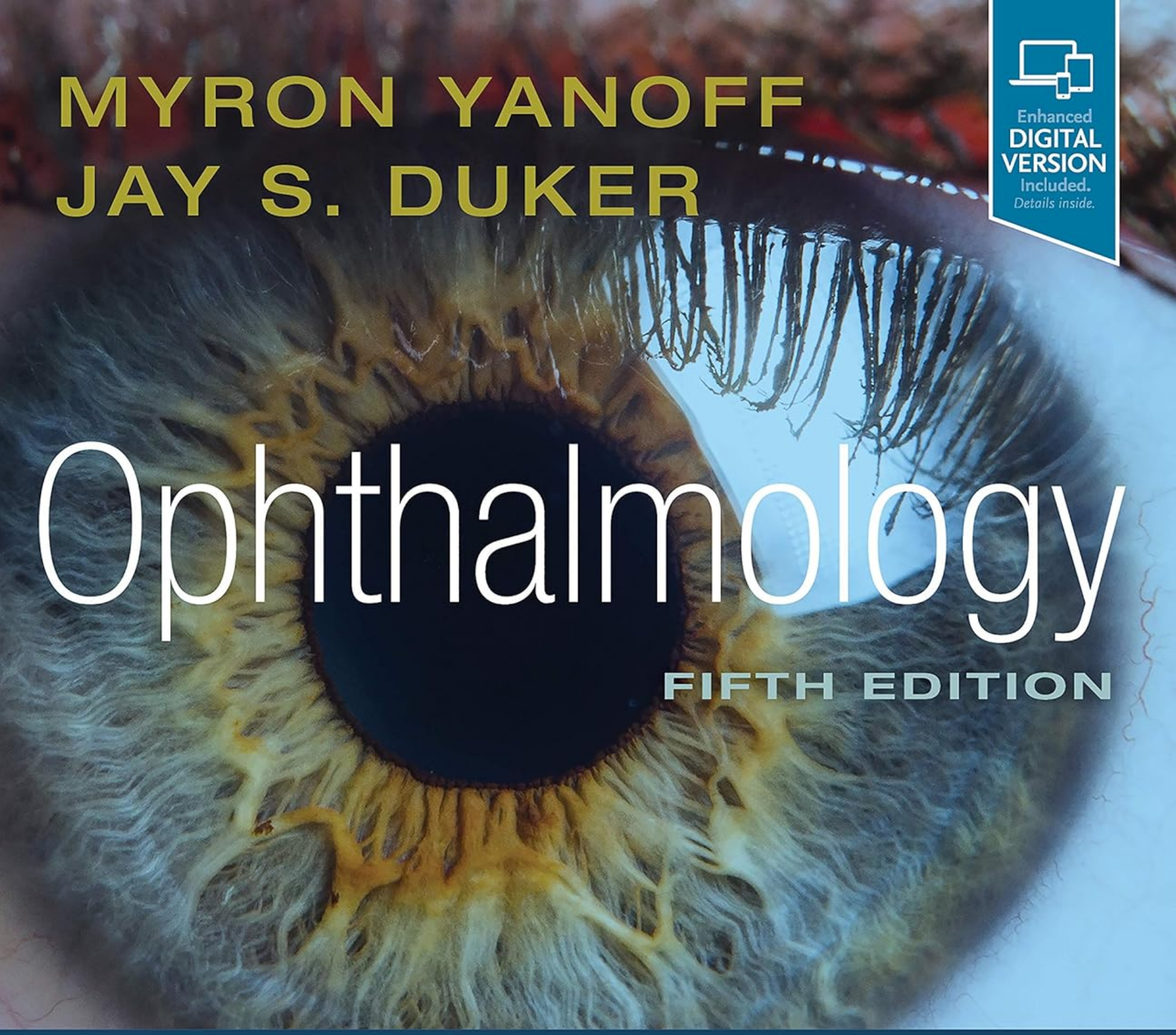

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Ophthalmology

FIFTH EDITION

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User Guide

COLOR CODING

Ophthalmology is organized into 12 parts, which are color-coded as follows for quick and easy reference:

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Preface

It's been 20 years since the first edition of Ophthalmology was published. We are delighted that our textbook now has gone to a fifth edition. The longevity of this title reflects the uniqueness and utility of its format; the hard work of our authors, editors, and publishers; and the pressing need in our field for updated, clinically relevant information. We continue to recognize the advantage of a complete textbook of ophthalmology in a single volume rather than multiple volumes. The basic visual science is admixed with clinical information throughout, and we have maintained an entire separate section dedicated to genetics and the eye.

Ophthalmology was never intended to be encyclopedic, but with each edition we strived to make it quite comprehensive, readable, and easy to access. Like the fourth edition, this edition is thoroughly revised, with new section editors and many new authors. Chapters have been rewritten and restricted to reflect the new way diseases are diagnosed, categorized, and treated. We have discarded out-of-date material and have added numerous new items. Extra references and other material have been moved online to keep the book itself as one volume.

Preface to First Edition

Over the past 30 years, enormous technologic advances have occurred in many different areas of medicine—lasers, molecular genetics, and immunology to name a few. This progress has fueled similar advances in almost every aspect of ophthalmic practice. The assimilation and integration of so much new information makes narrower and more focused ophthalmic practices a necessity. As a direct consequence, many subspecialty textbooks with extremely narrow focus are now available, covering every aspect of ophthalmic practice. Concurrently, several excellent multivolume textbooks detailing all aspects of ophthalmic practice have been developed. Yet there remains a need for a complete single-volume textbook of ophthalmology for trainees, nonophthalmologists, and those general ophthalmologists (and perhaps specialists) who need an update in specific areas in which they do not have expertise. *Ophthalmology* was created to fill this void between the multivolume and narrow subspecialty book.

This book is an entirely new, comprehensive, clinically relevant, single-volume textbook of ophthalmology, with a new approach to content and presentation that allows the reader to access key information quickly. Our approach, from the outset, has been to use templates to maintain a uniform chapter structure throughout the book so that the material is presented in a logical, consistent manner, without repetition. The majority of chapters in the book follow one of three templates: the disease-oriented template, the surgical procedure template, or the diagnostic testing template. Meticulous planning went into the content, sectioning, and chapter organization of the book, with the aim of presenting ophthalmology as it is practiced, rather than as a collection of artificially divided aspects. Thus, pediatric ophthalmology is not in a separate section but is integrated into relevant sections across the book. The basic visual science and clinical information, including systemic manifestations, is integrated throughout, with only two exceptions. We dedicated an entire section to genetics and the eye, in recognition of the increasing importance of genetics in ophthalmology. Optics and refraction are included in a single section as well because an understanding of these subjects is fundamental to all of ophthalmology.

To achieve the same continuity of presentation in the figures as well as in the text, all of the artworks have been redesigned from the authors' originals, maximizing their accessibility for the reader. Each section is color coded for easy cross-referencing and navigation through the book. Despite the extensive use of color in artworks and photographs throughout, the cost of this comprehensive book has been kept to a fraction of the multivolume sets. We hope to make this volume more accessible to more practitioners throughout the world.

Although comprehensive, *Ophthalmology* is not intended to be encyclopedic. In particular, in dealing with surgery, we do not stress specific techniques or describe rarer ones in meticulous detail. The rapidly changing nature of surgical aspects of ophthalmic practice is such that the reader will need to refer to one or more of the plethora of excellent books that cover specific current techniques in depth. We concentrate instead on the areas that are less volatile but, nevertheless, vital surgical indications, general principles of surgical technique, and complications. The approach to referencing is parallel to this: For every topic, all the key references are listed, but with the aim of avoiding pages of redundant references where a smaller number of recent classic reviews will suffice. The overall emphasis of *Ophthalmology* is current information that is relevant to clinical practice superimposed on the broad framework that comprises ophthalmology as a subspecialty.

Essential to the realization of this ambitious project is the ream of Section Editors, each bringing unique insight and expertise to the book. They have coordinated their efforts in shaping the contents list, finding contributors, and editing chapters to produce a book that we hope will make a great contribution to ophthalmology.

We are grateful to the editors and authors who have contributed to *Ophthalmology* and to the superb, dedicated team at Mosby.

Myron Yanoff
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July 1998

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Dedication

We would like to dedicate this book to our wives, Karin Yanoff and Julie Starr-Duker, and to our children—Steven, David, and Alexis Leyva-Yanoff; Joanne Grune-Yanoff; and Jake, Claire, Bear, Becca, Sam, Colette, and Elly Duker—all of whom play such an important part in our lives and without whose help and understanding we would have never come this far.

Fundamentals of Human Genetics

1.1

Janey L. Wiggs

Definition: The central principles of human genetics with relevance to eye disease.

Key Features

- Gene structure and expression.
- Organization and inheritance of the human genome.
- Mutations and clinical phenotypes.
- Gene-based therapies.

DNA AND THE CENTRAL DOGMA OF HUMAN GENETICS

The regulation of cellular growth and function in all human tissue is dependent on the activities of specific protein molecules. In turn, protein activity is dependent on the expression of the genes that contain the correct DNA sequence for protein synthesis. The DNA molecule is a double-stranded helix. Each strand is composed of a sequence of four nucleotide bases—adenine (A), guanine (G), cytosine (C), and thymine (T)—joined to a sugar and a phosphate. The order of the bases in the DNA sequence forms the genetic code that directs the expression of genes. The double-stranded helix is formed as a result of hydrogen bonding between the nucleotide bases of opposite strands.[1] The bonding is specific, such that A always pairs with T, and G always pairs with C. The specificity of the hydrogen bonding is the molecular basis of the accurate copying of the DNA sequence that is required during the processes of DNA replication (necessary for cell division) and transcription of DNA into RNA (necessary for gene expression and protein synthesis; Fig. 1.1.1).

Gene expression begins with the recognition of a particular DNA sequence called the promoter sequence as the start site for RNA synthesis by the enzyme RNA polymerase. The RNA polymerase "reads" the DNA sequence and assembles a strand of RNA that is complementary to the DNA sequence. RNA is a single-stranded nucleic acid composed of the same nucleotide bases as DNA, except that uracil takes the place of thymine. Human genes (and genes found in other eukaryotic organisms) contain many DNA sequences that are not translated into polypeptides and proteins. These sequences are called intervening sequences or introns. Introns do not have any known specific function, and although they are transcribed into RNA by RNA polymerase, they are spliced out of the initial RNA product (termed heteronuclear RNA, or hnRNA) to form the completed messenger RNA (mRNA). Untranslated RNA may have specific functions. For example, antisense RNA and micro RNAs (miRNA) appear to regulate expression of genes.[2] The mRNA is the template for protein synthesis. Proteins consist of one or more polypeptide chains, which are sequences of specific amino acids. The sequence of bases in the mRNA directs the order of amino acids that make up the polypeptide chain. Individual amino acids are encoded by units of three mRNA bases, termed codons. Transfer RNA (tRNA) molecules bind specific amino acids and recognize the corresponding three-base codon in the mRNA. Cellular organelles called ribosomes bind the mRNA in such a configuration that the RNA sequence is accessible to tRNA molecules and the amino acids are aligned to form the polypeptide. The polypeptide chain may be processed by a number of other chemical reactions to form the mature protein (Fig. 1.1.2).

HUMAN GENOME

Human DNA is packaged as chromosomes located in the nuclei of cells. Chromosomes are composed of individual strands of DNA wound about proteins called histones. The complex winding and coiling process culminates in the formation of a chromosome. The entire collection of human chromosomes includes 22 paired autosomes and two sex chromosomes. Women have two copies of the X chromosome, and men have one X and one Y chromosome (Fig. 1.1.3).

The set consisting of one of each autosome as well as both sex chromosomes is called the *human genome*. The chromosomal molecules of DNA from one human genome, if arranged in tandem end to end, contain approximately 3.2 billion base pairs (bp). The Human Genome Project was formally begun in 1990 with the defined goals to: identify all the approximately 20,000–25,000 genes in human DNA; determine the sequences of the 3 billion chemical base pairs that make up human DNA; store this information in publicly available databases; improve tools for data analysis; transfer related technologies to the private sector; and address the

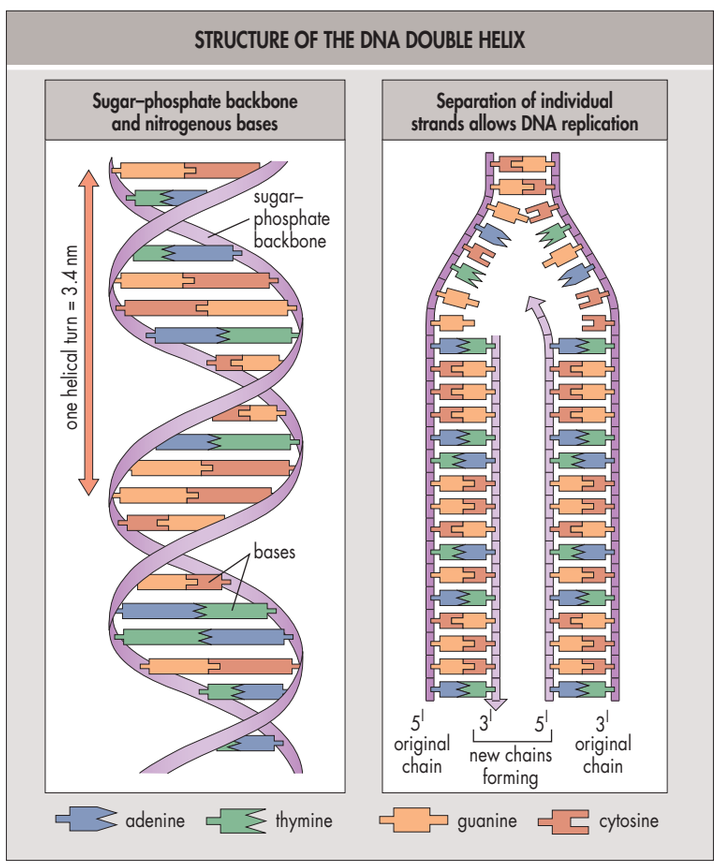

Fig. 1.1.1 Structure of the DNA Double Helix. The sugar–phosphate backbone and nitrogenous bases of each individual strand are arranged as shown. The two strands of DNA pair by hydrogen bonding between the appropriate bases to form the double-helical structure. Separation of individual strands of the DNA molecule allows DNA replication, catalyzed by DNA polymerase. As the new complementary strands of DNA are synthesized, hydrogen bonds are formed between the appropriate nitrogenous bases.

