



MANAGEMENT OF GENETIC SYNDROMES

Third Edition

Edited by

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We dedicate this book to our families:

Helene and Maurice Bletterman (deceased)

Joshua Cassidy

Francine Nofle

Jack and Barbara Robinson

Christopher Visher

For all they taught us, for their tolerance, and for all their love and encouragement.

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FOREWORD TO THE THIRD EDITION

Cassidy and Allanson have done it again: produced a new edition of the one must-have book on management of genetic disorders for health care providers of all specialties. To incorporate advances in medical genetics into their practices, clinicians need an expert-authored resource that provides up-to-date information on available diagnostic approaches and practical day-to-day, age-oriented management. *Management of Genetic Syndromes* does not require that clinicians become genetics experts or fluent in genetics lingo. It is written with the knowledge that persons with inherited disorders are found in all medical practices and, similar to people with other medical conditions, these individuals will benefit most when their health care providers are comfortable with the issues that need to be addressed to assure the best medical and quality-of-life outcomes. This book presents to clinicians in primary care and specialty practice the information necessary to allow the clinician to decide for their patients with rare inherited disorders which care is within the scope of his or her practice and which specific needs should be referred out to other specialists.

Management of Genetic Syndromes is a boon to busy primary care practitioners who, I am told, have 90 seconds in which to answer a question brought up during a patient visit. If clinicians do not have a reliable, easy-to-use resource, those questions will go unanswered. The logical division of chapters by disorder and the thoughtful and consistent layout of each chapter into sections on diagnosis first (how can you provide disorder-specific care if you can't be sure that you have the correct diagnosis?) followed by detailed management issues by organ system for all ages allows the busy clinician to hone in on an authoritative answer in a predictable "place." Eliminating the guess work about specific care issues is tremendously valuable to busy clinicians who want to assure the best care for their patients, but cannot take the

time to second guess the exact needs for an individual with a one-of-a-kind disorder in their practice. Similar to all quality information resources, *Management of Genetic Syndromes* provides citations to more detailed documentation of diagnostic and management recommendations for those clinicians with the time or inclination to learn more.

In these days of hype on pending cutting-edge treatment for genetic disorders and "personalized" medicine, clinicians need a filter that can separate what is really known about treatment and what is hypothesis-driven wishful thinking for which no prescription can be written. *Management of Genetic Syndromes* provides this filter, thus assuring clinicians and families that clinicians have at their fingertips information that will be most useful.

Although the promise of the Human Genome Project to provide gene-based therapy for inherited disorders is still a long way from reality, other aspects of the discoveries of the molecular basis of inherited disorders have benefited those with and at risk for inherited disorders. One example is surveillance of those at risk for a potential complication of an inherited disorder, which enables early diagnosis and, hence treatment to improve outcome. For example, in families with an inherited cancer predisposition, such as a hereditary colon cancer syndrome, at-risk relatives benefit from knowing who has inherited the family-specific mutation and who has not, so that those at greatest risk are screened using disease-specific protocols starting at the appropriate age and those who are not at increased risk are advised to follow population-based screening protocols. *Management of Genetic Syndromes* emphasizes the practical approach to the risk-defining use of molecular genetic testing with outcome-oriented surveillance. The reader does not need to be familiar with the jargon or principles of molecular genetics to understand how to

use this approach for the benefit of patients in his or her practice.

Those with genetic disorders and their families often appreciate transparency in the care that they receive and they want access to the same information as their health care providers. The workman-like, practical approach to management in this book provides a “checklist-like” view that enables clinician and patient to follow together the issues to be addressed and their timelines. The chapters in *Management of Genetic Syndromes* are excellent “handouts” at clinic visits. In my academic clinical practice of medical genetics, my colleagues and I have on hand a ready supply of copies of the chapters of *Management of Genetic Syndromes*, which we read before the clinic visit and then provide to families at the time of their clinic appointment and to the referring clinicians with the clinic note. We know that, although the primary audience for this book is not affected individuals and their families, and, therefore, it was not written at the appropriate level for this audience, the clear, no-nonsense presentation style makes the content accessible to those families seeking to partner with their physician in their care.

