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Pediatric Oculoplastic Surgery

Second Edition

Springer

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James A. Katowitz • William R. Katowitz
Editors

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Forewords by Linton A Whitaker MD and
Geoffrey E. Rose, DSc, FRCS, FrCOpht

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This book was supported by funds from
The Edwin and Fannie Gray Hall Center for Human Appearance
at The Children's Hospital of Philadelphia and
The University of Pennsylvania Perelman School of Medicine

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ISBN 978-3-319-60812-9 ISBN 978-3-319-60814-3 (eBook)
https://doi.org/10.1007/978-3-319-60814-3

Library of Congress Control Number: 2017959646

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Carol and Nicole: for their ever-present love and support and to our children and grandchildren for the special joy they also bring to our lives.

Foreword

The title is symbolic of the inevitable trend, the maturing of a subspecialty area, the crystallization of a field by defining it with the written word, and a direction unchanged by managed care and forces attempting to reorganize the way medicine is practiced in the United States. James Katowitz, by dint of his personal philosophy, persistence, and exceptional ability, has helped to influence and define the new field. In contrast to present trends in medical care, the contributors to this book describe ever-increasing levels of specialization, excellence, and expertise. Patients and physicians demand it because it is possible to do it. With inquiring minds and the constant search for answers to unsolved problems, along with an incessantly rising level of expectation by the public, the direction is inevitable. Thus, while ophthalmology and plastic surgery are mature specialties, oculoplastic surgery develops and gives birth to pediatric oculoplastic surgery. The birthing process is not easy and becomes a defined being only by a limited number of individuals making it happen. That, in essence, is what this book and these individuals are about.

Concepts and techniques common to plastic surgery and ophthalmology originated with the need for repair in the oculo-orbital region, with vaguely conceived techniques ultimately giving rise to the specialty designations. By the twentieth century, specialty lines had been drawn in several areas of surgery, resulting in the founding of the American Board of Ophthalmology in 1916 and the American Board of Plastic Surgery in 1936. Perhaps the first person to bridge the specialties in a way defined in writing was John C. Mustarde in Scotland, an ophthalmologist and a plastic surgeon, resulting in his book about a new specialty, published in 1966 [1]. He bridged the worlds of plastic surgery and ophthalmology perhaps better than anyone else before or since. Of particular importance was his relationship with Paul Tessier, which led to extraordinarily creative surgical methods for orbital problems. Combined with an increasing emphasis on appearance and cosmetically superior outcomes of surgery, new possibilities for reconstructive and aesthetic surgery emerged. The American Society of Ophthalmic Plastic and Reconstructive Surgery came into being in 1969, and J.C. Mustarde became an honorary member. As an honorary member since 1984, I have had the good fortune to observe firsthand a maturing of the field.

In 1979, Iliff, Iliff, and Iliff published *Oculoplastic Surgery* [2]. In their preface, the authors described ophthalmic reconstructive surgery as "a new sub-specialty having emerged." This had been preceded by *Surgery of the Eyelids and Lacrimal System* by Jones and Wobig [3], which had not defined the emerging field of oculoplastic surgery as precisely. In 1972, before either of these publications appeared, Paul Tessier brought about the beginning of craniofacial surgery at our institution. Since then, James Katowitz and I worked together closely for 30 years. The demands of cranio-orbital surgery required constant and ready collaboration between craniofacial plastic surgery and ophthalmology. This became the foundation of a working relationship and, because cranio-orbital surgery has increasingly focused on pediatric malformations, the evolution of this book. Initially, medial and lateral canthopexies and ptosis procedures were done by the plastic surgery service, while lacrimal drainage procedures were done by the ophthalmology service. As a consequence of regular conferences and discussions that ultimately resulted in a collaboration in adults in the Center for Human Appearance at Penn, and after developing an understanding of what each of us did best, we created divisions

among ourselves. I understood that if I did ptosis procedures, I would need to take care of the problems of the cornea and the eye. Jim Katowitz understood that canthopexies involved the skeletal structure. Consequently, I did the majority of the latter, and he the majority of the former as well as drainage procedures. We both did cosmetic procedures. The two began to overlap, and we continued to have an ongoing relationship that was beneficial to both of us. In our medical center, the plastic surgeons have continued to do procedures oriented to the bone in the orbital area, building on Tessier's pioneering works of the 1960s, and in the purely cosmetic soft tissue areas. Although each group will define its own method of handling the crossovers, the need to work together is of critical importance and is illustrated by the breadth of specialties represented in this book. Of primary importance is the understanding that has evolved that function and appearance cannot be separated. While in the orbital region function may dominate, appearance is never far behind. In fact, they usually enhance one another. This understanding is critical for all specialties performing surgery in this area.

James Katowitz has made a substantial contribution by his postgraduate training program, a capacity to work and think with others, and setting a high standard that is defined by this book. All of these factors keep him at the leading edge. With the philosophies of form and function working together and teamwork between specialties, an important concept continues and is increasingly clarified.