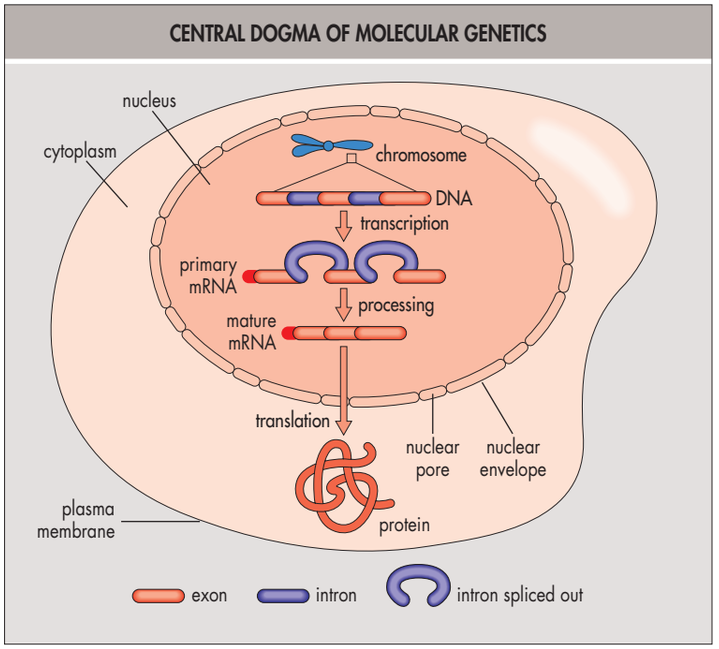

Fig. 1.1.2 The Central Dogma of Molecular Genetics. Transcription of DNA into RNA occurs in the nucleus of the cell, catalyzed by the enzyme RNA polymerase. Mature mRNA is transported to the cytoplasm, where translation of the code produces amino acids linked to form a polypeptide chain, and ultimately a mature protein is produced.

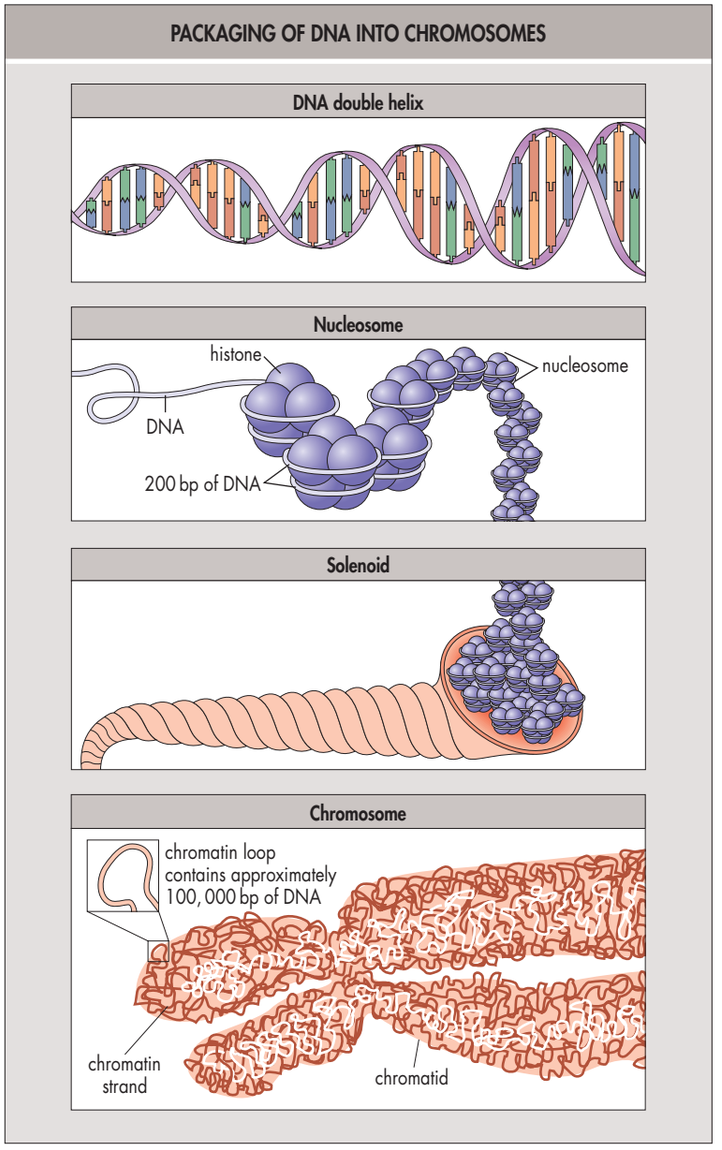

Fig. 1.1.3 The Packaging of DNA Into Chromosomes. Strands of DNA are wound tightly around proteins called histones. The DNA–histone complex becomes further coiled to form a nucleosome, which in turn coils to form a solenoid. Solenoids then form complexes with additional proteins to become the chromatin that ultimately forms the chromosome.

ethical, legal, and social issues that may arise from the project. One of the most important goals, the complete sequence of the human genome, was completed in draft form in 2001.[3] Catalogs of variation in the human genome sequence have also been completed, with the microsatellite repeat map in 1994,[4] the release of the HapMap from the International HapMap Consortium in 2004,[5] and more recently a catalog of variants from the 1000 genomes project.[6] dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) is a database listing single nucleotide polymorphisms (SNPs) that are single-letter variations in a DNA base sequence. SNPs are bound together to form haplotypes, which are blocks of SNPs that are commonly inherited together. This binding occurs through the phenomenon of linkage disequilibrium. Within a haplotype block, which may extend for 10,000–100,000 bases of DNA, the analysis of only a subset of all SNPs may "tag" the entire haplotype. The International HapMap project has performed an initial characterization of the linkage disequilibrium patterns between SNPs in multiple different populations. The SNP haplotype blocks identified can be examined for association with human disease, especially common disorders with complex inheritance. Knowledge about the effects of DNA variations among individuals can lead to new ways to diagnose, treat, and prevent human disease. This approach has been used successfully to identify the risk loci for age-related macular degeneration,[7–9] myopia,[10,11] primary open-angle glaucoma,[12–14] and Fuchs' endothelial dystrophy.[15]

Mitosis and Meiosis

In order for cells to divide, the entire DNA sequence must be copied so that each daughter cell can receive a complete complement of DNA. The growth phase of the cell cycle terminates with the separation of the two sister chromatids of each chromosome, and the cell divides during mitosis. Before cell division, the complete DNA sequence is copied by the enzyme DNA polymerase in a process called DNA replication. DNA polymerase is an enzyme capable of the synthesis of new strands of DNA using the exact sequence of the original DNA as a template. Once the DNA is copied, the old and new copies of the chromosomes form their respective pairs, and the cell divides such that one copy of each chromosome pair belongs to each cell (Fig. 1.1.4). Mitotic cell division produces a daughter cell that is an exact replica of the dividing cell.

Meiotic cell division is a special type of cell division that results in a reduction of the genetic material in the daughter cells, which become the reproductive cells—eggs (women) and sperm (men). Meiosis begins with DNA replication, followed by a pairing of the maternal and paternal chromosomes (homologous pairing) and an exchange of genetic material between chromosomes by recombination (Fig. 1.1.5). The homologous chromosome pairs line up on the microtubule spindle and divide such that the maternal and paternal copies of the doubled chromosomes are distributed to separate daughter cells. A second cell division occurs, and the doubled chromosomes divide, which results in daughter cells that have half the genetic material of somatic (tissue) cells.

BASIC MENDELIAN PRINCIPLES

Two important rules central to human genetics emerged from the work of Gregor Mendel, a nineteenth century Austrian monk. The first is the principle of segregation, which states that genes exist in pairs and that only one member of each pair is transmitted to the offspring of a mating couple. The principle of segregation describes the behavior of chromosomes in meiosis. Mendel's second rule is the law of independent assortment, which states that genes at different loci are transmitted independently. This work also demonstrated the concepts of dominant and recessive traits. Mendel found that certain traits were dominant and could mask the presence of a recessive gene.

At the same time that Mendel observed that most traits segregate independently, according to the law of independent assortment, he unexpectedly found that some traits frequently segregate together. The physical arrangement of genes in a linear array along a chromosome is the

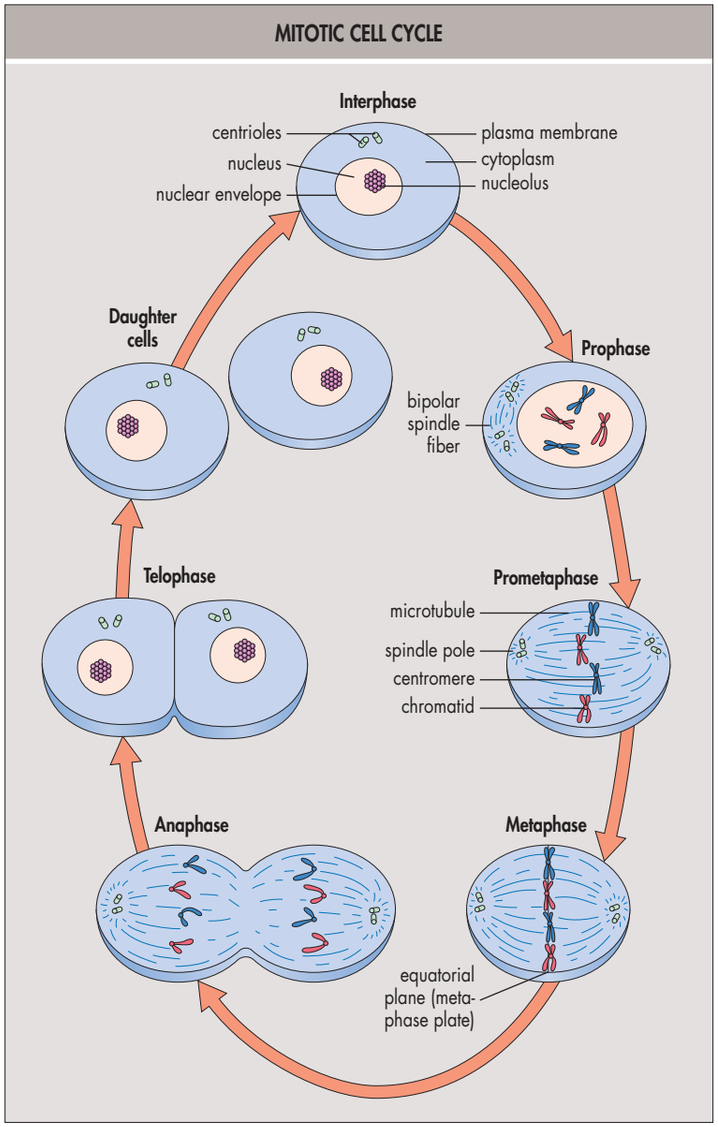

Fig. 1.1.4 The Mitotic Cell Cycle. During mitosis, the DNA of a diploid cell is replicated, which results in the formation of a tetraploid cell that divides to form two identical diploid daughter cells.

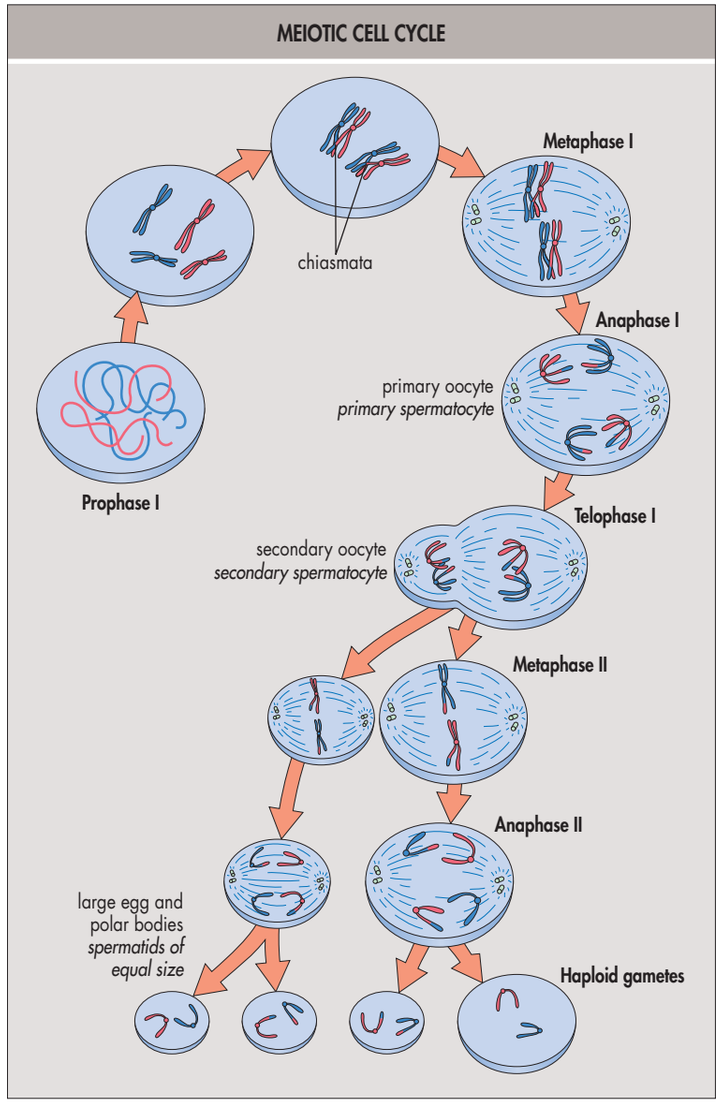

Fig. 1.1.5 The Meiotic Cell Cycle. During meiosis, the DNA of a diploid cell is replicated, which results in the formation of a tetraploid cell that divides twice to form four haploid cells (gametes). As a consequence of the crossing over and recombination events that occur during the pairing of homologous chromosomes before the first division, the four haploid cells may contain different segments of the original parental chromosomes. For brevity, prophase II and telophase II are not shown.