Increasingly, families play a key role in the management of their inherited disorder, which most commonly is a chronic lifelong condition that may affect other family members of all generations. Consumer-oriented health information sources have grown exponentially with the discovery of the

molecular genetic basis of inherited disorders, the growing use of the Internet, and the development of hundreds of disease-oriented patient advocate groups. Consumer health information resources, which often provide the most practical day-to-day information available for patients and their families, are a valuable adjunct to clinic visits. The essential role of consumer health information is acknowledged by *Management of Genetic Syndromes* by providing information on these resources in an easy-to-find location at the end of each chapter.

Management of Genetic Syndromes is an unparalleled medical genetics information resource for students, be they medical students, residents in primary care fields or specialty fields, or participants in continuing medical education. It is the one book I tell them to buy.

When I see the *Management of Genetic Syndromes* in a clinician’s office, I respect that clinician for taking the initiative to anticipate the needs of his or her patients with rare inherited disorders and know that the clinician, his or her patient, and the patient’s family will be grateful for the practical approach of this trusted colleague on the bookshelf.

ROBERTA A. PAGON, MD

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FOREWORD TO THE SECOND EDITION

It was not very many years ago that the coupling of the terms “management” and “genetic syndromes” would have been regarded as an oxymoron. With the exception of the inborn errors of metabolism, the notion of managing genetic disorders would have been considered quite foreign and of managing genetic *syndromes*, by which we mean conditions in which several organ systems and/or parts of the body are affected, even more so. The principal role of the medical geneticist was to diagnose these conditions as best as he or she could. Management, such as it was, was essentially symptomatic and was usually left to primary care physicians and medical specialists with little direct knowledge of the syndromes themselves. The literature on genetic syndromes reflected this situation. It was, for the most part, descriptive, and the emphasis was on diagnosis. Although many admirable reference books on diagnosis were written, most notable of which was (and still is), *Smith’s Recognizable Patterns of Human Malformations*, it was frequently difficult to find definitive information about how to manage these conditions once the diagnoses had been made.

However, much has changed recently with regard to genetic syndromes, with perhaps the most important change being societal, not medical or scientific. It is now generally accepted that persons with genetic syndromes, whether associated with mental retardation or not, *should*, if possible, be treated. This was not always so, and a graphic example of how thinking has altered is provided by Down syndrome, certainly one of the quintessential genetic syndromes. Within my professional lifetime, there has been a shift from exclusion from society, generally by institutionalization, to rearing at home, educational inclusion, and participation in all aspects of daily life. Similarly, a policy of nonintervention, often with certain death, when major heart or gastrointestinal abnormalities were present has been replaced by aggressive

surgical correction. Guidelines for the prevention of known complications have been developed, and their implementation is now commonplace. As a result, these changes have led, even without any specific therapy for Down syndrome, to an increase in lifespan, better cognitive development, and an overall improvement in the quality of life, both physically and socially.

In addition to the attitudinal shift, there have been many medical and scientific advances that have altered our approach to genetic syndromes. The mutations that cause many of the monogenic or contiguous gene syndromes are now known, and more are being discovered almost daily. The functions of the genes that these mutations affect are gradually being elucidated. For the aneuploidies, the mapping of the human genome is providing information about how many and which genes are at dosage imbalance. All of this has changed genetic syndromes from being curiosities that could not be understood to disorders that can be rationally approached in terms of cause and potential therapy, another and quite major change in attitude. This information has also led to the development of molecularly based tests that are greatly improving disease diagnosis and are permitting discrimination among conditions that had hitherto been confused with one another. In the future, this genetic information promises to lead to therapies that are tailored to individual diseases. In addition, medical diagnostic procedures and therapeutic approaches have become much more powerful. These include, for example, the various forms of imaging, surgical techniques such as for complex congenital heart defects or ambiguous genitalia, and highly specific and potent pharmacological agents. And, finally, more is continually being learned about the long-term consequences of genetic syndromes—about their natural histories—which is essential if comprehensive approaches to management are to be developed.