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Preface

This book represents a personal effort to summarize more than 50 years of experience in managing oculoplastic problems in children. Many of the contributors are individuals who have trained as oculoplastic surgery fellows at the Children's Hospital of Philadelphia (CHOP) as approved by the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). The remainder represent affiliated subspecialists and international colleagues who share our team management approach to patient care.

We have been particularly fortunate to have been associated with this unique institution (the oldest pediatric hospital in the Western hemisphere) and to work with so many individuals of world renown. These gifted physicians and surgeons have always been graciously available for consultation, often without a scheduled appointment.

What is presented in each chapter of this book is not an encyclopedic representation of every surgical pediatric condition, but rather a logical approach to the evaluation and management of a wide spectrum of oculoplastic problems as encountered in children. Our philosophy has been one involving a cooperative team approach to patient care, utilizing the expertise of related disciplines for the benefit of the patient.

We have tried to highlight useful diagnostic approaches and provide the reader with specific steps in management that have proven successful in our hands. In some instances, the management steps may seem either too radical or not aggressive enough when compared to similar problems in adults. It is important to stress, however, that children are not just "little adults." Pediatric specialists require special skills: patience and compassion in relating to children and their family members, as well as diagnostic and surgical acumen and an intuitive "feel" for creative problem-solving. Although we have reached definitive solutions in many areas, others remain frustratingly elusive. It is our collective hope, however, that these chapters may provide new insights for improving the reader's appreciation and skills in the diagnosis and management of pediatric oculoplastic problems.

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Foreword to the Second Edition

In the presence of the superb and comprehensive parent edition of *Pediatric Oculoplastic Surgery*, it is a real challenge to eclipse the "gold-standard" first edition. As editors for this new work, James and William Katowitz have undoubtedly succeeded, both by assembling a large group of distinguished and experienced authors and by exploring exciting areas of recent change that would not normally appear in an oculoplastic textbook.

Throughout the work, it is very evident that "a child is not just a small adult." The work – a treasure trove of "gems" – covers the development of childhood periocular tissues, details of the way childhood tissues heal after surgery (injury), and the special "tricks" for assessment of the child with adnexal disease. Knowledge of the development of tissues and structures in childhood is particularly important in its relation to the outcomes for surgery: Unlike adults, during growth, children will have many years of developmental change, which will inevitably alter the final result in terms of both structure and function; failure to anticipate these changes will lead to unexpected long-term surgical outcomes.

Unusual for specialist textbooks on oculoplastic surgery, the editors are to be congratulated on incorporating authoritative chapters on subjects like pediatric anesthesia, neuro-ophthalmology, systemic diseases, otorhinolaryngology, and general plastic surgery. Likewise, chapters covering the psychology of the child, care of the child's mental health, and aesthetic rehabilitation are particularly welcome – as is the emphasis on functional and visual development in these children. Although perhaps somewhat daunting to the clinician, coverage of the rapidly changing fields of genetics, molecular biology, and pathology is included, and these chapters provide valuable insight into the future of the diagnosis – and possible treatments – of these diseases.

The clinical chapters are both comprehensive and spectacular – addressing all areas of eyelid, lacrimal, orbital, and socket disease and surgery. The work truly is a mine of information that can happily be used both as a reference text and as a resource to dip into for the reader's enjoyment. I personally would regard this wonderful resource as one that should rightly find pride-of-place on the desk of any pediatric ophthalmologist or reconstructive surgeon interested in pediatric oculoplastic disorders.

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Acknowledgments

We would like to express our deep appreciation to the Trustees of the Edwin and Fannie Gray Hall Trust – Richard B. Goldbeck, William T. Luskus, Esquire, and Robert E. Curran, Esquire – for their dedication and support in helping in the care and rehabilitation of so many children. This book would not have been possible without their support through the Edwin and Fannie Gray Hall Center for Human Appearance (CHA). We would also like to thank Ardis Ryder for her assistance in this work at CHA.

Of primary importance, also, has been Linton A. Whitaker, MD, who was not only instrumental in founding and developing the CHA, but has also been a colleague, mentor, and friend to both of us, beginning with the development of our Craniofacial Surgical Team at The Children's Hospital of Philadelphia (CHOP) in 1972. The evolution of a new subspecialty, pediatric oculoplastic surgery, would not have been possible without his foresight and insight, appreciating the overlap of surgical skills in our multidisciplinary team, and providing the leadership for such a smooth and noncompetitive interaction that has been one of the most gratifying and unique attributes of the CHA.

The challenge of writing this book would not have been possible without the dedication and assistance of a great many individuals. First and foremost are the oculoplastic fellows who have contributed so much, not only to the evolution of this book but also to the evolving new subspecialty of pediatric oculoplastic surgery. This book also reflects an evolutionary partnership which has included so many of our colleagues at CHOP and others both nationally and internationally who have shared in the exploration of new pediatric diagnostic and surgical techniques.