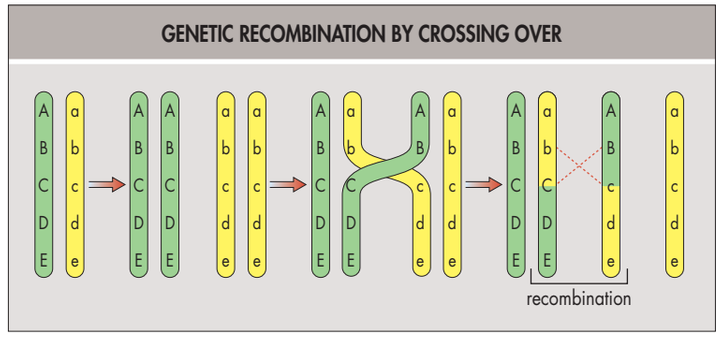

Fig. 1.1.6 Genetic Recombination by Crossing Over. Two copies of a chromosome are copied by DNA replication. During meiosis, pairing of homologous chromosomes occurs, which enables a crossover between chromosomes to take place. During cell division, the recombined chromosomes separate into individual daughter cells.

explanation for this surprising observation. On average, a recombination event occurs once or twice between two paired homologous chromosomes during meiosis (Fig. 1.1.6). Most observable traits, by chance, are located far away from one another on a chromosome, such that recombination is likely to occur between them, or they are located on entirely different chromosomes. If two traits are on separate chromosomes, or a recombination event is likely to occur between them on the same chromosome, the resultant gamete formed during meiosis has a 50% chance of inheriting different alleles from each loci, and the two traits respect the law of independent assortment. If, however, the loci for these two traits are close together on a chromosome, with the result that a recombination event occurs between them only rarely, the alleles at each loci are passed to descendent gametes "in phase." This means that the particular alleles present at each loci in the offspring reflect the orientation in the parent, and the traits appear to be "linked." For example, in Mendel's study of pea plants, curly leaves were always found with pink flowers, even though the genes for curly leaves and pink flowers are located at distinct loci. These traits are linked, because the curly leaf gene and the pink-flower gene are located close to each other on a chromosome, and a recombination event only rarely occurs between them. Recombination and linkage are the fundamental concepts behind genetic linkage analysis.

MUTATIONS

Mutations are changes in the gene DNA sequence that result in a biologically significant change in the function of the encoded protein. If a particular gene is mutated, the protein product might not be produced, or it might be produced but function poorly or even pathologically (dominant negative effect). *Point mutations* (the substitution of a single base pair) are the most common mutations encountered in human genetics. *Missense mutations* are point mutations that cause a change in the amino

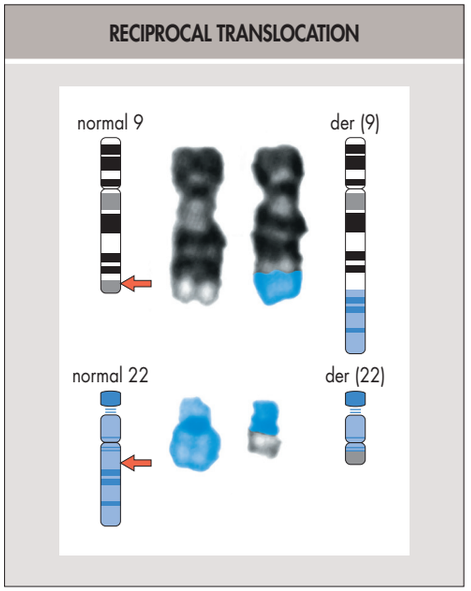

Fig. 1.1.7 Reciprocal Translocation Between Two Chromosomes. The Philadelphia chromosome (responsible for chronic myelogenous leukemia) is shown as an example of a reciprocal chromosomal translocation that results in an abnormal gene product responsible for a clinical disorder. In this case an exchange occurs between the long arm of chromosome 9 and the long arm of chromosome 22.

acid sequence of the polypeptide chain. The severity of the missense mutation is dependent on the chemical properties of the switched amino acids and on the importance of a particular amino acid in the function of the mature protein. Point mutations also may decrease the level of polypeptide production because they interrupt the promoter sequence, splice site sequences, or create a premature stop codon.

Gene expression can be affected by the insertion or deletion of large blocks of DNA sequence. These types of mutations are less common than point mutations but may result in a more severe change in the activity of the protein product. A specific category of *insertion mutations* is the expansion of trinucleotide repeats found in patients affected by certain neurodegenerative disorders. An interesting clinical phenomenon, "anticipation," was understood on a molecular level with the discovery of trinucleotide repeats as the cause of myotonic dystrophy.[16] Frequently, offspring with myotonic dystrophy were affected more severely and at an earlier age than their affected parents and grandparents. Examination of the disease-causing trinucleotide repeat in affected pedigrees demonstrated that the severity of the disease correlated with the number of repeats found in the myotonic dystrophy gene in affected individuals. This phenomenon has been observed in a number of other diseases, including Huntington's disease.[17]

Chromosomal rearrangements may result in breaks in specific genes that cause an interruption in the DNA sequence. Usually, the break in DNA sequence results in a truncated, unstable, dysfunctional protein product. Occasionally, the broken gene fuses with another gene to cause a "fusion polypeptide product," which may have a novel activity in the cell. Often, such a novel activity results in an abnormality in the function of the cell. An example of such a fusion protein is the product of the chromosome 9;22 translocation that is associated with many cases of leukemia (Fig. 1.1.7).[18,19]

A set consisting of one of each autosome as well as an X or a Y chromosome is called a haploid set of chromosomes. The normal complement of two copies of each gene (or two copies of each chromosome) is called diploidy. Rarely, as a result of abnormal chromosome separation during cell division, a cell or organism may have three copies of each chromosome, which is called *triploidy*. A triploid human is not viable, but some patients have an extra chromosome or an extra segment of a chromosome. In such a situation, the abnormality is called trisomy for the chromosome involved. For example, patients with Down syndrome have three copies of chromosome 21, also referred to as trisomy 21.[20]

If one copy of a pair of chromosomes is absent, the defect is called *haploidy*. Deletions of the X chromosome are frequently the cause of Duchenne's muscular dystrophy.[21]

Polymorphisms are changes in DNA sequence that don't have a significant biological effect. These DNA sequence variants may modify disease processes, but alone are not sufficient to cause disease. Human DNA sequence is highly variable and includes single nucleotide polymorphisms (SNPs), microsatellite repeat polymorphisms (20–50 bp repeats of CA or GT sequence), variable number of tandem repeat polymorphisms (VNTR, repeats of 50–100 bp of DNA), or larger insertion deletions.[22]

GENES AND PHENOTYPES

The relationship between genes and phenotypes is complex. More than one genetic defect can lead to the same clinical phenotype (genetic heterogeneity), and different phenotypes can result from the same genetic defect (variable expressivity). Retinitis pigmentosa is an excellent example of genetic heterogeneity, as it may be inherited as an X-linked, autosomal dominant, autosomal recessive, or digenic trait, and more than 200 causative genes have been identified.[23] Other ocular disorders that are genetically heterogeneous include congenital cataract, glaucoma, and age-related macular degeneration. Different genes may contribute to a common phenotype because they affect different steps in a common pathway. Understanding the role of each gene in the disease process can help define the cellular mechanisms that are responsible for the disease.

For many genes, a single mutation that alters a critical site in the protein results in an abnormal phenotype. For some diseases, the resulting phenotypes are remarkably similar regardless of the nature of the mutation. For example, a wide variety of mutations in *RB1* cause retinoblastoma. Other diseases, however, exhibit variable expressivity, in which an individual's mutation may be responsible for severe disease, mild disease, or disease that is not clinically detectable (incomplete penetrance). There are many examples of ocular disease demonstrating variable expressivity, including Kjer's autosomal dominant optic atrophy,[24] Axenfeld–Rieger syndrome,[25] and aniridia.[26]

Different mutations in the same gene can also result in different phenotypes (allelic heterogeneity). Allelic heterogeneity accounts for the different phenotypes of dominant corneal stromal dystrophies caused by mutations in the *TGFB1/BIGH3*.[27] The phenotypic expression of a mutation may depend on its location within a gene. Such variable expressivity based on the location of the mutation is exemplified by mutations in the *rds* gene, which may cause typical autosomal dominant retinitis pigmentosa or macular dystrophy depending on the position of the genetic defect.[28]

PATTERNS OF HUMAN INHERITANCE

The most common patterns of human inheritance are autosomal dominant, autosomal recessive, X-linked recessive, and mitochondrial. Fig. 1.1.8 shows examples of these four inheritance patterns. Other inheritance patterns less commonly encountered in human disease include X-linked dominant, digenic inheritance (polygenic), pseudodominance, and imprinting. Fig. 1.1.9 defines the notation and symbols used in pedigree construction.

Autosomal Dominant

A disease-causing mutation that is present in only one of the two gene copies at an autosomal locus (heterozygous) is a dominant mutation. For example, a patient with dominant retinitis pigmentosa will have a defect in one copy of one retinitis pigmentosa gene inherited from one parent who, in most cases, is also affected by retinitis pigmentosa. The other copy of that gene, the one inherited from the unaffected parent, is normal (wild type). Affected individuals have a 50% chance of having affected siblings and a 50% chance of passing the abnormal gene to their offspring; 50% of children of an affected individual will be affected. For a dominant disease, males and females transmit the disease equally and are affected equally.

True dominant alleles produce the same phenotype in the heterozygous and homozygous states. In humans, most individuals affected by a disease caused by a dominant allele are heterozygous, but occasionally homozygous mutations have been described. In cases where the homozygous individual is more severely affected than the heterozygous individual, the disease is more appropriately noted to be inherited as a semidominant trait. For example, alleles in the *PAX3* gene, causing Waardenburg's syndrome, are semidominant, because a homozygote with more severe disease compared with their heterozygote relatives has been described.[29]

In some pedigrees with an autosomal dominant disease, some individuals who carry the defective gene do not have the affected phenotype. However, these individuals can still transmit the disease gene to offspring and have affected children. This phenomenon is called reduced penetrance. The gene responsible for retinoblastoma *(RB1)* is only 90% penetrant, which means that 10% of the individuals who inherit a mutant copy of the gene do not develop the tumor.[30]

Autosomal Recessive

Diseases that require both copies of a gene to be abnormal for development are inherited as recessive traits. Heterozygous carriers of mutant genes are

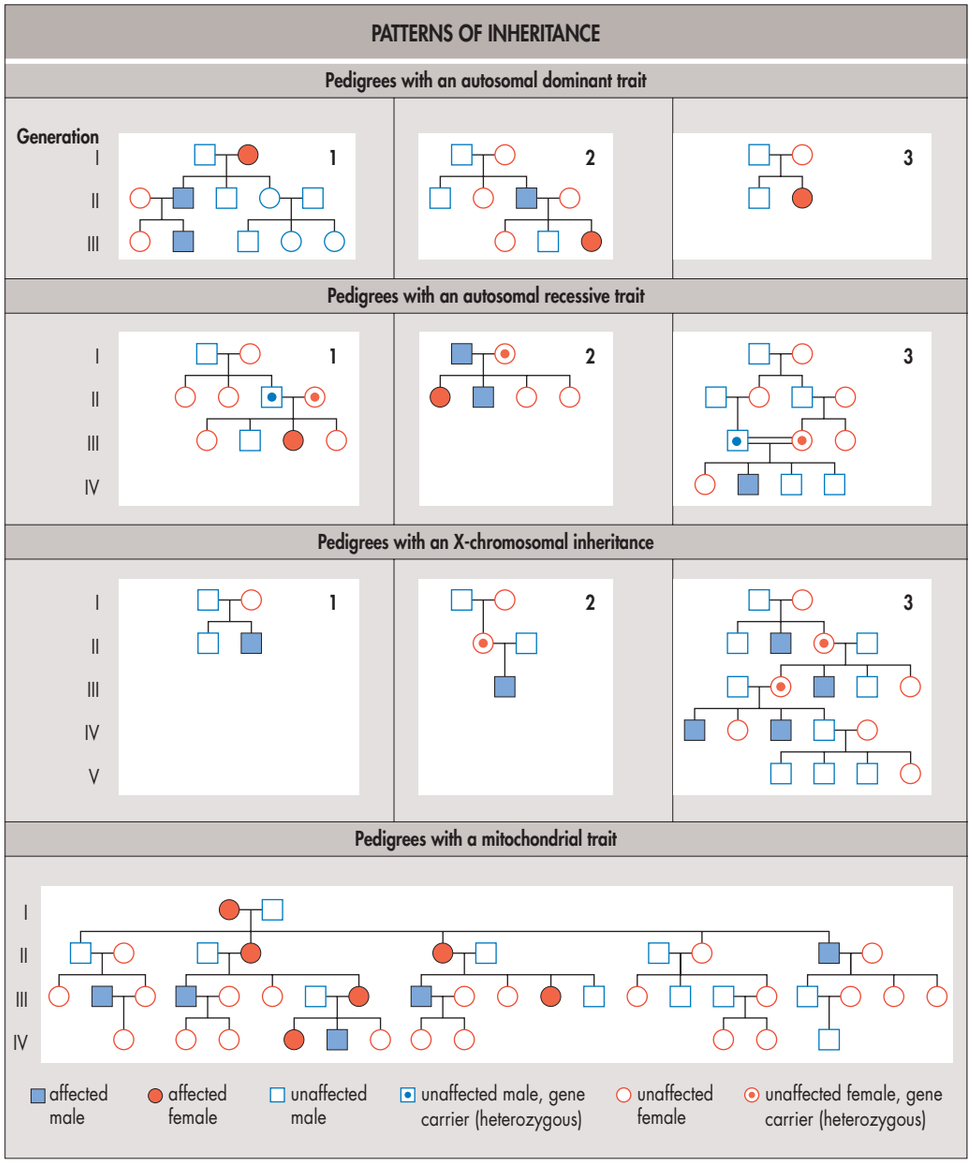

Fig. 1.1.8 Patterns of Inheritance. For pedigrees with an autosomal dominant trait, panel 1 shows inheritance that originates from a previous generation, panel 2 shows segregation that originates in the second generation of this pedigree, and panel 3 shows an apparent "sporadic" case, which is actually a new mutation that arises in the most recent generation. This mutation has a 50% chance of being passed to offspring of the affected individual. For pedigrees with an autosomal recessive trait, panel 1 shows an isolated affected individual in the most recent generation (whose parents are obligatory carriers of the mutant gene responsible for the condition), panel 2 shows a pair of affected siblings whose father is also affected (for the siblings to be affected, the mother must be an obligate carrier of the mutant gene), and panel 3 shows an isolated affected individual in the most recent generation who is a product of a consanguineous marriage between two obligate carriers of the mutant gene. For pedigrees with an X-chromosomal trait, panel 1 shows an isolated affected individual whose disease is caused by a new mutation in the gene responsible for this condition, panel 2 shows an isolated individual who inherited a mutant copy of the gene from the mother (who is an obligate carrier), and panel 3 shows segregation of an X-linked trait through a multigeneration pedigree (50% of the male offspring are affected, and their mothers are obligate carriers of the disease). For pedigrees with a mitochondrial trait, the panel shows a large, multigeneration pedigree—men and women are affected, but only women have affected offspring.

usually clinically normal. The same recessive defect might affect both gene copies, in which case the patient is said to be a *homozygote*. Different recessive defects might affect the two gene copies, in which case the patient is a *compound heterozygote*. In a family with recessive disease, both parents are unaffected carriers, each having one wild-type gene (allele) and one mutant gene (allele). Each parent has a 50% chance of transmitting the defective allele to a child. Because a child must receive a defective allele from both parents to be affected, each child has a 25% chance of being affected (50% × 50% = 25%), and 50% of the offspring will be carriers of the disease. If the parents are related, they may be carriers of the same rare mutations, and there is a greater chance that a recessive disease can be transmitted to offspring. Males and females have an equal chance of transmitting and inheriting the disease alleles.