So, if societal attitudes have changed and genetic and medical information and capabilities are rapidly expanding, who should be undertaking the management of persons with genetic syndromes? Who should be reading this book? There is no simple answer to this question, because in a sense each syndrome must be dealt with on its own merits. Given the multitude of systems that these syndromes may affect and the different combinations of abnormalities that may occur in one compared with another, the approach to management needs to be quite flexible. Nevertheless, someone must be responsible for the overall coordination of care. Who this will be will depend on local circumstances, but the important thing is that it be someone who is knowledgeable and willing to act in the interests of the affected individual.

In most instances, persons with genetic syndromes are usually managed by a mix of genetic professionals, primary care physicians, and medical and other specialists. By “genetic professional” I mean medical geneticists, genetic counselors and genetic nurses, and laboratory geneticists who have special knowledge about and experience in dealing with a large number of genetic syndromes that are individually quite uncommon or rare. For the most part, genetic professionals have traditionally been engaged in the diagnosis and counseling of these conditions. Unlike the situation with inherited metabolic disorders, in which geneticists do participate directly in therapy, their involvement in the therapeutic aspects of the management of genetic syndromes has generally involved referrals to appropriate specialists for specific forms of medical or surgical therapy. Primary care physicians, in addition to providing day-to-day care of individuals with genetic syndromes, often act as intermediaries in the referral process. And, beyond this list of medical personnel, a variety of other professionals and social and educational organizations, both governmental and voluntary, also provide many services to affected individuals and their families.

In some instances, the medical specialists, genetic professionals, and allied health professionals work together in multidisciplinary clinics devoted to individual disorders (e.g., Marfan or Down syndrome) or groups of related disorders (craniofacial anomalies or skeletal dysplasias) or perhaps even to birth defects more generally. These clinics provide a coordinated approach to management that is usually more efficient from the point of view of providers and of affected individuals and their families than is possible when many independent providers are involved in the care of the patient and may be a model for the provision of services in the future.

Regardless of how the services are organized and of who is actually coordinating management, many providers with different degrees of knowledge about any particular condition are likely to be involved. It is, therefore, essential that each understand what he or she is dealing with and what will be required to properly care for the affected individual and his or her family, and it is here that this volume, *Management of*

Genetic Syndromes, uniquely fills a void that has long existed in the literature on genetic syndromes. Gathered together within a reasonably compact volume are authoritative descriptions written for a diverse readership of the management of over 50 of the most common conditions that fall within the rubric of genetic syndromes (including two that are primarily teratogenic, but are usually grouped with the others). The concept of what is entailed in management is broadly interpreted. Therefore, each chapter begins with considerations of etiology, pathogenesis, genetics, and diagnosis (including diagnostic criteria, testing, and differential diagnosis), all of which are necessary if the patient and his or her condition are to be fully understood. These are then followed by detailed discussions of what might be considered to be at the heart of management—the evaluation of each of the relevant systems and the treatment of the abnormalities that are likely to be present. The chapter concludes with selected references and a listing of available support groups and other resources. The evaluation and treatment sections are greatly enhanced by the use of an outline form of presentation, with bullets to highlight individual points.

When it appeared in 2001, the first edition of this book was eagerly seized upon by the medical genetics community. The need was there, and there was nothing else like it. From my own personal experience and observation in a genetics service that handles a large number of persons with genetic syndromes, I can testify that the book rapidly proved to be of great value to all of the clinic personnel—geneticists and counselors, physicians and nonphysicians, students, residents, and fellows. The rapid appearance of this second edition indicates that my own experience has been more generally shared, and the near doubling of the number of conditions covered will make the book even more valuable than before. Given the rapid progress that is being made in genetics and medicine and in the ability to diagnose and treat genetic syndromes, it is likely that frequent revisions will be required.