We would especially like to thank N. Scott Adzick, MD, who, as Chairman of the Department of Surgery at CHOP, has been so supportive of our oculoplastic fellowship program. Similarly, much appreciation goes to the administrative leaders at CHOP led by Madeline Bell, President and CEO, for their continuing support and encouragement of this fellowship program.

We would very much like to thank our friend and colleague, Monte Mills, MD, who as Chairman of the Division of Ophthalmology at CHOP, has continued to support the evolution of this new subspecialty. Our thanks go as well to David Schaffer, MD, who was instrumental in developing the Pediatric Ophthalmology Division at CHOP as well as our oculoplastic fellowship program. Our appreciation also goes to Joan O'Brien, MD, Chairman of the Department of Ophthalmology at the Scheie Eye Institute and the University of Pennsylvania Perelman School of Medicine, who has been a strong supporter of our oculoplastic program as well.

Our office staff, which has helped guide patients and their families through often difficult decisions, deserves special thanks. A long chain of individuals form links in this process, beginning with our Division Manager, Jenny Bartelle, our surgical schedulers, Carol Lanni and Nicole DeCicco as well as the many ophthalmic technicians and patient-care coordinators who have contributed over the years. Special thanks must go to Sonia Zhu who has managed our photographic imaging databases over the past two decades.

We are especially indebted to our secretarial support staff, and especially, Suzanne McCullough, who has provided editorial assistance. Our operating room nursing staff has also been wonderful in so many ways. Beginning with the development of our craniofacial surgery team, oculoplastic specialty nursing was improved under the tutelage of Ivy Fenton Kuhn, who

also deserves much praise and admiration for her organizational skills and tireless efforts in her current role as a Divisional Nurse Practitioner, offering compassionate care and support to so many oculoplastic patients and their families.

We would also like to acknowledge our many friends for their support, and in particular, Gregory G. Alexander, not only for assisting in the development and evolution of the CHA, but for being such a special friend. Likewise, we also want to thank his associate, Stanley A. Pelli, for his efforts in assisting the Hall Trustees in support of our work at CHA.

In addition, we would like to thank a number of individuals from Springer International Publishing AG: First and foremost, our Developmental Editor, Connie Walsh, for her extraordinary editing skills and for so patiently pulling together all of the many facets of production in a timely fashion. We also would like to thank Rebekah Collins, the Senior Editor in charge of this project as well as Asja Parrish, our Assistant Editor. And last but not least, the production team from **SPi Global**, led by Jayashree Dhakshnamoorthy and Sivakumar Krishnamoorthy, for creating such an exciting layout as well as keeping the entire production effort on schedule.

Most importantly, we would also like to express our gratitude and admiration to Krystyna Srodulski, our illustrator, whose work is truly remarkable. Oculoplastic surgery is essentially a visual specialty, and her work not only illuminates the text but also guides the reader to a much better understanding of the surgical steps required for managing pediatric oculoplastic problems than would otherwise have been possible.

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Part IV The Orbit

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Part I

General and Subspecialty Overviews

Genetic Considerations in Oculoplastic Disorders

1

Elizabeth Bhoj, Emma Bedoukian, Lama Khatib, and Bart Peter Leroy

Manifestations of Genetic Disorders

Disorders that have a genetic basis can be broadly classified into one of three main categories: (1) single-gene disorders, (2) chromosomal disorders, or (3) multifactorial disorders. All of these categories are represented among oculoplastic disorders [1, 2].

Single-gene disorders, also called Mendelian disorders, are caused by an error in a single gene. This error may involve one or both copies of that single gene. This may result in transmission of the erroneous genetic information, with a 50% chance of transmission if one gene has an error and a 100% chance of transmission if both genes have errors. Disorders that are based on a single-gene mutation usually demonstrate characteristic pedigree (family history) patterns. Neurofibromatosis type I, due to a mutation in the *NF1* gene, is an example of a single-gene disorder.

In chromosomal disorders, the genetic error can either be additional or missing genetic material, referred to as duplication and deletion, respectively. The deletion or duplication may affect a single gene, multiple genes, or an entire chromosome. For example, 22q11.2 deletion syndrome, formerly known as DiGeorge syndrome (dysmorphic features, congenital heart disease, immunologic abnormalities, and behavioral abnormalities), is due to a small deletion in the long arm of chromosome 22. Down syndrome, on the other hand, is the result of an entire extra copy of chromosome 21 [3].

Multifactorial disorders are more complex. Imprinted disorders, such as Prader-Willi syndrome, will not always follow a classic pedigree and will be covered in more depth later [4]. The combination of genetic and environmental factors results in a phenotype, and it can be difficult to determine how much genetics has contributed to the disease [5]. These disorders tend to show familial patterns, but do not follow the classic pedigrees of single-gene disorders.