X-Linked Recessive

Mutations of the X chromosome produce distinctive inheritance patterns, because males have only one copy of the X chromosome and females have two. Most X-linked gene defects are inherited as X-linked recessive traits. Carrier females are typically unaffected because they have both a normal copy and a defective copy of the disease-associated gene. Carrier males are affected because they only have one defective X chromosome and they do not have a normal gene copy to compensate for the defective copy. All of the daughters of an affected male will be carriers of the disease gene because they will inherit the defective X chromosome. None of the sons of an affected male will be affected or be carriers because they will inherit the Y chromosome. Each child of a carrier female has a 50% chance of inheriting the disease gene. If a son inherits the defective gene, he will be affected. If a daughter inherits the defective gene, she will be a carrier. An important characteristic of X-linked recessive disorders is that males never transmit the disease to sons directly (male-to-male transmission).

Usually female carriers of an X-linked disease gene do not have any clinical evidence of the disease. However, for some X-linked diseases, mild clinical features can be found in female carriers. For example, in X-linked retinoschisis, affected males are severely affected, whereas carrier females have a visually insignificant but clinically detectable retinal abnormality.[31] Mild phenotypic expression of the disease gene can be caused by the process of *lyonization*. In order for males (with one X chromosome) and females (with two X chromosomes) to have equal levels of expression of X-linked genes, female cells express genes from only one of their two X chromosomes. The decision as to which X chromosome is expressed is made early in embryogenesis, and the line of descending cells faithfully adheres to the early choice. As a result, females are mosaics, with some cells in each tissue expressing the maternally derived X chromosome and the remainder expressing the paternally derived X chromosome. When one of the X chromosomes carries an abnormal gene, the proportion of cells that express the mutant versus the normal gene in each tissue can vary.

Females can also be affected by an X-linked recessive disease if the father is affected and the mother coincidentally is a carrier of a mutation in the disease gene. In this case, 50% of daughters would be affected, because 50% would inherit the X chromosome from the mother carrying the disease gene, and all the daughters would inherit the X chromosome from the father carrying the disease gene. Because most X-linked disorders are rare, the carrier frequency of disease genes in the general population is

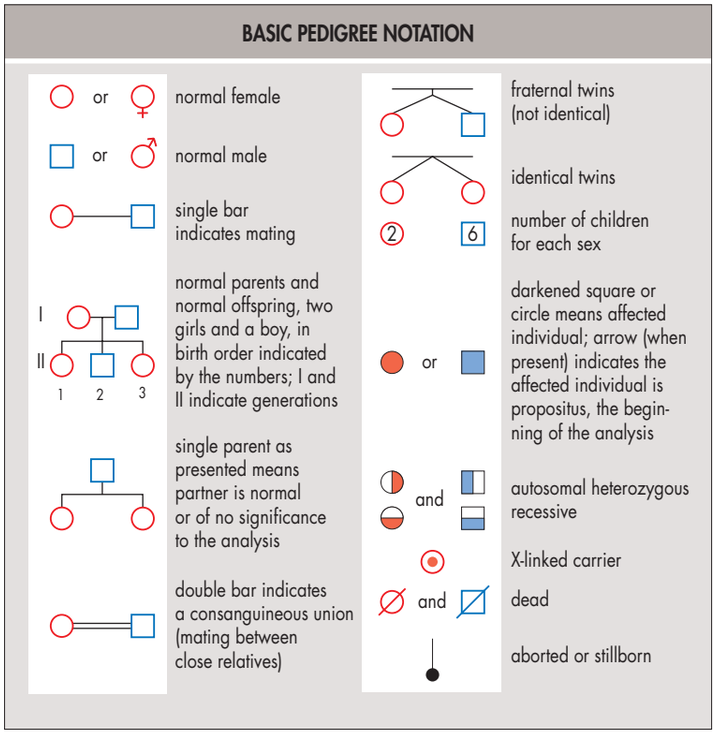

Fig. 1.1.9 Basic Pedigree Notation. Typical symbols used in pedigree construction are defined.

low, and the chance that a carrier female would mate with a male affected by the same disease is quite low.

Mitochondrial Inheritance

Mitochondria are small organelles located in the cytoplasm of cells. They function to generate ATP for the cell and are most abundant in cells that have high energy requirements, such as muscle and nerve cells. Mitochondria have their own small chromosome—16,569 bp of DNA encoding for 13 mitochondrial proteins, 2 ribosomal RNAs, and 22 tRNAs. Mutations occurring in genes located on the mitochondrial chromosome cause a number of diseases, including Leber's hereditary optic atrophy[32] and Kearns–Sayre syndrome.[33] Mutations occurring on the mitochondrial chromosome are inherited only from the mother because virtually all human mitochondria are derived from the maternal egg. Fathers do not transmit mitochondria to their offspring.

Cells vary in the number of mitochondria they contain, and when cells divide, the mitochondria are divided randomly. As a result, different cells can have varying numbers of mitochondria, and if a fraction of the mitochondria contain a mutated gene, different cells will have a varying proportion of healthy versus mutant mitochondria. The distribution of mutant mitochondria is called *heteroplasmy,* and the proportion of mutant mitochondria can vary from cell to cell and can also change with age. Differences in the relative proportions of mutant mitochondria can partly explain the observed variable severity of mitochondrial diseases and also the variable age of onset of mitochondrial diseases.

Pseudodominance

This term describes an apparent dominant inheritance pattern due to recessive defects in a disease gene. This situation arises when a parent affected by a recessive disease (two abnormal copies of the disease gene) has a spouse who is a carrier of one abnormal copy of the disease gene. Children from this couple will always inherit a defective gene copy from the affected parent and will have a 50% chance of inheriting the defective gene copy from the unaffected carrier parent. On average, half of the children will inherit two defective gene copies and will be affected. The pedigree would mimic a dominant pedigree because of apparent direct transmission of the disease from the affected parent to affected children and because approximately 50% of the children will be affected. Pseudodominant transmission is uncommon, because few people are asymptomatic carriers for any particular recessive gene.

X-Linked Dominant Inheritance

This inheritance pattern is similar to X-linked recessive inheritance, except that all females who are carriers of an abnormal gene on the X chromosome are affected rather than unaffected. All of the male offspring are also affected. Incontinentia pigmenti is probably inherited as an X-linked dominant trait. Affected females have irregularly pigmented atrophic scars on the trunk and the extremities and congenital avascularity in the peripheral retina with secondary retinal neovascularization.[34] This and other X-linked dominant disorders occur almost always in females, and it is likely that the X chromosome gene defects causing these diseases are embryonic lethals when present in males.

Digenic Inheritance and Polygenic Inheritance

Digenic inheritance occurs when a patient has heterozygous defects in two different genes, and the combination of the two gene defects causes disease. Individuals who have a mutation in only one of the genes are normal. Digenic inheritance is different from recessive inheritance, because the two mutations involve different disease genes. In some retinitis pigmentosa families, mutation analysis of the peripherin gene and the *ROM1* gene showed that the affected individuals harbor specific mutations in both genes. Individuals with a mutation in only one copy of either gene were unaffected by the disease.[35] Triallelic inheritance has been described in some families affected by Bardet–Biedl syndrome (BBS). In these pedigrees, affected individuals carry three mutations in one or two BBS genes (12 BBS genes have been identified),[36] and unaffected individuals have only two abnormal alleles. In some families, it has been proposed that BBS may not be a single-gene recessive disease but a complex trait requiring at least three mutant alleles to manifest the phenotype. This would be an example of triallelic inheritance.[37]

If the expression of a heritable trait or predisposition is influenced by the combination of alleles at three or more loci, it is polygenic. Because of the complex inheritance, conditions caused by multiple alleles do not demonstrate a simple inheritance pattern. These complex traits may also be influenced by environmental conditions. Examples of phenotypes in ophthalmology that exhibit complex inheritance because of contributions of multiple genes and environmental factors are myopia,[38] age-related macular degeneration,[39] and adult-onset open-angle glaucoma.[40]

Imprinting

Some mutations give rise to autosomal dominant traits that are transmitted by parents of either sex, but they are expressed only when inherited from a parent of one particular sex. In families affected with these disorders, they would appear to be transmitted in an autosomal dominant pattern from one parent (either the mother or the father) and would not be transmitted from the other parent. Occasionally, the same mutation gives rise to a different disorder depending on the sex of the parent transmitting the trait. These parental sex effects are evidence of a phenomenon called *imprinting.* Although the molecular mechanisms responsible for imprinting are not completely understood, it appears to be associated with DNA methylation patterns that can mark certain genes with their parental origin.[41]

MOLECULAR MECHANISMS OF DISEASE

Autosomal Dominant

Disorders inherited as autosomal dominant traits result from mutations that occur in only one copy of a gene (i.e., in heterozygous individuals). Usually, the parental origin of the mutation does not matter. However, if the gene is subject to imprinting, then mutations in the maternal or paternal copy of the gene may give rise to different phenotypes.

Haploinsufficiency

Under normal circumstances, each copy of a gene produces a protein product. If a mutation occurs such that one copy of a gene no longer produces a protein product, then the amount of that protein in the cell has been reduced by half. Mutations that cause a reduction in the amount of protein or lead to inactivation of the protein are called *loss-of-function* mutations. For many cellular processes, this reduction in protein quantity does not have consequences, i.e., the heterozygous state is normal, and these mutations may be inherited as recessive traits (see later section). However, for some cellular processes there is an absolute requirement for the full dosage of protein product, which can only be furnished if both copies of

a particular gene are active. Diseases that are caused by inheritance of a single mutation reducing the protein level by half are inherited as dominant traits.

Gain-of-Function Dominant Negative Effect

Autosomal dominant disorders can be caused by mutant proteins that have a detrimental effect on the normal tissue. Mutations in one copy of a gene may produce a mutant protein that can accumulate as a toxic product or in some other way interfere with the normal function of the cell. The mutant protein may also interfere with the function of the normal protein expressed by the remaining normal copy of the gene, thus eliminating any normal protein activity. It is possible to have gain-of-function mutations that can also be dominant negative because the new function of the protein also interferes with the function of the remaining normal copy of the gene.

Autosomal and X-Linked Recessive

Recessive disorders result from mutations present on both the maternal and paternal copies of a gene. Mutations responsible for recessive disease typically cause a loss of biological activity, either because they create a defective protein product that has little or no biological activity or because they interfere with the normal expression of the gene (regulatory mutations). Most individuals heterozygous for recessive disorders, both autosomal and X-linked, are clinically normal.

GENE THERAPY

Mutations in the DNA sequence of a particular gene can result in a protein product that is not produced, works poorly, or has acquired a novel function that is detrimental to the cell. Gene-based therapies can involve delivery of a normal gene to disease tissue, replacing or augmenting protein activity with other proteins or small molecules, decreasing abnormal gene expression, or genome-editing techniques to repair the mutation. Therapeutic genes can be delivered to specific tissues using modified viruses as vectors[42] (Fig. 1.1.10). A successful example of this approach is the restoration of vision in a canine model of Leber's congenital amaurosis using a recombinant adeno-associated virus carrying the normal gene *(RPE65)*.[43] Human trials using a similar approach also successfully restored vision in patients with *RPE65* mutations.[44]

Diseases caused by mutations that create a gene product that is destructive to the cell (dominant negative or gain of function mutations) need to be treated using a different approach. In these cases, genes or oligonucleotides—in particular antisense molecules—that can reduce expression of the mutated gene are introduced into the cell.[45] Gene editing using CRISPR/Cas9 (Fig. 1.1.11) is another potentially useful approach for gain of function or loss of function mutations.[46] Recent advances have produced highly potent in vivo gene therapy vectors for targeting retina.[47] In addition, new methods are emerging to introduce therapeutic genes into damaged tissue using nonviral mechanisms based on nanotechnology.[48]

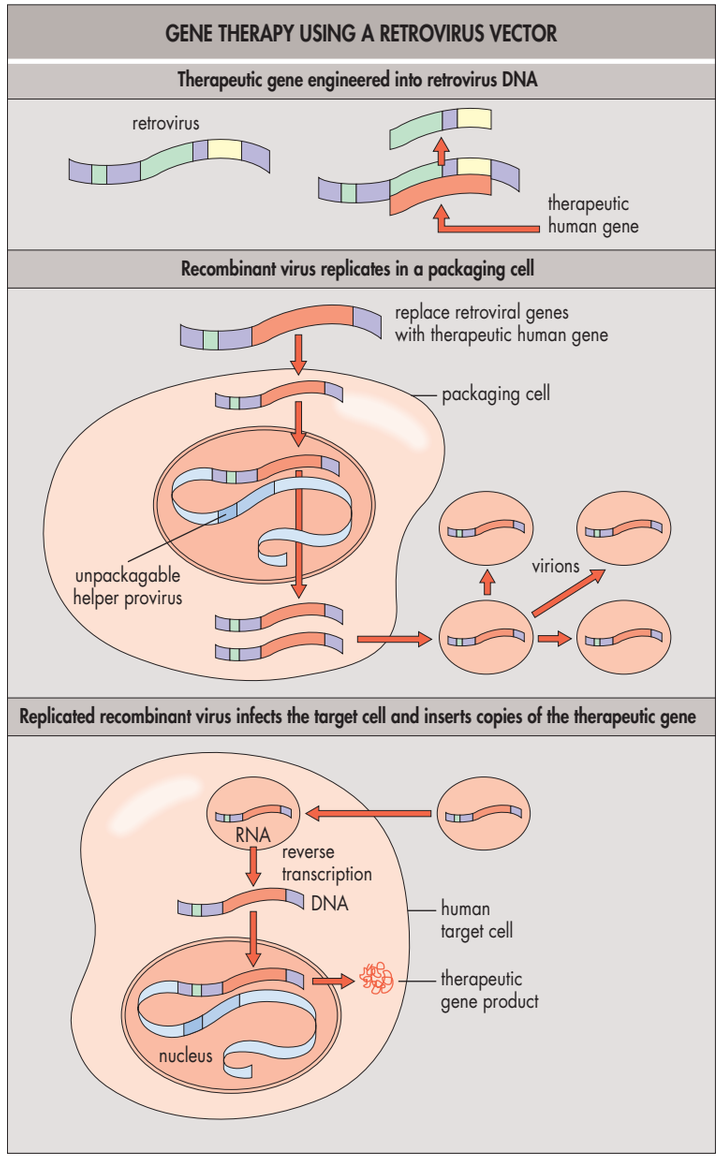

Fig. 1.1.10 Gene Therapy Using a Retrovirus Vector. A therapeutic gene is engineered genetically into the retrovirus DNA and replaces most of the viral DNA sequences. The "recombinant virus" that carries the therapeutic gene is allowed to replicate in a special "packaging cell" that also contains normal virus that carries the genes required for viral replication. The replicated recombinant virus is allowed to infect the human diseased tissue, or "target cell." The recombinant virus may invade the diseased tissue but cannot replicate or destroy the cell. The recombinant virus inserts copies of the normal therapeutic gene into the host genome and produces the normal protein product.