CHARLES J. EPSTEIN

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FOREWORD TO THE FIRST EDITION

This is a book whose time has come. Genetic disorders and syndromes are usually thought of as being rare, and yet for affected individuals, their families, and their primary and specialty care physicians, it is essential to have reliable information about the natural history and management of the specific disorders.

The thirty conditions described in this book may seem rare (with incidences between 1 in 600 and 1 in 60,000). However, when you put together all the individual cases or a particular condition in North America, in Europe, and in the world, a very large number of affected individuals will benefit from the information in this book. In the past it has been difficult to bring together information of this type about specific disorders, and that is why this book fills a very important niche. It becomes a model for how to organize information that is needed for the families and primary care providers to manage the many, many other genetic disorders, congenital anomalies, and syndromes that are known to occur. The book is written in understandable language appropriate for families and for primary care and specialty physicians. It is a major contribution.

Over the last two decades, remarkable progress has been made with regard to developing diagnostic tests and unraveling the human genome. Within the next few years all of the human genes will have been defined. The next major goal in genetics will be to understand how genes interact and function, both in the course of development and over a lifetime. In addition to the remarkable progress in basic and clinical genetics, there has been increasing communication and access to information. Through the Internet, the public has access to research reports and data that were usually not readily available in the past. However, it is essential to put that information into a meaningful form and context. That is exactly what this book does. The communication explosion has allowed the networking of researchers and families. The development of

parent/lay support groups has led to a cooperation between researchers and families that has helped to define the natural history and the variation that can be seen in a specific disorder.

What every family and physician wants is to provide the best care possible for the affected individual. Nobody wants to miss the opportunity for that individual to reach his or her full potential, to benefit from a useful therapy, or to avoid a complication. Parents need an understanding of what will happen over time so that they can plan. They don't want to waste money and effort going from expert to expert or doing test after test. They need a realistic approach to what they should expect both in childhood and adulthood. They also usually want to know whether there is some risk of recurrence of the condition in their other children, in other family members, and in the affected individual's offspring. They want to know whether prenatal diagnosis is available, and they want to know the spectrum of variation that can occur. The beauty of this new book is that it provides that kind of information for each specific disorder in a logical and understandable form. Most families and physicians will focus in on the chapter relevant to a specific individual. However, they can't help but glance at other chapters and see the remarkable spectrum of complications that are *not* present in the disorder of interest to them. They are likely to benefit from this broader perspective.

Most pediatricians will have heard of all thirty disorders; however, some primary care and specialty physicians may not have heard of a specific disorder until they have the affected individual in their practice. The book should help to alert health care professionals to consider these conditions and should lead to appropriate testing to make a correct diagnosis, reducing the time it takes to make a specific diagnosis. Two-thirds of the conditions in this book have a specific diagnostic test, but the other one-third require "pattern recognition" and an alert, trained health care professional to consider the diagnosis.

It can be expected that additional advances will be made over the next few decades leading to better understanding and better management. So this book is already dated! There is still a lot to be learned! In fact, every family and every affected individual will contribute to that increased knowledge by giving feedback to the authors. Disorder-specific parent/lay support groups will continue to play an important role in improving our understanding. The authors of each chapter have worked together with the support groups and are very aware that it is the process of working together with these groups and the members' willingness to provide information that has led to present-day understanding. We are all very grateful to each of the parents and affected individuals who have taken part in studies that have advanced our knowledge.