In general, characteristic features in a patient and a family member should raise the suspicion for a genetic syndrome. Typically, when a condition affects multiple family members, at unusually early ages or with varying degrees of severity, further inquiry should be prompted. A three-generation pedigree is usually sufficient, but in rare diseases an extended pedigree to include ancestors or extended family members is recommended. If the patient has multiple anomalies or dysmorphic features that cannot be explained by another cause (such as fetal alcohol syndrome), he or she should be referred for a full genetic examination (Fig. 1.1).

As mentioned earlier, the expression of a gene in an organism is called a phenotype. If one copy of the gene is required for the phenotypic trait to be expressed (heterozygous state), the gene is termed dominant. If two copies of a gene are required for phenotypic expression (homozygous state), the gene is called recessive.

The chromosomes that determine the sex of the individual are the X and the Y chromosome. Genetically, an individual with an X and a Y (an XY individual) will be male, and an individual with two X chromosomes (an XX individual) will be female. Mutations expressed in an allele on the X chromosome are usually more severe in males than females, because males have only one copy of the X chromosome, while females have two copies. In other words, when females have a mutation involving one allele on one X chromosome,

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J.A. Katowitz, W.R. Katowitz (eds.), *Pediatric Oculoplastic Surgery*, https://doi.org/10.1007/978-3-319-60814-3_1

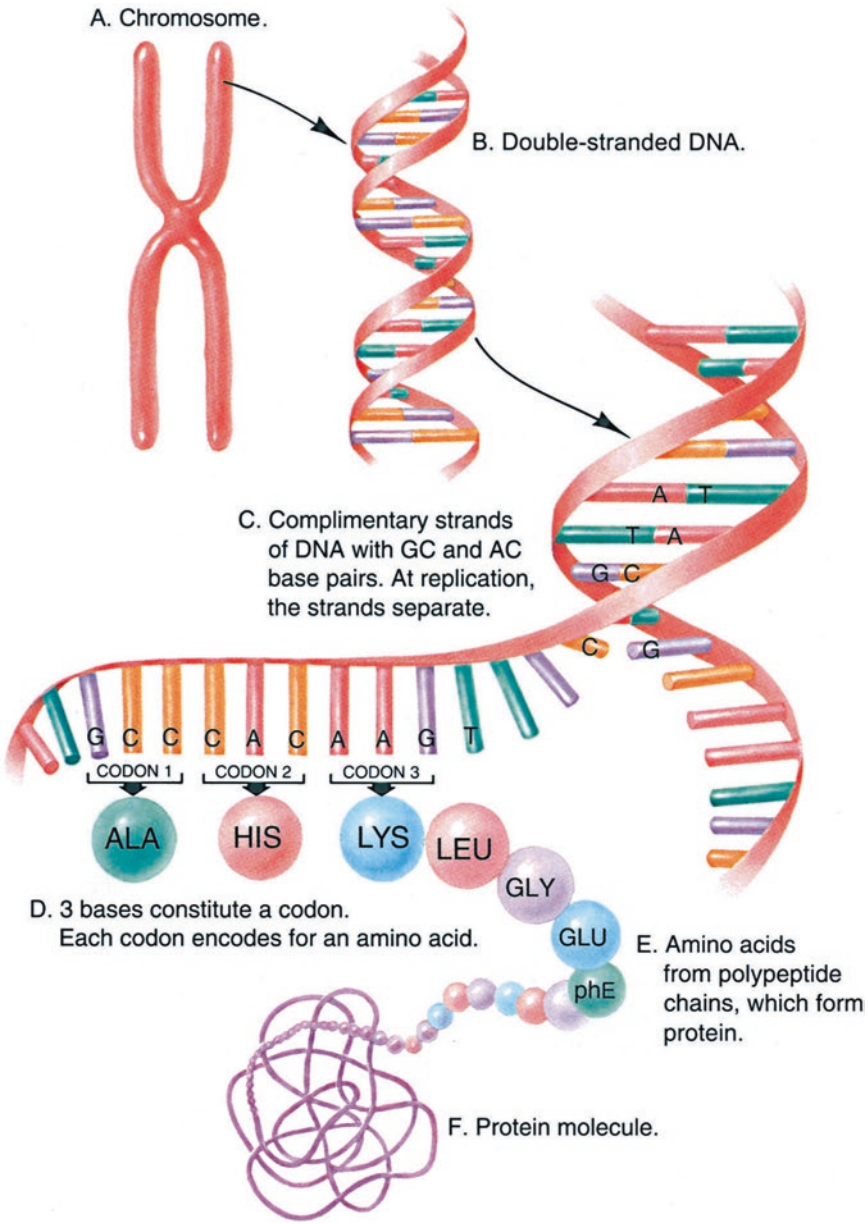


Fig. 1.1 From chromosome to protein

the paired allele on the other X chromosome may produce enough of its product if not mutated, whereas an XY individual does not have an additional copy of the X chromosome in reserve. Rare variations of the genetic constitution exist with some individuals having an XXY or XXXY genome. These individuals are phenotypically male due to the presence of the Y chromosome, with extra copies of the X chromosome.