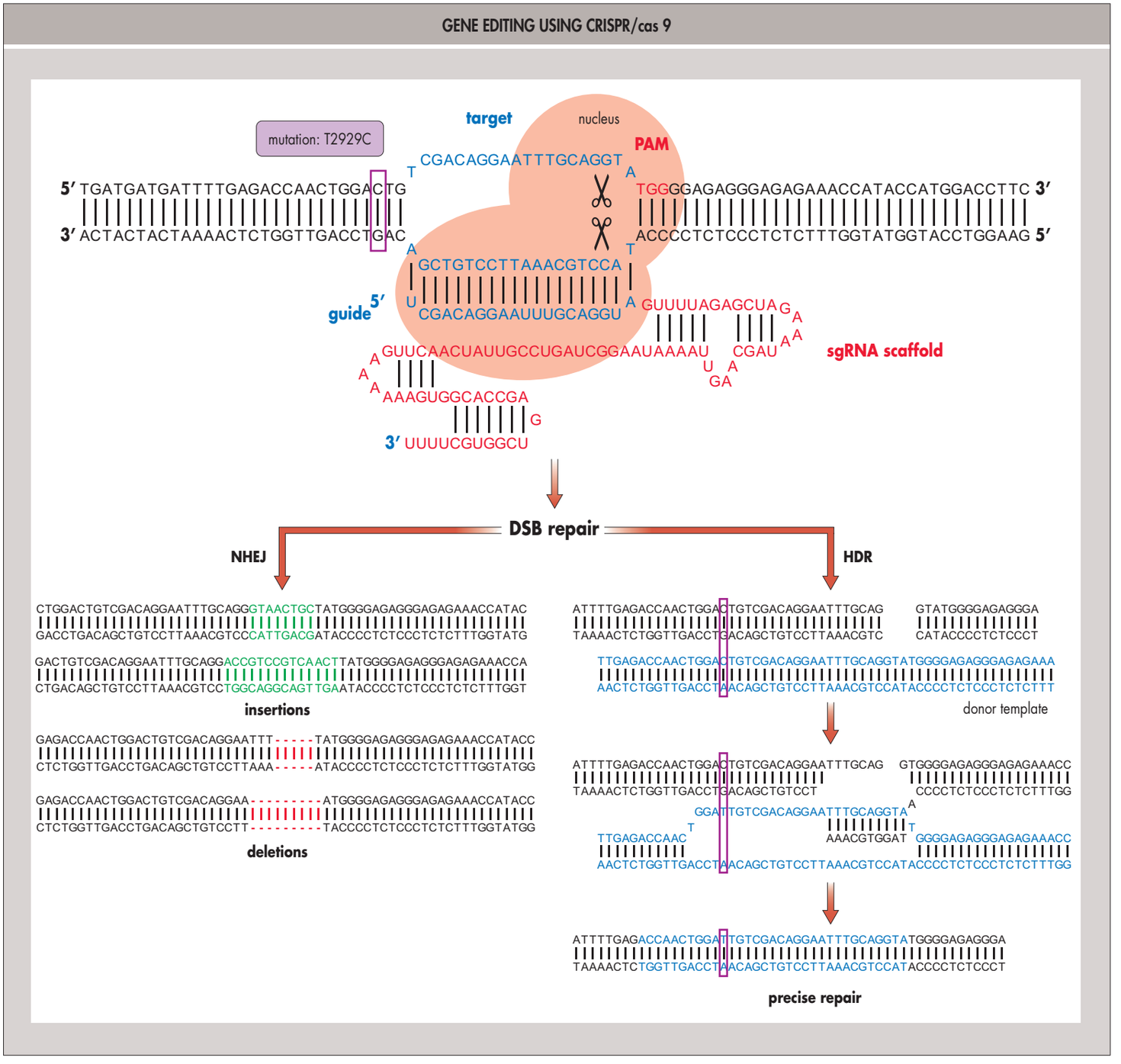

Fig. 1.1.11 **Gene Editing Using CRISPR/Cas9.** The CRISPR/Cas-DNA binding creates a double-stranded DNA break (DSB), which can be repaired through nonhomologous end joining (NHEJ) or homology directed repair (HDR) pathways. Here, the *Streptococcus pyogenes* Cas9 nuclease, with a "NGG" protospacer adjacent motif (PAM) sequence, has been directed to target the region containing the BEST1 c929T > C (Ile310Thr) mutation. The guide RNA is complementary to the non-PAM strand, and the DNA cut site is three nucleotides from the PAM sequence. Double strand DNA breaks typically undergo repair by NHEJ, which results in deletions and insertions of variable length. DNA nicks are generally repaired through HDR, where a donor template can be used to incorporate precise genomic modifications. (Adapted from Hung SS, McCaughey T, Swann O, et al. Genome engineering in ophthalmology: application of CRISPR/Cas to the treatment of eye disease. Prog Retin Eye Res 2016;53:1–20.)

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Molecular Genetics of Selected Ocular Disorders

1.2

Janey L. Wiggs

Definition: The molecular mechanisms underlying selected inherited eye disorders as defined by the responsible genetic mutations.

Key Features

- Inherited disorders affecting the ocular anterior segment.
- Genetic defects causing abnormal ocular development.
- Inherited retinal degenerations.
- Retinoblastoma.
- Disorders involving the optic nerve and extraocular muscles.

INTRODUCTION

Tremendous advances in the molecular genetics of human disease have been made in the past 20 years. Many genes responsible for inherited eye diseases have been isolated and characterized, and the chromosomal location of a number of additional genes has been determined. Identifying and characterizing genes responsible for human disease has led to DNA-based methods of diagnosis; novel therapeutic approaches, including gene therapy; and improved knowledge about the molecular events that underlie the disease processes. The disorders discussed in this chapter represent important examples of major advances in human ocular molecular genetics.

Although all inherited disorders are the result of gene mutations, the molecular consequences of a mutation are quite variable. The type of mutation responsible for a disease usually defines the inheritance pattern. For example, mutations that create an abnormal protein detrimental to the cell are typically autosomal dominant, because only one mutant gene is required to disrupt normal cell function. Mutations that result in proteins that have reduced biological activity (loss of function) may be inherited as autosomal dominant or autosomal recessive conditions, depending on the number of copies of normal genes (and the amount of normal protein) required. Disorders may be caused by mutations in mitochondrial DNA that result in a characteristic maternal inheritance pattern. Also, mutations in genes carried on the X chromosome result in characteristic inheritance patterns.

DOMINANT CORNEAL DYSTROPHIES

The autosomal dominant corneal dystrophies are an excellent example of dominant negative mutations that result in the formation of a toxic protein. Four types of autosomal dominant dystrophies that affect the stroma of the cornea are well characterized[1]:

- Groenouw (granular) type I.
- Lattice type I.
- Avellino (combined granular-lattice).
- Reis–Bücklers.

Although all four corneal dystrophies affect the anterior stroma, the clinical and pathological features differ. The granular dystrophies typically form discrete, white, localized deposits that may obscure vision progressively. Histopathologically, these deposits stain bright red with Masson trichrome and have been termed "hyalin." In lattice dystrophy, branching amyloid deposits gradually opacify the visual axis. These deposits exhibit a characteristic birefringence under polarized light after staining with Congo red. Avellino dystrophy includes features of both granular and lattice dystrophies. Reis–Bücklers dystrophy appears to involve primarily Bowman's layer and the superficial stroma.

All four dystrophies were mapped genetically to a common interval on chromosome 5q31, and mutations in a single gene, *TGFB1* (also known as *BIGH3*), located in this region were found in affected individuals.[2] The product of this gene, keratoepithelin, is probably an extracellular matrix protein that modulates cell adhesion. Four different missense mutations, which occur at two arginine codons in the gene, have been found (Fig. 1.2.1). Interestingly, mutations at one of these arginine codons cause lattice dystrophy type I or Avellino dystrophy, the two dystrophies characterized by amyloid deposits. Mutations at the other arginine codon appear to result in either granular dystrophy or Reis–Bücklers dystrophy. The mutation analysis of this gene demonstrates that different mutations within a single gene can result in different phenotypes.

The mutation that causes Avellino and lattice dystrophies abolishes a putative phosphorylation site, which probably is required for the normal structure of keratoepithelin. Destruction of this aspect of the protein structure leads to formation of the amyloid deposits that are responsible for opacification of the cornea. Consequently, the mutant protein is destructive to the normal tissue. Mutations at the R555 (arginine at amino acid position 555) appear to result in either granular dystrophy or Reis–Bücklers dystrophy. These phenotype–genotype correlations demonstrate the variable expressivity of mutations in this gene and the significance of alteration of the arginine residues 124 and 555.

ANIRIDIA, PETER'S ANOMALY, AUTOSOMAL DOMINANT KERATITIS

Some cellular processes require a level of protein production that results from the expression of both copies of a particular gene. Such proteins may be involved in a variety of biological processes. Certain disorders are caused by the disruption of one copy of a gene that reduces the protein level by half. Such a reduction is also called "haploinsufficiency."

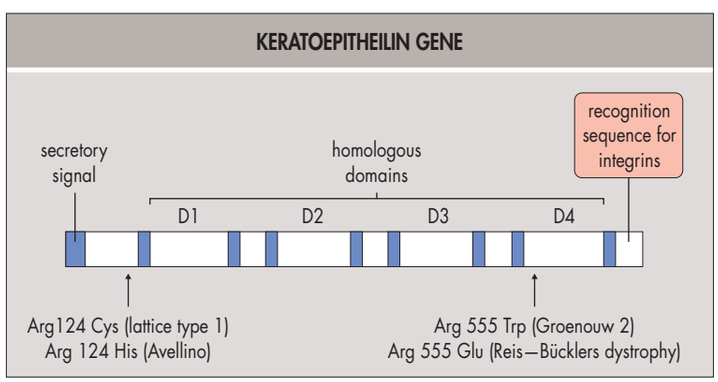

Fig. 1.2.1 Keratoepithelin Gene. Arrows point to the location of the reported mutations.

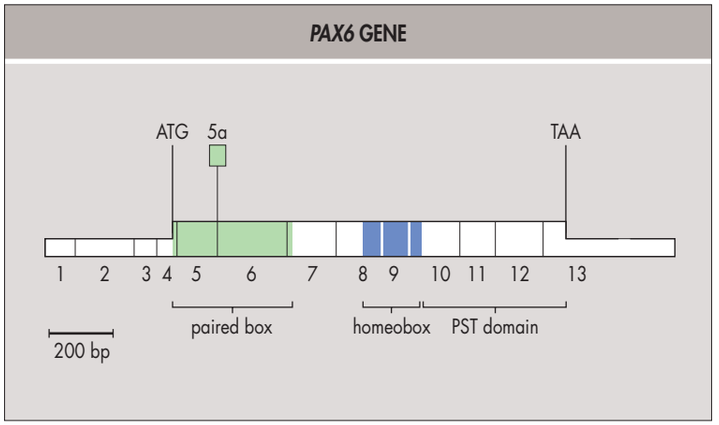

Fig. 1.2.2 The *PAX6* Gene. (Data with permission from Glaser T, et al. PAX6 gene mutations in aniridia. In: Wiggs JL, editor. Molecular genetics of ocular disease. New York: Wiley–Liss; 1995. p. 51–82.)

Mutations in the *PAX6* gene are responsible for aniridia, Peter's anomaly, and autosomal dominant keratitis.[3] Most of the mutations responsible for these disorders alter the paired-box sequence within the gene (Fig. 1.2.2) and result in inactivation of one copy of the *PAX6* gene. The paired-box sequence is an important element that is necessary for the regulatory function of the protein. Losing half the normal paired-box sequence, and probably other regulatory elements within the gene, appears to be the critical event that results in the associated ocular disorders. The protein plays an important role in ocular development, presumably by regulating the expression of genes that are involved in embryogenesis of the eye. A reduction in the amount of active gene product alters the expression of these genes, which results in abnormal development. The genes that code for the lens crystallin proteins are one class of genes developmentally regulated by the *PAX6* protein.

The clinical disorders caused by mutations in *PAX6* exhibit extensive phenotypic variability. Similar mutations may give rise to aniridia, Peter's anomaly, or autosomal dominant keratitis. Variation in the phenotype associated with a mutation is termed "variable expressivity" and is a common feature of disorders that arise from haploinsufficiency. It is possible that the variability of the mutant phenotype results from the random activation of downstream genes that occurs when only half the required gene product is available.

RIEGER'S SYNDROME

Rieger's syndrome is an autosomal dominant disorder of morphogenesis that results in abnormal development of the anterior segment of the eye. Typical clinical findings may include posterior embryotoxon, iris hypoplasia, iridocorneal adhesions, and corectopia. Approximately 50% of affected individuals develop a high-pressure glaucoma associated with severe optic nerve disease. The cause of the glaucoma associated with this syndrome is not known, although anomalous development of the anterior chamber angle structures is usually found.

Genetic heterogeneity of Rieger's syndrome is indicated by the variety of chromosomal abnormalities that have been associated with the condition, including deletions of chromosome 4 and chromosome 13. Genes for Rieger's syndrome are located on chromosomes 4q25, 13q14, and 6p25. Iris hypoplasia is the dominant clinical feature of pedigrees linked to the 6p25 locus, whereas pedigrees linked to 4q25 and 13q14 demonstrate the full range of ocular and systemic abnormalities found in these patients.

The genes located on chromosomes 4q25 and 6p25 have been identified.[4] The chromosome 4q25 gene *(PITX2)* codes for a bicoid homeobox transcription factor. Like *PAX6*, this gene is expressed during eye development and is probably involved in the ocular developmental processes. The chromosome 6p25 gene *FOXC1* (also called *FKHL7*) is a member of a forkhead family of regulatory proteins. *FOXC1* is expressed during ocular development, and mutations alter the dosage of the gene product. There is some indication that the FOXC1 protein and the PITX2 protein interact during ocular development. The identification of other genes responsible for Rieger's syndrome and anterior segment dysgenesis is necessary to determine whether these genes are part of a common developmental pathway or represent redundant functions necessary for eye development.