To write a book about management, it is necessary to know the natural history of the disorder. The authors of each of these chapters have a wealth of experience and knowledge that has been collected over the last couple of decades. Understanding the natural history not only tells us what to expect at various ages but also how to recognize various complications. It is important to understand the natural history of the condition to determine whether various therapies actually improve the outcome. It is important to understand the natural history to recognize subgroups representing the variability and heterogeneity within the disorder. It is important to understand the natural history to learn the mechanisms that lead to the disorder, e.g., what sort of gene is likely to be involved? Where is the mutation in the gene? How does that mutation relate to severity of complications? How big is the deletion? Does that size relate to severity of complications? How does this gene act against the background of other genes or pathways? Is it possible to recognize a cellular mechanism leading to this disorder? Are there parent-of-origin effects on the expression of the gene or the mutation rate? Are there hot spots that have markedly increased mutation rates? Does the place on the chromosome where the gene lies put it at increased risk for mutation? These are only a few of the questions we hope to answer over the next few decades.

No one is more motivated than the family or the affected individual to learn about these disorders. It is important for them to be as knowledgeable as possible. The families of an affected person usually know more about the condition than most of the physicians they visit. It is important for families to continue to ask questions and to gain as much knowledge as possible to ensure the best outcome for the affected individual. It is important for families and affected individuals to keep their own records about the affected individual, such as a notebook of their visits to health care facilities, copies of the reports, and the results of the tests that have been done. It is also important to keep a photographic record of changes over time.

Once a family or an affected individual becomes involved in collecting information about the disorder, they often develop quite creative ideas that challenge the standard way of thinking about the disorder. Part of the advantage of participating in a support group is that those ideas then can

be shared with the medical advisors and researchers and may lead to new knowledge.

Much of our understanding of these disorders is based on the manifestations in childhood, on feeding, on growth and development, and on social skills. However, information on adults is also beginning to accumulate and has been included in this book. In some conditions there is a stable situation, in others there is improvement with aging, and in still others deterioration can be expected. For many of the conditions described in this book, behavioral patterns have been recognized.

How should a family and their primary care physician use the experts? It would be impossible for the authors of these chapters to see every individual with the condition, but it is usually helpful for a family and the affected individual to see a clinical geneticist, to visit a developmental center, or to use the multidisciplinary team that is available in their area. Over the years, specialty clinics to deal with specific conditions have been developed. At some time it is probably appropriate to visit such a clinic at least once to review the affected individual's progress and to consider any special complications or responses. On the other hand, it is very important to have a knowledgeable primary care physician who cares for day-to-day medical needs and is aware of the unique complications of the condition.

The parent/lay support groups form an international network keeping up with new information on the specific disorders, and new information is sure to come. Some new information will come through organized studies of natural history; other data will come through clinical trials of new therapies; and further information will come from basic work on cellular mechanisms and biochemical pathways. For many of these disorders animal models will be developed, such as mice with the specific disorder, so that various therapies can be considered before trials in human beings. We live in a very exciting age and can anticipate major advances over the next few decades for each of the disorders described in this book. The international network of families, affected individuals, and researchers should and will communicate about new ideas, innovative approaches, and better understanding about these conditions.

We have begun to enter an era of evidence-based medicine. Only by having natural history information is it possible to understand the benefits of new interventions and therapies. We will hope that this book is outdated very rapidly because of such new developments, but in the meanwhile this book on management of common genetic syndromes is extremely welcome to families and health care providers alike.

JUDITH G. HALL

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PREFACE

This book is designed to assist primary care physicians, medical specialists, other care providers, and families in assuring optimal care for individuals who have multiple problems that are components of genetic syndromes. It represents the combined experience and knowledge of many experts in medical genetics and related fields, each of whom has spent years participating in the diagnosis and clinical management of a specific genetic syndrome. Most of the chapter authors have conducted major clinical research on “their” respective disorders.