The translation of genetic code into functional products is quite complex and beyond the scope of this introductory chapter. In summary, start and stop codons regulate the transcription of a gene, and various forms of RNA are involved in this process (tRNA for translational RNA, mRNA for messenger RNA, etc.), in addition to other types of interactive genes. A gene will not entirely get translated into a protein; exons are those stretches of a gene that are ultimately expressed in a protein, and introns are those intervening genetic sequences that are removed before protein translation. Roughly 25–38% of the total DNA is spanned by genes; however only 1.1–1.4% of DNA consists of exons. The function of the rest of human DNA is yet unknown and is an area of active research.

Two important sets of genes that deserve a brief mention are suppressor and anti-suppressor genes [6]. A suppressor

gene's function is to suppress the phenotypic expression of another gene. An anti-suppressor's function is to suppress the suppressor gene. The interaction and balance are extremely complex, yet exquisitely elegant. It should be noted that many genes are solely expressed, or activated, in certain tissue types. Thus a mutated gene will only cause disease in a particular tissue in which it is producing the product or diseased protein. One of the most studied cancers to date is retinoblastoma. The expression of retinoblastomas is due to the inactivation of a tumor suppressor gene affecting the retina [6–8]. Normal function of the suppressor gene is to inhibit the retinoblastoma gene from functioning. Loss of this suppressive factor allows the retinoblastoma gene to become active and produce a tumor.

Genetic changes that cause an abnormal phenotype in an individual are termed "pathogenic variants" and are also called mutations; these affect the gene in which they are found. Other changes will have no effect at all and are termed "benign variants" or polymorphisms. It can be very difficult to predict how some variants are going to affect the patient's phenotype, and these are termed "variants of uncertain significance." Additional functional studies on the particular variant may determine if it is pathogenic or benign. Generally, variants that are found in exons are more likely to be pathogenic if they result in a codon that translates into a different amino acid or a stop codon that truncates the protein product.

Another way to categorize variants of genetic changes is by structure. Point mutations change just one nucleotide, but can cause either a missense or nonsense variant. A missense variant changes just one codon in the sequence and may be tolerated by the gene or not. A nonsense mutation is very often pathogenic as it causes a premature stop codon to be inserted and prevents translation of the rest of the protein. Frameshift mutations are also often pathogenic, as they result from the addition or subtraction of nucleotides in such a way that the reading frame of the rest of the gene is disrupted, resulting in incorrect amino acids in the protein product. A splice site mutation results in insertion, deletion, or changes in the number of nucleotides in the specific site at which splicing of RNA takes place and can change the way the exons assemble. Inheritance patterns should be taken into account when interpreting each variant. Mutations that are not found in the parents are termed spontaneous or de novo and are more likely to cause sporadic disease. A database of variant alleles, collected from both affected and healthy individuals, allows an estimate of the allele frequency in the population. This measure allows for some prediction about the pathogenicity of a variant, as common variants are unlikely to cause rare diseases.

Genes and Environmental Influences

Environmental factors play an important role in genetics, but it is very difficult to determine how much of a disorder is due to genetic error and how much of it is due to environmental influences. For instance, monozygotic twins originate from a single fertilized egg and therefore contain virtually the same genetic makeup. However, if these genetically identical individuals are raised in different environments, they become different individuals with different medical conditions. These differences would be mainly due to environmental factors and not genetic differences. Conversely, just as two genetically identical individuals may develop differently in different environments, genetically different individuals may develop similarly in the same environment.

The timing of an environmental influence or insult plays a significant role on its effect to an individual. Environmental factors that have no influence on one developmental stage may cause drastic results in a different stage. A developing embryo is typically sensitive to temperature and toxins during embryogenesis (3–8 weeks of gestational age), whereas these influences may have little or no effect at all later on. A mature organism is the consequence of the sum and timing of these genetic and environmental interactions.

Genotype and Phenotype

The term genotype describes the genetic constitution of an individual organism or the complete set of genes inherited by that individual. The phenotype of an individual is the set of observable characteristics resulting from the interaction of its genotype with the environment [5].

Penetrance and Expressivity

Penetrance is the probability that a specific gene will have any phenotypic expression at all. When calculating penetrance, the phenotype is considered either present or absent, regardless of varying clinical presentations. It is empirically calculated by dividing the number of people who have both the genotype and phenotype by the total number of people with the genotype alone. When the gene is expressed, but the phenotype differs in individuals with the same genotype, the phenotype has variable expressivity. Many disorders demonstrate variability in the spectrum and severity of abnormalities. For example, in neurofibromatosis type I, every person with an *NF1* pathogenic mutation will show symptoms, but the manifestation and severity will differ from person to person.