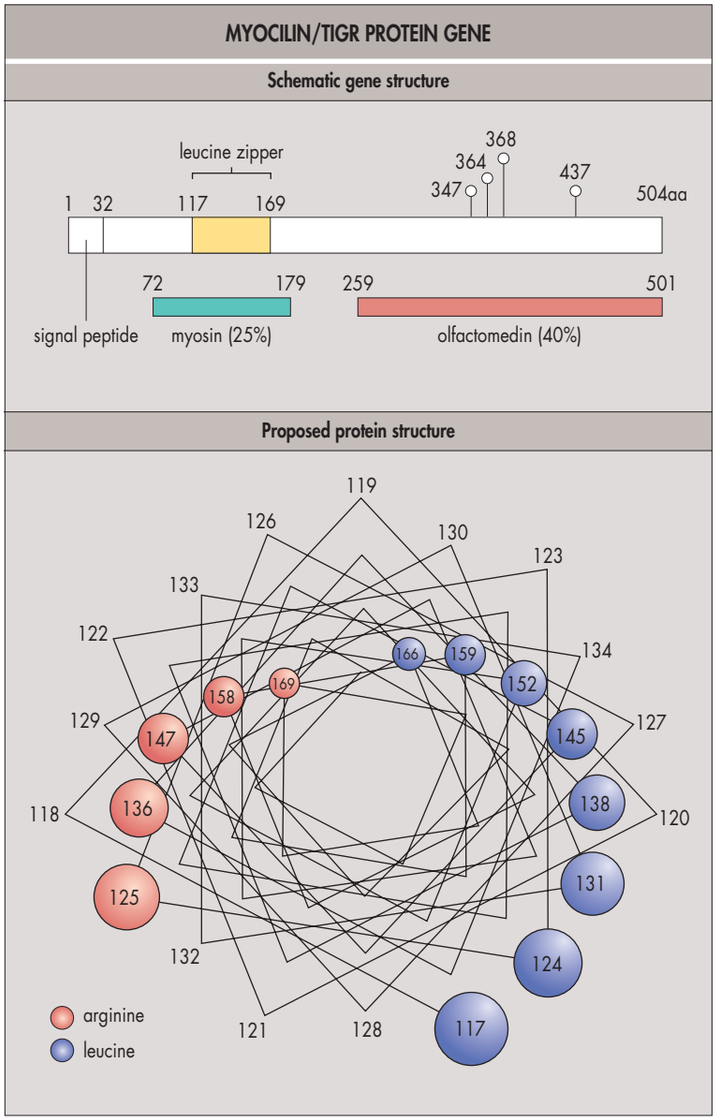

Fig. 1.2.3 *MYOC* (Myocilin). The myosin-like domain, the olfactomedin-like domain, and the leucine zipper are indicated. Amino acids altered in patients with juvenile- or adult-onset glaucoma are shown. (Reprinted by permission of Federation of the European Biochemical Societies from Orteto J, Escribano J, Coca-Prados M. Cloning and characterization of subtracted cDNAs from a human ciliary body library encoding TIGR, a protein involved in juvenile open angle glaucoma with homology to myosin and olfactomedin. FEBS Lett 1997;413:349–53.)

JUVENILE GLAUCOMA

Primary juvenile open-angle glaucoma is a rare disorder that develops during the first two decades of life. Affected patients typically present with a high intraocular pressure (IOP), which ultimately requires surgical therapy. Juvenile glaucoma may be inherited as an autosomal dominant trait, and large pedigrees have been identified and used for genetic linkage analysis. One gene responsible for this condition, *MYOC,* codes for the myocilin protein and is located on chromosome 1q23 *(GLC1A)*.

Myocilin has been shown to be expressed in the human retina, ciliary body, and trabecular meshwork. The protein has several functional domains, including a region homologous to a family of proteins called olfactomedins. Although the function of the protein and the olfactomedin domain is not known, nearly all the mutations associated with glaucoma have been found in the olfactomedin portion of the protein (Fig. 1.2.3).[5] Mutations in myocilin also have been associated with some cases of adult-onset primary open-angle glaucoma. Patients with only one copy of the myocilin gene (because of chromosomal deletion removing the second copy of the gene) or without any functional myocilin (caused by homozygosity of a stop-codon polymorphism in the first part of the gene) do not develop glaucoma. Collectively these results suggest that mutations in myocilin cause a gain-of-function or dominant negative effect rather than a loss-of-function or haploinsufficiency. The role of myocilin in IOP

elevation is not completely known, but in vitro studies show that myocilin mutants are misfolded and detergent resistant. Myocilin mutations may be secretion incompetent and accumulate in the endoplasmic reticulum (ER) inducing ER stress. Recent studies using a transgenic mouse model indicate that compounds that relieve ER stress can also reduce the mutation-associated elevation of IOP.[6]

CONGENITAL GLAUCOMA

Congenital glaucoma is a genetically heterogeneous condition, with both autosomal recessive and autosomal dominant forms reported. Two genes responsible for autosomal recessive congenital glaucoma have been identified, *CYP1B1,* a member of the cytochrome P-450 family of proteins (cytochrome P-4501B1)[7] and *LTBP2* (latent transforming growth factor beta binding protein 2).[8] Mutations in *CYP1B1* have been identified in patients with autosomal recessive congenital glaucoma from all over the world but especially in areas where consanguinity is a custom.[9] Responsible mutations disrupt the function of the protein, implying that a loss of function of the protein results in the phenotype.[9] Recurrent mutations are likely to be the result of founder chromosomes that have been distributed to populations throughout the world.[10,11] Because the defects responsible for congenital glaucoma are predominantly developmental, cytochrome P-4501B1 and latent transforming growth factor beta binding protein 2 must play a direct or indirect role in the development of the anterior segment of the eye.

NONSYNDROMIC CONGENITAL CATARACT

At least one-third of all congenital cataracts are familial and are not associated with other abnormalities of the eye or with systemic abnormalities. A number of different genes can contribute to congenital cataract, including some that code for the crystallin proteins.[12] The human γ-crystallin genes constitute a multigene family that contains at least seven highly related members. All seven of the γ-crystallin genes have been assigned to chromosome 2q34-q35. Of the genes mapped to this region, only two of them, γ-C and γ-D, encode abundant proteins. Two of the genes, γ-E and γ-F, are pseudogenes, which means they are not expressed in the normal lens. A pedigree affected by the Coppock cataract, a congenital cataract that involves primarily the embryonic lens, was shown to be linked genetically to the region that contains the γ-crystallin genes. In individuals affected by the Coppock cataract, additional regulatory sequences have been found in the promoter region of the γ-E pseudogene.[13] This result implies that the γ-E pseudogene is expressed in affected individuals and that expression of the pseudogene is the event that leads to cataract formation. A number of other genes have been associated with hereditary cataract. A useful collection of mutations and phenotypes can be found at the OMIM website (Table 1.2.1).

RETINITIS PIGMENTOSA

The molecular genetics of retinitis pigmentosa (RP) is exceedingly complex. The disease can exhibit sporadic, autosomal dominant, autosomal recessive, X-linked, or digenic inheritance. At least 200 genes are known to be associated with RP, and a number of genes have been mapped but not yet found. Most of these genes are expressed preferentially in the retina, but some are expressed systemically. A useful resource listing genes responsible for various forms of retinal diseases, including retinitis pigmentosa, can be found at the RetNet website (http://www.sph.uth.tmc.edu/Retnet/).

Mutations in rhodopsin can cause an autosomal dominant form of RP that provides an interesting example of how mutant proteins can interfere with normal cellular processes. Initially, one form of autosomal dominant RP was mapped to chromosome 3q24. With a candidate gene approach, the rhodopsin gene was identified as the cause of the disease in affected families.[14] Many of the first mutations detected in the rhodopsin protein were missense mutations located in the C-terminus of the gene (Fig. 1.2.4). To explore the pathogenical mechanisms of these mutations, transgenic mice were created that carried mutant copies of the gene.[15] Histopathological studies of these mice showed an accumulation of vesicles that contained rhodopsin at the junction between the inner and outer segments of the photoreceptors. The vesicles probably interfere with the normal regeneration of the photoreceptors, thus causing photoreceptor degeneration. Because the C-terminus of the nascent polypeptide is involved in the transport of the maturing protein, the accumulation of rhodopsin-filled vesicles is likely to result from abnormal transport of the mutant rhodopsin to the membranes of the outer segments.

Null mutations (mutations that cause a prematurely shortened or truncated protein) also have been found in the rhodopsin gene in patients who have autosomal recessive retinitis pigmentosa (see Fig. 1.2.4).[16] Mutations responsible for recessive disease typically cause a loss of biological activity,

TABLE 1.2.1 Web-Based Resources for Inherited Human Ocular Disorders

NCBI	National Center for Biotechnology Information	http://www.ncbi.nlm.nih.gov/
OMIM	Online Mendelian Inheritance in Man	http://www.ncbi.nlm.nih.gov/omim
RetNet	Retinal disease genes	http://www.sph.uth.tmc.edu/Retnet/
Genes and Disease (NCBI Bookshelf)	Systemic inherited disorders	http://www.ncbi.nlm.nih.gov/books/NBK22183/
UCSC	Human genome sequence browser	http://www.genome.ucsc.edu

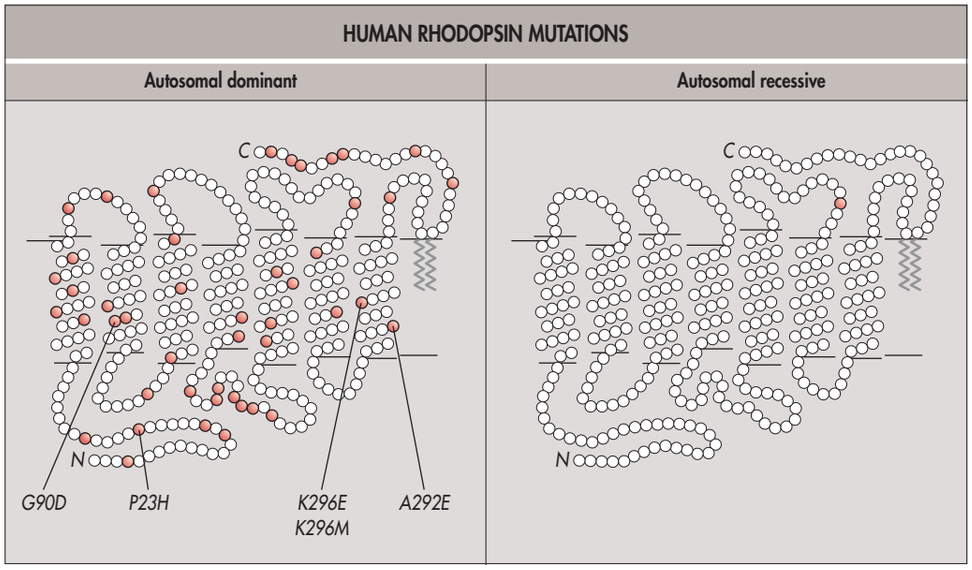

Fig. 1.2.4 Human Rhodopsin Mutations. The red circles indicate the amino acids altered by mutations in the gene in patients who have autosomal dominant retinitis pigmentosa. The translational stop site that results from a nonsense mutation is indicated as a red circle in a patient who has autosomal recessive retinitis pigmentosa.

either because they create a defective protein product that has little or no biological activity or because they interfere with the normal expression of the gene (regulatory mutations). Most individuals heterozygous for autosomal recessive disorders are clinically normal. Unlike the missense mutations responsible for the dominant form of the disease, the null mutations in rhodopsin produce an inactive protein that is not destructive to the cell. Null mutations result in retinitis pigmentosa only when they are present in both copies of the gene. Mutations in just one copy of the gene (heterozygous individuals) do not have a clinically detectable phenotype.

STARGARDT DISEASE

Stargardt disease is characterized by progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, with the frequent appearance of orange–yellow flecks distributed around the macula. The choroid is characteristically dark on fluorescein angiography in about 80% of cases. The disease results in a loss of central acuity that may have a juvenile to adult onset and is inherited as an autosomal recessive trait. Inactivation of both copies of the responsible gene is necessary to cause the disease. Mutations in a photoreceptor cell-specific ATP-binding transporter gene (*ABCA4* or *ABCR*) have been found in affected patients.[17,18] Most disease-related mutations are missense mutations in conserved amino acid positions. The retina-specific ABC transporter (ABCA4) responsible for Stargardt disease is a member of a family of transporter proteins and is expressed in rod photoreceptors, which indicates that this protein mediates the transport of an essential molecule either into or out of photoreceptor cells. Accumulation of a lipofuscin-like substance in *ABCA4*-related disease may result from inactivation of this transporter protein.

X-LINKED JUVENILE RETINOSCHISIS

Retinoschisis is a maculopathy caused by intraretinal splitting; the defect most likely involves retinal Müller cells. Retinoschisis is inherited as an X-linked recessive trait. X-linked recessive disorders, like autosomal recessive disorders, are caused by inactivating mutations. Because men have only one X chromosome, one mutant copy of a gene responsible for an X-linked trait results in the disease. Usually women are heterozygous carriers of recessive X-linked traits and do not demonstrate any clinical abnormalities. Mutations in the gene coding for retinoschisin have been shown to be the cause of the disease.[19] The protein is involved in cell–cell interaction and may be active in cell adhesion processes during retinal development. Most retinoschisis gene *(XLRS1)* mutations cause a loss of protein function.

NORRIE'S DISEASE

Norrie's disease is an X-linked disorder characterized by progressive, bilateral, congenital blindness associated with retinal dysplasia that has been referred to as a "pseudoglioma." The disease can include mental retardation and hearing defects. Norrie's disease is inherited as an X-linked recessive trait, and a causative gene has been identified on the X chromosome that has a tertiary structure similar to transforming growth factor-β.[20] Norrie's disease is a member of the familial exudative vitreoretinopathy (FEVR) syndromes, which are genetically heterogeneous inherited blinding disorders of the retinal vascular system, and to date three other loci have been mapped.[21] Mutations in the Norrie's disease gene have been found in a small subset of patients with severe retinopathy of prematurity (ROP), although defects in this gene do not appear to be a major factor in ROP.[22]

SORSBY'S MACULAR DYSTROPHY

Sorsby's macular dystrophy is an autosomal dominant disorder characterized by early onset bilateral and multifocal choroidal neovascularization resulting in macular edema, hemorrhage, and exudation. The disease typically begins at about 40 years of age. Missense mutations in the gene that codes for tissue inhibitor metalloproteinase-3 (TIMP-3) have been found in affected individuals.[23] This protein is involved in remodeling of the extracellular matrix. Inactivation of the protein may lead to an increase in activity of the metalloproteinase, which may contribute to the pathogenesis of the disease.[23]

GYRATE ATROPHY

Hyperornithinemia results from deficiency of the enzyme ornithine ketoacid aminotransferase and has been shown to be the cause of gyrate atrophy, an autosomal recessive condition characterized by circular areas of chorioretinal atrophy. Mutations in the gene for ornithine ketoacid aminotransferase mapped to chromosome 10q26 have been associated with the disease in affected individuals.[24] Most of the responsible mutations are missense mutations, which presumably result in an inactive enzyme. One mutation has been found in homozygous form in the vast majority of apparently unrelated cases of gyrate atrophy in Finland, an example of a founder effect that produces a common mutation in an isolated population.