The syndromes selected for inclusion in this book are those that are sufficiently common as to be regularly encountered in clinics specializing in genetics, development, neurology, or craniofacial disorders. Many of these disorders would not have been seen in the practice of most primary care physicians or non-genetics specialists. When they are encountered, the physician typically has little knowledge of how to confirm the diagnosis, identify the associated problems and clinical manifestations, and optimally care for the affected individual. This lack of knowledge is due only partly to infrequent exposure to the disorder. For many of these conditions, very little concerning management has been published, and a search for this knowledge is extremely time-consuming, often provides incomplete information, and is frequently futile. This book was designed to provide that knowledge, based on the cumulative experience of an expert or experts on each condition. As a result, a significant proportion of the information found in this source will be personal experience or observation. In most cases, there is no established “standard of care” based on controlled trials or outcome studies. Nonetheless, the editors have sought to provide the reader with information that is as reliable as possible. Where available, reference to evidence-based studies and other published sources has been included: where

unavailable, reference to the author(s)’ “personal experience” or “personal observation” has been noted, to reflect non-peer-reviewed information.

Deciding on which disorders to include is no mean task, and there are some disorders for which there is little accumulated experience in management. There are several disorders that are included in this third edition that were not in the first two editions. Others will be included in future editions as new experience accumulates. In addition to more than 50 genetic (or probably genetic) conditions, two teratogenic disorders, fetal alcohol syndrome and fetal anticonvulsant syndrome, are also included because of their frequency and because genetic factors influence susceptibility.

The editors hope that this continues to be a useful text to primary care physicians, medical geneticists, and other medical specialists, educators, and other providers of care for the individuals and families affected with these common genetic syndromes. Similar to those with more frequent medical conditions, they deserve the best possible medical, educational, and psychological care.

We are appreciative of the two editors from Wiley-Liss, Collette Bean for giving us the opportunity to compile this book, and Thomas Moore for his assistance in editing. Most importantly, we thank the contributors and the many patients for their willingness to have their photographs published in this book and for their participation in the clinical research that provided the information for its content.

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INTRODUCTION

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THE ORGANIZATION OF THIS BOOK

Each chapter of this book is dedicated to the diagnosis and management of a specific syndrome that is encountered with regularity in specialty programs and occasionally in primary care practice. The authors of each chapter are acknowledged “experts” who have considerable personal experience in the management of the disorder. Each chapter thus contains unpublished information based on that experience and on the author’s personal approach to management in addition to a review of published information. Whenever available, evidence-based treatments are included. Each chapter format is similar, providing general information on incidence and inheritance, pathogenesis and etiology, diagnostic criteria and testing, and differential diagnosis. The myriad manifestations of each syndrome are presented system by system, with emphasis on the features, evaluation, management, and prognosis. The first two “systems” in each chapter are “Growth and Feeding” and “Development and Behavior.” After these, the systems relevant to the specific disorder are discussed, usually in order of importance for that disorder. Every attempt has been made to include whatever is known about the disorder in adulthood. Each chapter concludes with a listing of family support organizations and some resources available to families and professionals in print and electronic formats. Photographs of physical findings important for diagnosis or management are provided, and sometimes figures of other aspects, including mechanism of pathogenesis. Selected references stressing management issues and citations of good review articles have been included.

This introductory chapter is designed to inform the reader about genetics-related terms used in this book, inheritance patterns, general methods for genetic testing, measurement methods, and the role of the medical geneticist and genetic counselor in the care of genetic disorders. It also provides some important references to additional resources of information about genetic disorders, differential diagnoses, genetic testing, and support organizations.

While we have sought to place the chapters in alphabetical order by name, for ease of locating, some chapters pose challenges in that regard. In particular, this is true of the disorders that are caused by a chromosomal abnormality and also have an associated name, most of which are deletion syndromes. In this edition, we have clustered the chromosomal syndromes under “Deletion” (Deletion 4p for Wolf-Hirschhorn syndrome, Deletion 22q11.2 for Velo-Cardio-Facial/DiGeorge syndrome, and Deletion 22q13 for Phalen-McDermid syndrome). The disorders with more than one causative genetic mechanisms are left under the commonly used name (e.g., Klinefelter syndrome, Smith-Magenis syndrome, and Prader-Willi syndrome). While we realize that this organization is not perfect, we hope that this will facilitate finding the reader’s chapter of interest.