Anatomy of the Human Genome

The human genome typically consists of 23 pairs of chromosomes: 22 paired autosomes and 1 pair of sex chromosomes (X and Y chromosomes). Genetic material is stored in the form of deoxyribonucleic acid (DNA), and this message is relayed when the DNA is transcribed to ribonucleic acid (RNA). RNA in turn is translated into the functional products, the polypeptides, or proteins. The building blocks or monomers of DNA and RNA are the nucleotides. There are four nucleotides in DNA, two purines, adenine (A) and guanine (G), and two pyrimidines, thymine (T) and cytosine (C). The formation and operation of the entire human body are encoded by the sequence of these four nucleotides. There is additional genetic material in the mitochondria, which is not part of these 23 pairs of chromosomes.

The information contained in the DNA is translated by the genetic code. The genetic code consists of three adjacent nucleotide bases. The adjacent nucleotides together are called a codon. Each codon corresponds to a particular amino acid. For example, if cytosine, guanine, and adenine were sequential nucleotides (CGA), the corresponding codon corresponds to the amino acid arginine. Three letters summarize each of the 20 amino acids. A series of codons produces a sequence of amino acids that constitute the genetic message. This sequence in turn may translate into the polypeptide chain of a protein molecule. This collection of codons that are transcribed together in a coordinated manner is called a gene; humans have about 20,000 genes.

A specific location on a chromosome is called a locus, which provides the chromosomal address of a gene. Since there are two copies of each of the 23 chromosomes, there are two copies of each gene (an exception is the X and Y chromosomes in males). Variations of the same gene are called alleles. If the two alleles present on each of the two chromosomes are identical, they are homozygous; if the alleles are different, they are heterozygous. Most genes are very complex and comprise multiple alleles for a specific locus.

Modes of Inheritance

With the rapid expansion of the knowledge on genetic disorders, it is essential to have a fundamental understanding of the common inheritance patterns. This helps the clinician have an improved understanding of the disease and therefore more accurately counsel families with regard to diagnosis, prognosis, and recurrence risk. Failure to inform the patient of the inheritance risks has been the cause of much litigation [9–12]. One of the most effective ways of presenting genetic information about a family is through a pedigree. A pedigree usually involves at least three generations back from the patient (proband) and includes information on the age, health, relationships, and previous genetic testing in the family. Using pedigrees allows for patterns consistent with common modes of inheritances to be easily demonstrated (see Fig. 1.2 for common pedigree symbols).

Autosomal Dominant Inheritance

In autosomal dominant inheritance, offspring who are affected can either be the first in their family (if the mutation is de novo) or can have an affected parent who carries at least one copy of the affected gene (while the other parent has two normal alleles) (Fig. 1.3). If a child's parent is a carrier, then they would have a 50% chance of receiving the affected parent's abnormal allele, termed *A*, and a 50% chance of receiving the normal allele, *a*. The other allele, obtained from the normal parent, would be normal. Therefore, the overall risk

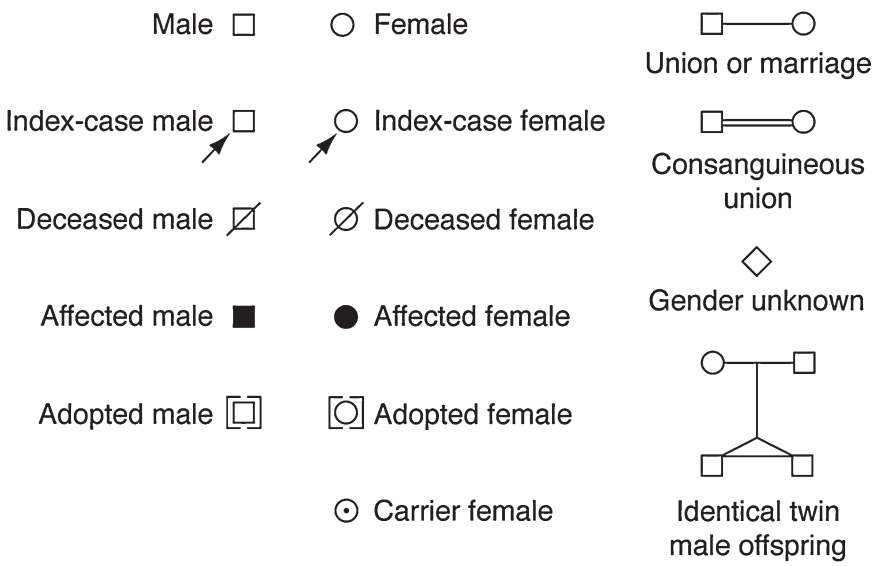


Fig. 1.2 Standard pedigree nomenclature. © 2016 American Academy of Ophthalmology