Identification of the enzyme defect responsible for this disease makes it an interesting candidate for gene therapy. Previous studies indicated that a lower ornithine level, achieved through a strict low-arginine diet, may retard the progression of the disease.[25] Replacement of the abnormal gene—or genetic engineering to produce a supply of normal enzyme—may result in a reduction of ornithine levels without dietary restrictions.

COLOR VISION

Defective red–green color vision affects 2%–6% of men and results from a variety of defects that involve the color vision genes. In humans, the three cone pigments—blue, green, and red—mediate color vision. Each visual pigment consists of an integral membrane apoprotein bound to the chromophore 11-*cis* retinal. The genes for the red and green pigments are located on the X chromosome, and the gene for the blue pigment is located on chromosome 7. The X chromosome location of the red and green pigment genes accounts for the X-linked inheritance pattern observed in red or green color vision defects.

The common variations in red or green color vision are caused by the loss of either the red or the green cone pigment (dichromasy) or by the production of a visual pigment with a shifted absorption spectrum (anomalous trichromasy). A single amino acid change (serine to alanine) in the red photopigment gene is the most common color vision variation. Among Caucasian men, 62% have serine at position 180 in the red pigment protein, and 38% have alanine in this position. Men who carry the red pigment with serine at position 180 have a greater sensitivity to long-wavelength radiation than do men who carry alanine at this position.[26] Recent work suggests that gene therapy could correct color vision defects.[27]

RETINOBLASTOMA

A gene responsible for the childhood eye tumor retinoblastoma was identified in 1986 on chromosome 13q14.[28] The gene product is involved in regulation of the cell cycle. Absence of this protein in an embryonic retinal cell results in the uncontrolled cell growth that eventually produces a tumor.[29] Susceptibility to hereditary retinoblastoma is inherited as an autosomal dominant trait. Mutations in the retinoblastoma gene result in underproduction of the protein product or production of an inactive protein product. A retinal cell that has only one mutant copy of the retinoblastoma gene does not become a tumor. However, inactivation of the remaining normal copy of the retinoblastoma gene is very likely in at least one retinal cell out of the millions present in each retina. Among individuals who inherit a mutant copy of the retinoblastoma gene, 90% sustain a second hit to the remaining normal copy of the gene and develop a tumor (Fig. 1.2.5).[30] Fifty percent of the offspring of individuals affected by hereditary retinoblastoma will inherit the mutant copy of the gene and are predisposed to develop the tumor. Approximately 10% of individuals who inherit a mutation do not sustain a second mutation and do not develop a tumor. The offspring of these "carrier" individuals also have a 50% chance of inheriting the mutant copy of the retinoblastoma gene (see Fig. 1.2.5).

ALBINISM

Autosomal recessive diseases often result from defects in enzymatic proteins. Albinism is the result of a series of defects in the synthesis of melanin pigment.[31] Melanin is synthesized from the amino acid tyrosine, which is first converted into dihydroxyphenylalanine through the action of the copper-containing enzyme tyrosinase. An absence of tyrosinase results in one form of albinism. Mutations in the gene that codes for tyrosinase are responsible for tyrosinase-negative ocular cutaneous albinism. Most of the mutations responsible for this disease cluster in the binding sites for copper and disrupt the metal ion–protein interaction necessary for enzyme function.[32] Both copies of the gene for tyrosinase must be mutated before a significant interruption of melanin production occurs. Heterozygous individuals do not have a clinically apparent phenotype, which suggests that one functional copy of the gene produces sufficient active enzyme for the melanin level to be phenotypically normal (Fig. 1.2.6).

LEBER'S OPTIC NEUROPATHY

Mutations in mitochondrial DNA are an important cause of human disease. Disorders that result from mutations in mitochondrial DNA demonstrate a maternal inheritance pattern. Maternal inheritance differs from mendelian inheritance, in that men and women are affected equally, but only affected females transmit the disease to their offspring. The characteristic segregation and assortment of mendelian disorders depend on the meiotic division of maternal and paternal chromosomes found in the nucleus of cells. In contrast, mitochondrial DNA is derived from the maternal egg and replicates and divides with the cell cytoplasm by simple fission. A mutation that occurs in mitochondrial DNA is present in all cells of the organism, which includes the gametes. Female eggs have abnormal mitochondria that may be passed to offspring. Sperm contain mitochondria but do not transmit mitochondria to the fertilized egg. A man who carries a mitochondrial DNA mutation may be affected by the disease, but he cannot transmit the disease to his offspring.

Leber's hereditary optic neuropathy (LHON) was one of the first diseases to be recognized as a mitochondrial DNA disorder.[33] In familial cases of the disease, all affected individuals were related through the maternal lineage, consistent with inheritance of human mitochondrial DNA.

Patients affected by LHON typically present in midlife with acute or subacute, painless, central vision loss that results in a permanent central scotoma and loss of sight. The manifestation of the disease varies tremendously, especially with respect to onset of visual loss and severity of the outcome. The eyes may be affected simultaneously or sequentially; the disease may progress rapidly over a period of weeks to months or slowly over several years. Within a family, the disease may also vary among affected members.

Several factors contribute to the variable phenotype of this condition. Certain mutations are associated with more severe disease, and some mitochondrial DNA haplotypes appear to be associated with more severe disease.[34] Another important factor that affects the severity of the disease is the heteroplasmic distribution of mutant and normal mitochondria. Not all mitochondria present in diseased tissue carry DNA mutations. During cell division, mitochondria and other cytoplasmic organelles are distributed arbitrarily to the daughter cells. Consequently, the daughter cells are likely to have unequal numbers of mutant and normal mitochondria (Fig. 1.2.7). Because the diseased mitochondria are distributed to developing tissues, some tissues accumulate more abnormal mitochondria than others. Hence, some individuals have more abnormal mitochondria in the optic nerve and develop a more severe optic neuropathy.

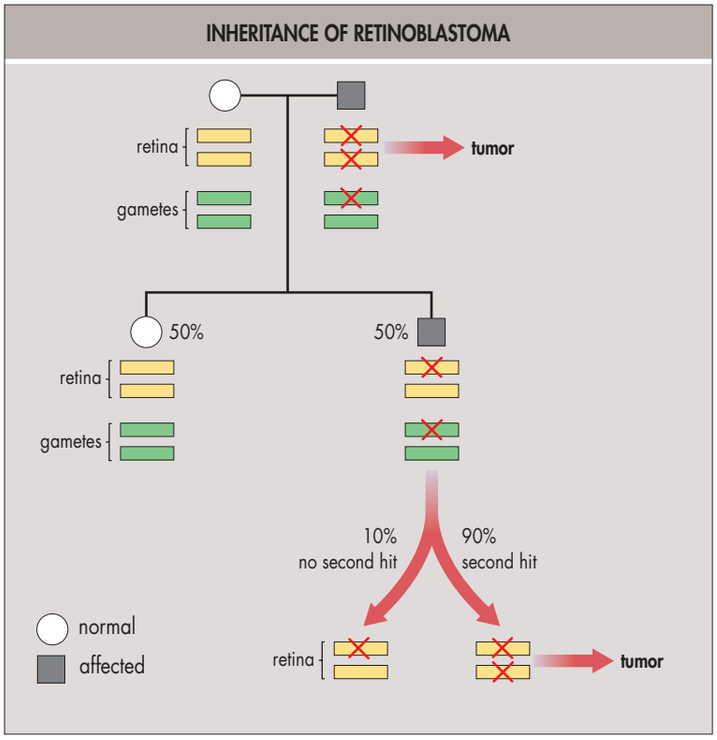

Fig. 1.2.5 Inheritance of Retinoblastoma. Individuals who inherit a mutation in the retinoblastoma gene are heterozygous for the mutation in all cells of the body. The "second hit" to the remaining normal copy of the gene occurs in a developing retinal cell and leads to tumor formation (see text for explanation).

CONGENITAL FIBROSIS SYNDROMES AND DISORDERS OF AXON GUIDANCE

Congenital fibrosis of the extraocular muscles and Duane's syndrome are inherited forms of congenital fibrosis and strabismus. At least 20 genes contribute to these conditions and other disorders of axon guidance,[35] with the *ARIX/PHOX2A* genes causing congenital fibrosis of extraocular muscles type 2[36] and the *SALL4* gene causing Duane's radial ray syndrome.[37]

AUTOSOMAL DOMINANT OPTIC ATROPHY

Of the inherited optic atrophies, autosomal dominant Kjer optic atrophy is the most common. This disease results in a progressive loss of visual acuity, centrocecal scotoma, and bilateral temporal atrophy of the optic nerve. The onset is typically in the first two decades of life. The condition is inherited as an autosomal dominant trait with variable expressivity, and mutations in *OPA1* have been found in a number of affected families.[38,39] *OPA1* codes for a dynamin-related GTPase that is targeted to mitochondria and may function to stabilize mitochondrial membrane integrity. It is interesting that this gene and the gene responsible for another optic atrophy, Leber's hereditary optic atrophy (see earlier), both function in the mitochondria, emphasizing the critical role of mitochondria in optic nerve function.

COMPLEX TRAITS

Human phenotypes inherited as polygenic or "complex" traits do not follow the typical patterns of mendelian inheritance. Complex traits are relatively

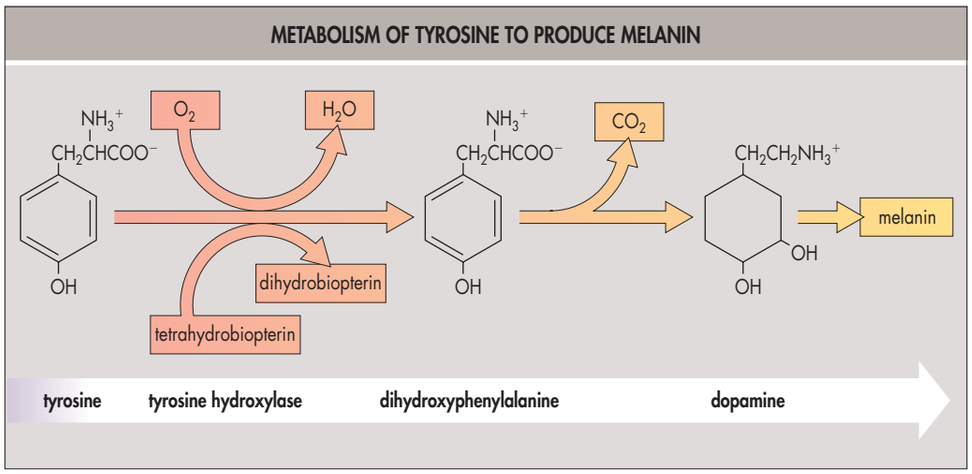

Fig. 1.2.6 Metabolism of Tyrosine to Produce Melanin. In the final step, dopamine is converted into an indole derivative that condenses to form the high-molecular-weight pigment melanin.

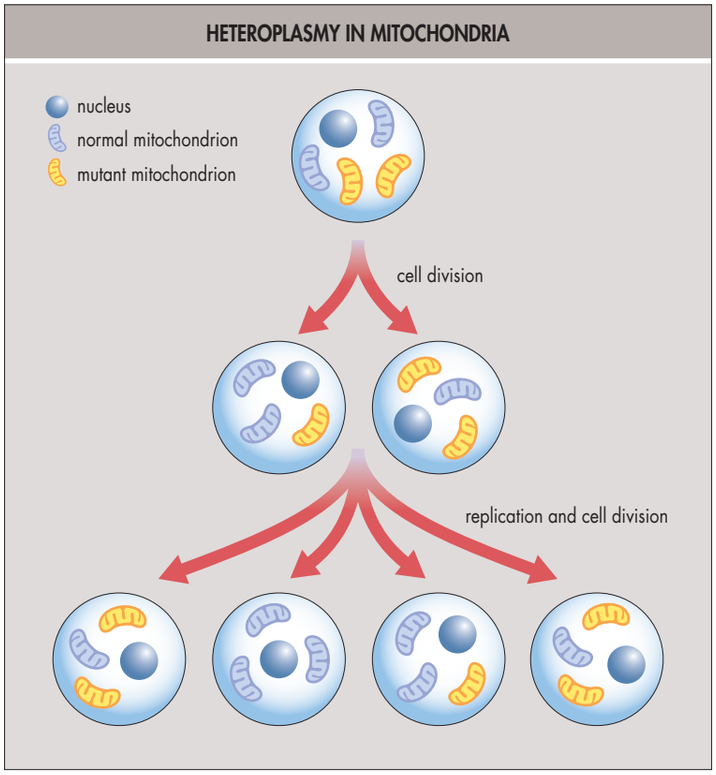

Fig. 1.2.7 Heteroplasmy in Mitochondria. Daughter cells that result from the division of a cell that contains mitochondria with mutant DNA may contain unequal numbers of mutant mitochondria. Subsequent divisions lead to a population of cells with different numbers of normal and abnormal mitochondria.

common disorders. Generally, DNA variants associated with these disorders are not causal but influence disease suspectibility.[40] Environmental factors may also contribute to complex disease risk. For example, genetic variants in complement factor H (CFH) and *LOC37718* are known to be major genetic risk factors for age-related macular degeneration,[41–44] and combined with smoking the risk is increased.[45] The genome-wide association study (GWAS) approach has also successfully identified genes contributing to other common complex ocular conditions and traits,[40] including primary open-angle glaucoma,[46,47] primary angle-closure glaucoma,[48] exfoliation syndrome and glaucoma,[49,50] myopia,[51,52] and Fuchs' endothelial dystrophy.[53]

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Genetic Testing and Genetic Counseling

1.3

Janey L. Wiggs

Definition: A genetic test is any clinical or laboratory investigation that provides information about the likelihood that an individual is affected with a heritable disease. The majority of genetic tests are based on molecular evaluations of genomic DNA designed to identify the DNA mutations responsible for the disease.

Key Features

- Indications and methods for genetic testing for ocular disorders.
- Genetic counseling and ethical issues.