CATEGORIZATION OF DISORDERS

The descriptive language for patterns of anomalies is somewhat unique to the field of dysmorphology and deserves a

brief review. The term **syndrome** is used to describe a broad error of morphogenesis in which the simultaneous presence of more than one malformation or functional defect is known or assumed to be the result of a single etiology. Its use implies that the group of malformations and/or physical or mental differences has been seen repeatedly in a fairly consistent and unique pattern. The initial definition of any syndrome occurs after the publication of several similar case reports. It becomes refined over time as newly described individuals suggest the inclusion of additional abnormalities and the exclusion of others. Thus, a syndrome comes to be defined by the coexistence of a small but variable number of “hallmark” abnormalities, whereas several other features may be observed at lower frequencies. Even after a particular syndrome is well established, the inherent variability or rarity can make diagnosis difficult.

In a specific individual, one or more of the hallmark features of a disorder may be absent and yet the person is affected. This has become very evident as genetic testing has advanced and demonstrated the broadness of the clinical spectrum for many disorders. It is important to stress that not all syndromes are associated with mental retardation. Generally, no one feature or anomaly is pathognomonic of a syndrome, and even experienced dysmorphologists may disagree about diagnosis. Often, the individual clinician will have had little direct experience of the syndrome. In this environment, the addition of objective methods of evaluation may be useful. Available techniques include direct measurement (anthropometry), standard photographs (photogrammetry), and radiologic assessment (cephalometry). Each method has advantages and disadvantages, and each has its proponents (for details, see Allanson, 1997).

The term **sequence** is used to designate a series of anomalies resulting from a cascade of events initiated by a single malformation, deformation, or disruption (Spranger et al., 1982). A well-known example is the Robin sequence, in which the initiating event is micrognathia. The small mandible then precipitates glossoptosis (posterior and upward displacement of the tongue in the pharynx) with resultant incomplete fusion of the palatal shelves. The initiating event may be a malformation of the mandible or a deformation caused by *in utero* constraint and thus inhibiting normal growth of the mandible. The individual components of a sequence may well involve quite disparate parts of the body. For example, lower limb joint contractures and bilateral equinovarus deformity may be found in a child with a meningomyelocele.

An **association** is a nonrandom occurrence in two or more individuals of multiple anomalies not known to represent a sequence or syndrome (Spranger et al., 1982). These anomalies are found together more often than expected by chance alone, demonstrating a statistical relationship but not necessarily a known causal one. For example, the VATER (VACTERL) association represents a simultaneous occurrence of two or more malformations that include

vertebral anomalies, anal atresia/stenosis, heart defects, tracheoesophageal fistula, radial ray defects, and renal and limb abnormalities. An association has limited prognostic significance, and the degree of variability may pose diagnostic problems for the clinician. Most affected children will not have all the anomalies described, which makes establishment of minimal diagnostic criteria difficult. Recognition of an association is useful in that it can guide the clinician, after discovery of two or more component malformations, toward a directed search for the additional anomalies. Associations are generally sporadic within a family and have a low empirical recurrence risk. It is most important to remember that associations are diagnoses of exclusion. Any child with multiple anomalies affecting several systems, with or without growth and/or intellectual retardation, should first be assessed to rule out a specific syndrome diagnosis and, lacking such a diagnosis, should have chromosome analysis.

