Genetics of Corneal Disease for the Ocular Surface Clinician

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ABSTRACT **Advances in the understanding of inherited corneal and external diseases may allow interventions that prevent the substantial vision impairment currently caused by these diseases. The observant clinician may first recognize inherited corneal and external diseases based on clinical examination and a careful family history. Researchers using positional cloning and candidate gene techniques have identified several disease-causing genes. Identification of the genes responsible for inherited corneal and external diseases will lead to more definitive diagnoses and represent the first step in development of effective therapies. Future endeavors are directed toward identifying additional inherited corneal and external diseases, the genes that cause them, and possible gene therapies to improve visual outcomes.**

KEY WORDS **candidate gene, corneal dystrophy, corneal genetics, gene testing, gene therapy, genotype-phenotype, inherited corneal disease, positional cloning**

I. INTRODUCTION

This is an exciting time in medicine and ophthalmology, as new technologies are allowing rapid advances in the discovery of etiologies and mechanisms of inherited disease and progress toward novel interventions and treatments. Genetic mutations associated with many diseases of the cornea and external eye have already been mapped to specific chromosomes. The clinician should be able to recognize possibly inherited disease, enabling accurate diagnosis that may lead to a treatment, patient counseling, or further research. Understanding corneal disease and genetics is important for clinicians and researchers, as both will play an important role in the understanding and management of inherited corneal disease.

II. GENETIC PRINCIPLES

Clinicians can contribute to identification of inherited disease by obtaining thorough family histories from their patients and looking for an inheritance pattern or family linkage. Similar clinical signs or symptoms in family members may suggest a genetic etiology. A family tree demonstrating affected and nonaffected family members can be diagrammed (Figure 1). Inheritance patterns include autosomal dominant, autosomal recessive, x-linked, y-linked, and mitochondrial. These patterns are described in Table 1. The likelihood of a genetic contribution to a particular disease entity can be demonstrated by twin studies that show high concordance in twin pairs. Sibling studies may also support possible genetic etiology. Keratoconus has been extensively studied in twins. Although many cases of keratoconus are sporadic, the twin studies suggest heritability.[1-6]

Genes are made up of sequences of **DNA** (deoxyribonucleic acid). The human genome contains approximately 50,000 genes. Variations in DNA sequence encode differences in proteins and, in turn, may determine individual characteristics or inherited traits. *Genotype* refers to the genetic makeup of an individual; *phenotype* refers to the observable physical characteristics.

The phenotype may be determined by the genotype, but it may also be modified by the environment or other factors. Different phenotypes may be caused by the same genotype. For example, Reis-Buckler's dystrophy (granular corneal dystrophy type III), Thiel-Behnke dystrophy (honeycomb dystrophy), and granular and lattice corneal dystrophy are all associated with mutations in the BigH3 gene.[7,8] Conversely, the same phenotype may result from different genotypes. For example, mutations in over 30 genes, including rhodopsin, peripherin, ROM1, cGMP

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Abbreviations are printed in **boldface** where they first appear with their definitions.

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OUTLINE

phosphodiesterase and cGMP-gated channel alpha subunit, are all associated with the same retinal disease, retinitis pigmentosa.[9] Among corneal diseases, posterior polymorphous dystrophy can be caused by mutations in VSX1 or COL8A2.[10-12] Fuchs' endothelial corneal dystrophy and keratoconus may be similar to retinitis pigmentosa and posterior polymorphous dystrophy with multiple different underlying mechanisms of disease. All of these diseases are relatively common in the population, and all have subtle variations in their severity (a spectrum of manifestation of the disease), lending support to the evidence that there may be different mechanisms causing disease, explaining milder or more severe manifestations.

DNA is composed of sequences of four possible deoxyribonucleic acids: adenine, cytosine, guanine, or thymine. A gene structure has segments that encode proteins, called *exons,* and noncoding segments that intervene between the exons, called *introns* (Figure 2). Regulatory elements, including the promoter that may control transcription of a gene, are usually found "upstream" or in front of the coding sequence. Transcription, also called *expression*, involves converting the DNA into ribonucleic acid (**RNA**). The RNA sequence then encodes or specifies the amino acid sequence that forms the protein. The synthesis of the protein from RNA is termed *translation*. Proteins fold into complex three-dimensional shapes that allow them to interact with other molecules. The amino acid sequence dictates the folding pattern and protein structure (Figure 3).

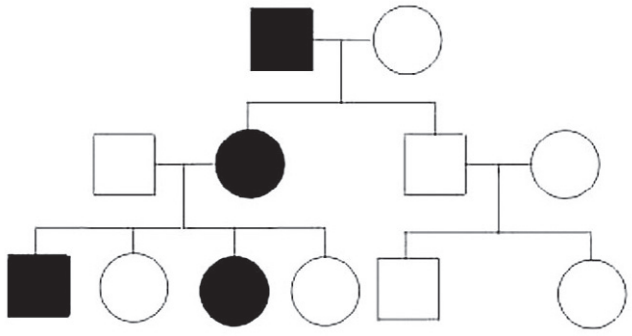

Figure 1. Pedigree with autosomal dominant inheritance pattern. Solid filled symbols demonstrate affected individuals.

Table 1. Inheritance Patterns

Autosomal dominant: The phenotype is expressed in those who have inherited only one copy of a particular gene mutation (heterozygotes). The gene is on only one copy of a gene pair from the set of 22 pairs of autosomes (non-sex chromosomes). Complete penetrance is assumed.

Autosomal recessive: The phenotype requires the presence of two copies of a gene mutation (homozygous) at a particular locus in order to be expressed. The gene is on both copies of the gene pair from the set of 22 pairs of autosomes (non-sex chromosomes).

X-linked dominant: The disorder is caused by a mutation in a gene in the X-chromosome. The phenotype is expressed in heterogygous females, as well as in hemizygous males (having only 1 X chromosome).

X-linked recessive: A mutation in a gene on the X chromosome causes the phenotype to be expressed in males who are hemizygous for the gene mutation (i.e., they have only one X chromosome) and in females who are homozygous for the gene mutation (i.e., they have a copy of the gene mutation on each of their two X chromosomes).

Y-linked inheritence: A mutation on the Y chromosome causes the phenotype to be expressed only in males. The transmission is only among males from father to son.

Mitochondrial inheritance: Mitochondria contain their own distinct genome, and mutations in these genes are responsible for a number of syndromes. Because ova contain mitochondria and sperm do not, these syndromes are maternally inherited.

From: Suzuki D, Griffiths A, Miller J, Lewontin R. An Introduction to Genetic Analysis. Fourth edition W.H. Freeman and Company. New York. 1989, Chapters 2, 3 and 20.

Diseases of the epithelium, including Meesmann's corneal dystrophy with mutations located in regions important for intermediate filament assembly, cause improperly folded proteins and accumulation of these proteins forming clinically evident microcysts.[13,14] Proteins may serve not only a structural role, but, alternatively, may have an enzymatic role. Mutations in genes that encode structural proteins usually have a dominant pattern of inheritance, whereas mutations in genes that encode enzymatic proteins are often inherited in a recessive fashion.

Although each cell has the complete genetic code encompassed in the DNA arranged in 23 pairs of chromosomes, not all genes are transcribed. A subset of genes is transcribed in a particular cell, giving it specialized tissue-specific characteristics and function.

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