GENETIC TESTING

Role of Genetic Testing in the Clinic

DNA-based genetic tests can identify individuals at risk for disease before any clinical evidence is present (presymptomatic testing).[1] This information coupled with effective genetic counseling and clinical screening can be useful. An effective presymptomatic test needs to meet the specificity and sensitivity expectations for any clinical test. Sensitivity is the number of affected individuals that are positive for a test compared with the total number of affected individuals (including those that tested negative for the test). Specificity is the number of unaffected individuals that are negative for the test compared with the total number of unaffected individuals tested (including those that tested positive for the test) (Fig. 1.3.1).

The identification of a mutation responsible for a disease through DNA-based genetic testing can establish a molecular diagnosis. For some disorders, such as juvenile open-angle glaucoma caused by mutations in *MYOC*,[2] specific mutations have been correlated with severity of disease or other clinical features that are useful prognostically. A molecular diagnosis may also help guide therapy and is required before gene-based therapies can be utilized. For example, mutations in a number of different genes can cause Leber's hereditary amaurosis, but only those patients with disease due to mutations in *RPE65* will benefit from novel *RPE65*-based therapies using gene replacement.[3]

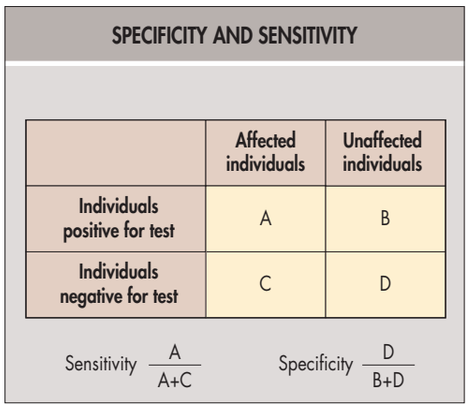

Fig. 1.3.1 Definition of Sensitivity and Specificity for a Laboratory Test. Sensitivity is defined as the number of affected individuals positive for the test (A) divided by the total number of affected individuals tested (A + C). Specificity is defined as the number of unaffected individuals negative for the test (D) divided by the total number of unaffected individuals tested (B + D).

Methods for DNA-Based Genetic Testing

Although genetic testing can be performed using DNA, RNA, or protein, DNA is the easiest to work with, and most genetic tests use this as the starting material. A biological sample from the patient is needed before genetic testing can be performed. The inclusion of family members may help the evaluation, but they are not absolutely required. DNA for testing can be obtained from a number of sources, including blood samples, mouthwash samples or buccal swabs, archived pathology specimens, or from hair.[4–6]

Genomic DNA sequencing is the most commonly used method to detect mutations. For many disorders, sequencing the entire responsible gene is necessary, including all exons, immediate flanking intron sequences with splice signals and 5′ and 3′ flanking regulatory regions. Some disorders are caused by a specific mutation in a gene, and genetic testing can be limited to an evaluation of a single gene. For other diseases, however, such as the inherited retinal degenerations, sequencing multiple genes may be required before a causative mutation is identified. For diseases with many causative genes, a panel test that allows for sequencing all genes at once is both more effective and more efficient.[7] Alternatively, whole exome sequencing (WES) that captures and sequences all coding regions of the genome can also be a preferred approach for disorders with many possible genetic mutations.[8] Genomic DNA sequencing will not usually identify large chromosomal abnormalities, including large copy number variations (deletions or insertions) or chromosomal translocations. Other techniques are necessary to detect large chromosomal abnormalities, including karyotyping and multiplex ligation-dependent probe amplification (MLPA).[9,10] For diseases that are caused primarily by a limited set of mutations (for example, the three mutations that commonly cause Leber's hereditary optic neuropathy (LHON),[11] specific tests such as allele-specific polymerase chain reaction (PCR) amplification or TaqMan assays can be used and can be more efficient than sequencing the entire gene (Table 1.3.1).

Current Recommendations for Genetic Testing for Ophthalmic Diseases

Currently, genetic testing is indicated for patients with clinical evidence of a disorder whose causative genes have been identified and for which

TABLE 1.3.1 Common Types of Genetic Tests

Method	Indication	Example
Single gene DNA sequencing	Different mutations distributed throughout a single gene are known to cause the inherited condition	Sequencing *OPA1* in patients with autosomal dominant optic neuropathy
Multiple gene DNA sequencing	Mutations in multiple genes are known to cause the condition	Inherited retinal degenerations
Multiplex ligation-dependent probe amplification (MLPA)	Detects deletions and duplications in genes known to cause the condition and that may be missed by sequence-based approaches	MLPA testing for *PAX6* deletions in patients with aniridia
TaqMan assay or allele-specific assay	Detects a single DNA base pair change and is used if a small set of mutations are primarily the cause of the condition	Three mutations commonly cause Leber's hereditary optic neuropathy (LHON)
Karyotype	Detects large chromosomal rearrangements including deletions, duplications, and translocations	Down syndrome

the identification of the genetic mutation contributing to the disease has sufficient specificity and sensitivity that testing will be clinically useful. Serious failures of a diagnostic test are false positives (individuals without the disease who test positively) and false negatives (individuals with the disease who test negatively). Although genes have been identified for some common complex disorders such as age-related macular degeneration, primary open-angle glaucoma, and exfoliation syndrome, in general, testing for these mutations is not sufficiently sensitive and specific that the test results are clinically meaningful. For example, over 90% of patients with exfoliation syndrome carry one of two missense changes in *LOXL1;* however, up to 80% of normal individuals also carry these same DNA sequence variants.[12] Clearly the identification of these missense mutations alone is not clinically useful. Examples of genetic tests that are useful include *RPE65* for Leber's hereditary amaurosis,[13] *PAX6* for aniridia,[14] *MYOC* for early onset primary open-angle glaucoma,[15] and *OPA1* for optic neuropathy,[16] as well as many other genes that are known to cause inherited ocular conditions.[17]

CLIA Laboratories

Laboratories in the United States offering genetic testing must comply with regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The Centers for Medicare and Medicaid Services administers CLIA and requires that laboratories meet certain standards related to personnel qualifications, quality control procedures, and proficiency testing programs in order to receive certification. This regulatory system was put in place to encourage safe, accurate, and accessible genetic tests. In addition to ensuring that consumers have access to genetic tests that are safe, accurate, and informative, these policies encourage the development of genetic tests, genetic technologies, and the industry that produces these products. A number of CLIA-certified laboratories performing genetic testing for eye diseases exist in the United States. For a list of CLIA-certified laboratories participating in the National Eye Institute (NEI)-sponsored eyeGENE network, see the NEI website at http://www.nei.nih.gov. CLIA-certified laboratories offering genetic testing can also be found at GeneTests: https://www.genetests.org/.

Genetic Reports

A genetic test report is a sensitive document that is the main form of communication between the CLIA laboratory and the physician requesting the genetic test. Genetic test reports may be shared with the patient and with genetic counselors. The report should include (1) the type of genetic test performed (i.e., sequencing or other methodology), (2) the gene or genes that were evaluated, (3) the results of the testing, (4) information about the pathogenicity of the sequence variants, (5) recommendations for clinical follow-up based on the results of testing, and (6) literature references providing additional information about the genes and mutations responsible for the disease. The report should be written clearly and have appropriate contact information.

Novel DNA sequence changes are frequently found as a result of genomic DNA sequencing. New DNA sequence changes (variants) may be benign polymorphisms or causative mutations. Additional studies must be done before the sequence change can be designated as disease causing. Demonstrating that the mutant protein has an abnormal function or evaluation of the mutant gene in an animal model would be an ideal test of pathogenicity, but these approaches are time consuming and may not be possible. Current approaches to evaluate the pathogenicity of a novel DNA sequence variant are based on (1) population data, (2) computational and predictive data from *in silico* estimates for pathogenicity such as SIFT[18] and PolyPhen-2,[19] (3) functional data, and (4) segregation data for families.[20]

GENETIC COUNSELING

Genetic counseling has become an important part of any clinical medicine practice. In 1975 the American Society of Human Genetics adopted this descriptive definition of genetic counseling[21]:

> Genetic counseling is a communication process which deals with the human problems associated with the occurrence or risk of occurrence 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 (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 a course of action that seems to them appropriate in their view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

Clinical Evaluation and Family History

An accurate diagnosis is the first step in productive genetic counseling. The patient–physician discussion of the natural history of the disease and of its prognosis and management is entirely dependent on the correct identification of the disorder that affects the patient. Risk assessment for other family members and options for prenatal diagnosis also depend on an accurate diagnosis. In some cases, appropriate genetic testing may help establish the diagnosis. Examination of other family members may be indicated to determine whether a particular finding is hereditary.

A complete family history of the incidence of the disorder is necessary to determine the pattern of inheritance of the condition. The mode of inheritance (i.e., autosomal dominant, autosomal recessive, X-linked, or maternal) must be known to calculate the recurrence risk to additional family members, and it helps confirm the original diagnosis. For the record of family information, the gender and birth date of each individual and his or her relationship to other family members are indicated using the standard pedigree symbols. It is also helpful to record the age of onset of the disorder in question (as accurately as this can be determined). The pedigree diagram must include as many family members as possible. Miscarriages, stillbirths, and consanguineous parents are indicated.

Occasionally a patient may appear to be affected by a condition that is known to be inherited, but the patient is unable to provide a family history of the disease. Several important explanations for a negative family history must be considered before the conclusion is made that the patient does not have a heritable condition. First, the patient may not be aware that other family members are affected by the disease. Individuals frequently are reluctant to share information about medical problems, even with close family members. Second, many disorders exhibit variable expressivity or reduced penetrance, which means that other family members may carry a defective gene that is not expressed or results in only a mild form of the disease that is not readily observed. Third, false paternity may produce an individual affected by a disease that is not found in anyone else belonging to the acknowledged pedigree. Genetic testing can easily determine the paternity (and maternity) of any individual if blood samples are obtained from relevant family members. Fourth, a new mutation may arise that affects an individual and may be passed to offspring, even though existing family members show no evidence of the disease.

Risk Prediction Based on Inheritance

Once the diagnosis and family history of the disorder are established, risk prediction in other family members (existing and unborn) may be calculated. The chance that an individual known to be affected by an autosomal dominant disorder will transmit the disease to his or her offspring is 50%. This figure may be modified depending on the penetrance of the condition. For example, retinoblastoma is inherited as an autosomal dominant trait, and 50% of the children of an affected parent should be affected. However, usually only 40%–45% of the children at risk are affected, because the penetrance of the retinoblastoma trait is only 80%–90%, which means that 5%–10% of children who have inherited an abnormal copy of the retinoblastoma gene do not develop ocular tumors.

An individual affected by an autosomal recessive trait will have unaffected children unless he or she partners with another individual affected by the disease or with an individual who is a carrier of the disease. Two individuals affected by an autosomal recessive disease produce only affected offspring. (There are some rare exceptions to this rule. If the disease is the result of mutations in two different genes, it is possible for two individuals affected by an autosomal recessive trait to produce normal children. Also, in rare cases, different mutations in the same gene may compensate for each other, and the resultant offspring will be normal.) If an individual affected by an autosomal recessive disease partners with a heterozygous carrier of a gene defect responsible for that disorder, the chance of producing an affected child is 50%. Among the offspring of an individual affected by an autosomal recessive disease, 50% will be carriers of the disorder. If one of these offspring partners with another carrier of the disease, the chance of producing an affected child is 25%.

BOX 1.3.1 Types of Clinical Genetics Services and Programs

Center-Based Genetics Clinic
- Outreach clinics
- Inpatient consultations

Specialty Clinics
- Metabolic clinic
- Spina bifida clinic
- Hemophilia clinic
- Craniofacial clinic
- Other single-disorder clinics (e.g., neurofibromatosis type 1 clinic)

Prenatal Diagnosis Program: Perinatal Genetics
- Amniocentesis/chorionic villus sampling clinics
- Ultrasound program
- Maternal serum α-fetoprotein program

Genetic Screening
- Newborn screening program/follow-up clinic
- Other population-screening programs (e.g., for Tay–Sachs disease)

Education/Training
- Healthcare professional
- General public
- School system
- Teratology information services

X-linked disorders are always passed from a female carrier who has inherited a copy of an abnormal gene on the X chromosome received from either her mother (who was a carrier) or her father (who was affected by the disease). Man-to-man transmission is not seen in diseases caused by defects in genes located on the X chromosome. Among sons born to female carriers of X-linked disorders, 50% are affected by the disease, and 50% of daughters born to female carriers of X-linked disorders are carriers of the disease. All the daughters of men affected by X-linked disorders are carriers of the disease.

Mitochondrial disorders are inherited by sons and daughters from the mother. The frequency of affected offspring and the severity of the disease in affected offspring depend on the number of abnormal mitochondria present in the egg that gives rise to the affected child. Diseased and normal mitochondria are distributed randomly in all cells of the body, including the female gametes. As a result, not all the eggs present in a woman affected by a mitochondrial disorder have the same number of affected mitochondria (heteroplasmy). Men affected by mitochondrial disorders only rarely have affected children, because very few mitochondria in the developing embryo are derived from the sperm used to fertilize the egg.[22]

With careful diagnosis and family history assessment, even sporadic cases of heritable disorders are identifiable. In such cases, an estimate of recurrence risk can be calculated using the available pedigree and clinical information and the statistical principle called Bayes' theorem. These individuals should be referred to clinical genetics services such as those commonly found in hospital settings (Box 1.3.1).

Indications to Refer for Genetic Counseling

Known Inherited Condition

Genetic counseling can be useful for a family with a member affected by an established diagnosis. In this case the goal of the counseling is to describe recurrence risks for other family members. For example, if a child has retinoblastoma and a positive family history, the family may be referred for genetic counseling to review recurrence risks. If diagnostic testing has been performed, that can also be discussed and will aid in the presentation of the recurrence risks, especially if other family members have been tested.

Ocular and Systemic Congenital Anomalies

Individuals with multiple ocular and systemic anomalies may or may not fit into a particular syndrome. In these situations, the experience of a geneticist in recognizing malformation patterns and understanding the variability of genetic conditions can aid diagnosis. If an underlying cause is identified, relatives can then undergo genetic counseling.

Specific Eye Diseases

A genetic evaluation is important for families with inherited eye diseases. Many ophthalmological diseases have a well-documented inheritance pattern, and describing the inheritance to family members may help identify affected relatives who could be diagnosed and treated early in the course of the disease. This is especially important in families with conditions such as dominantly inherited juvenile glaucoma.

Ocular Defects Associated With Genetic Diseases

Many genetic diseases have associated ocular defects. For example, a diagnosis of neurofibromatosis type 1 may be made in a child because Lisch nodules were detected on a clinical examination.[23] The child and family should be referred for genetic counseling to help define the recurrence risks for other family members.

Confidentiality

Confidentiality is an important issue in genetic testing and genetic counseling. Confidentiality issues should be discussed before the initiation of testing so there is consensus on how results are reported, who receives results, and where the information is documented.

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