazoo, and Royal Oak.

Other referral sources include The March of Dimes. Since the elimination of poliomyelitis as a public health problem, The March of Dimes has directed its efforts toward the prevention of birth defects and improving the outcome of pregnancy. They have funded the establishment of many diagnostic and counseling centers, many which are now supported by funds appropriated under the National Genetic Diseases Act. There are also many other organizations and support groups that are targeted toward those suffering from more specific genetic ailments, such as the Muscular Dystrophy Association.

## Conclusion

It is important for the optometrist to be able to recognize and somewhat understand the mechanics of transmission and expected course of a genetic ocular disease. In this way, the optometrist is more useful in providing management services to the patient, not only directly, as through treatment or vision aids, but indirectly, as through making the correct referrals for further treatment or genetic counseling.

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