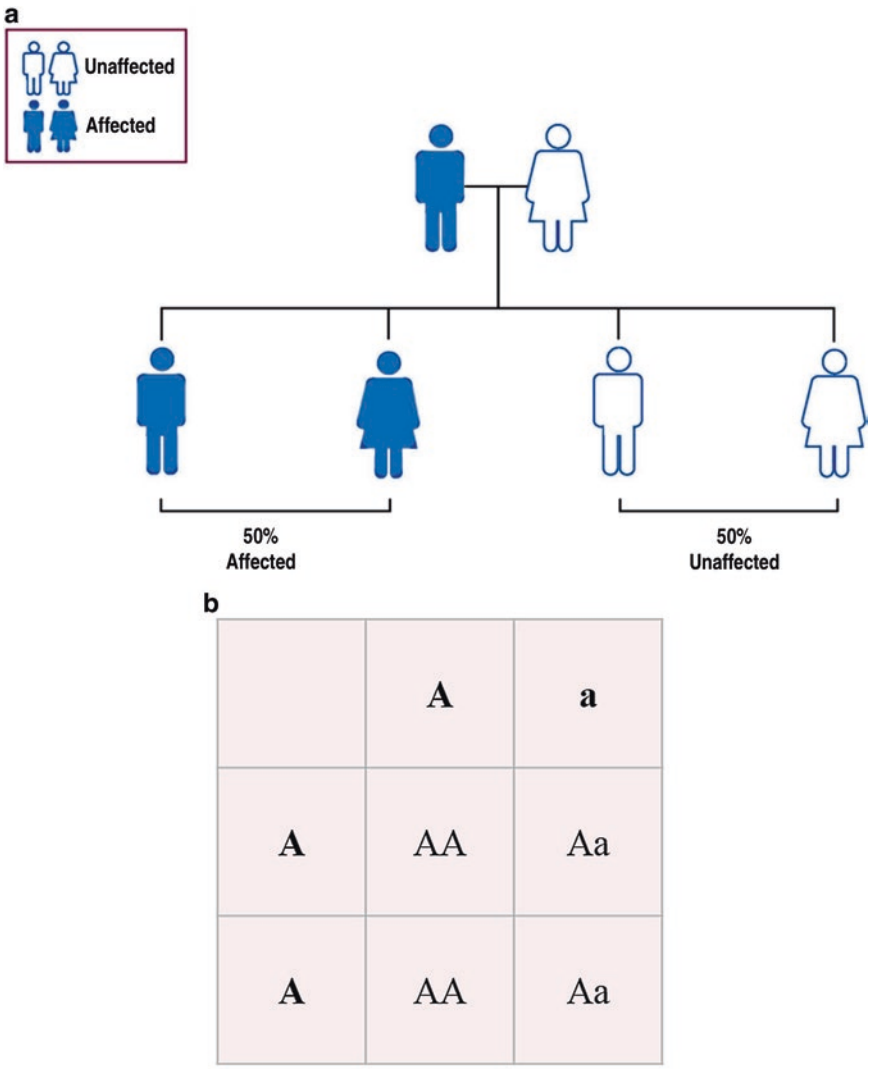


Fig. 1.3 Autosomal dominant inheritance with one parent affected. (**a**) Diagram (Illustration from Genetic Counseling Aids, 6th Edition, Copyright 2013, permission for use granted by Greenwood Genetic Center). (**b**) Punnett square showing possible combinations of alleles; affected (Aa), unaffected (AA)

of disease for each pregnancy would be 50%. Statistically, each pregnancy is an independent event unaffected by previous pregnancies.

An example of an autosomal dominant disorder is neurofibromatosis type I [13, 14]. This disease occurs in approximately one in 4000 births. There is a very high spontaneous or new mutation (de novo) rate [15]. Thus, when seeing an affected individual for the first time, the possibility that the disorder is due to a new mutation must be considered. That is, there might not always be a family history. If the proband is affected with a de novo mutation, then they have the chance to pass it on in their future pregnancies (50% per pregnancy), but the risk of disease to their siblings is low (<1%, not zero due to the possibility of germline mosaicism).

Another example of an autosomal dominant condition is BPES (blepharophimosis, ptosis, and epicanthus inversus syndrome) (Fig. 1.4).

Autosomal Recessive Inheritance

In autosomal recessive disorders, the affected individuals are homozygous for the mutant gene (Fig. 1.5, aa). Typically one mutant allele is acquired from each parent. Both unaffected parents of an affected individual are heterozygote carriers of the disease (Fig. 1.5, Aa). Therefore, the offspring's risk of inheriting two mutant alleles, one from each parent, is one in four (25%). Males and females are equally affected.

If a carrier (Aa) mates with an affected individual (aa), 50% of the offspring would be carriers and 50% would manifest the mutation (Fig. 1.6). Without close examination of the family pedigree, this could be confused with autosomal dominant transmission.

If a carrier of the recessive disease (phenotypically normal and heterozygous for the mutation, Rr) had offspring with a genetically normal individual (RR), all the offspring

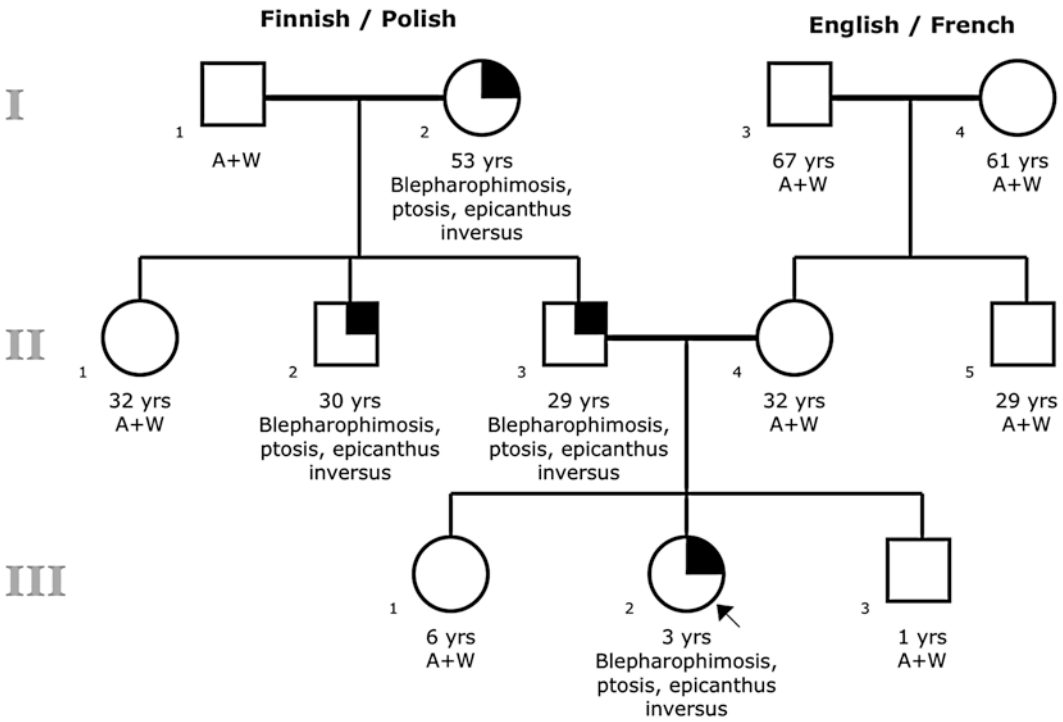
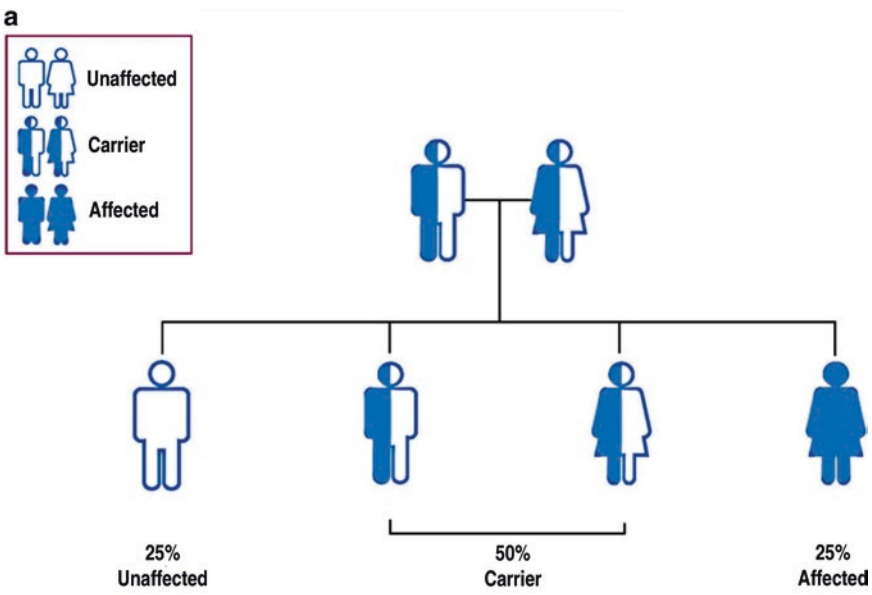


Fig. 1.4 Pedigree for family with BPES illustrates an example of autosomal dominant inheritance



b

	A	a
A	AA	Aa
a	Aa	aa

Fig. 1.5 Autosomal recessive inheritance with both parents carriers. (**a**) Diagram (Illustration from Genetic Counseling Aids, 6th Edition, Copyright 2013, permission for use granted by Greenwood Genetic Center). (**b**) Punnett square showing possible combinations of alleles; affected (aa), unaffected (Aa, aa)