MEASUREMENTS

Selected measurements, with comparison to normal standards, may be helpful in confirming the subjective impression of an abnormality. Common craniofacial dimensions, which provide details about facial shape and size, include head circumference, inner and outer canthal distances, ear length, position, and rotation. Evaluation of stature should include height (length), upper and lower body segment, arm span, hand length, palm length, and foot length. Normal standards for these and a wide variety of other standardized measurements can be found in the *Handbook of Physical Measurements* (Hall et al., 2007), *Growth References: Third Trimester to Adulthood* (Saul et al., 1998), and *Smith's Recognizable Patterns of Human Malformation* (Jones, 2005); however, ethnic background, for which norms may vary, should be taken into consideration. Increasingly, standard curves are being developed for particular syndromes. Many syndrome specific standards have been compiled and are referenced in the chapters of this book.

The best way to document dysmorphic features is to photograph them. The prudent clinician will often adopt an attitude of “watchful waiting” if the diagnosis is not apparent at the first assessment (Aase, 1990). As children’s facial and body features evolve with time, they may “grow into” a syndrome, and photographs provide serial documentation of these changes. There is great value to reassessment of the individual with multiple anomalies whose diagnosis is unclear, because there is significant diagnostic yield (Hall et al., 1988). The “art” of dysmorphology is eloquently discussed by Aase (1990). Photographs also facilitate consultations with colleagues and consultants by providing objective evidence of the patient’s physical findings. They can be compared with examples of other syndromes in

photographic databases such as POSSUM and the London Dysmorphology Database (see below).

COMMON GENETIC TERMINOLOGY

With the recent rapid advances in human genetics has come a proliferation of terms whose meaning may be unclear to some practitioners. Therefore, a summary of the common terms relating to genes and chromosomes and the major inheritance patterns is in order.

Genes are the individual pieces of coding information that we inherit from our parents, the blueprint, as it were, for an organism. It is estimated that 30,000 to 40,000 genes are required to develop and “operate” a human being. Individual genes occur in pairs, one inherited from each parent. The balance of the expression of these genes is extremely delicate, with significant abnormality resulting when this balance is disturbed for some genes. Variant forms of the same gene are known as **alleles**, and variation can have no apparent phenotypic effect or major consequences, depending on the specific gene and many other factors. When a variant has minimal phenotypic effect, it is often called a **polymorphism**.

Some syndromes are caused by a permanent structural or sequence change (or **mutation**) in a single gene. Many gene mutations cause their adverse effects through deficient gene expression (and often subsequent protein deficiency), which is called **haploinsufficiency**. This is often the case when a mutation in a gene results in failure to produce the gene product, which can be a so-called **null mutation** or a **protein truncation mutation**. However, other mutations cause their adverse effects by interfering with a process or causing a new adverse effect, and such mutations are called **dominant negative mutations**. The latter is often the result when a structurally abnormal protein is formed. Mutation results in alteration of the sequence and/or length of the bases composing the gene code. Such alterations may result in the substitution of one amino acid for another (a **missense mutation**), in the production of a sequence that does not correspond to the code for an amino acid (a **nonsense mutation**), or in a code that tells the translation machinery to stop prematurely. An unusual form of mutation that is present in a number of neurogenetic disorders, such as fragile X syndrome, myotonic dystrophy, Huntington disease, and the spinocerebellar ataxias, among others, is the so-called **triplet repeat expansion**. Some genes contain within them a string of three bases repeated a number of times. For example, CGG is repeated up to 50 times in the normal fragile X gene (CGGCGGCGG. . .). Under certain circumstances, this number becomes amplified, resulting in an increase in the number of such repeated triplets of bases. Thus, in individuals who are affected with fragile X syndrome, an X-linked cause of mental retardation, there may be hundreds of such repeated triplets. This triplet repeat expansion interferes (an

X-linked cause of mental retardation) with the normal function of the gene, causing abnormality (in this case, mental retardation). In fragile X syndrome, the gene actually becomes inactivated if the expansion exceeds a certain number of repeats. Please see Chapter 27 for a more detailed explanation of this type of mutation.

In recent years, some new types of changes in the genetic apparatus have been recognized to cause human disorders. An **epigenetic mutation** is a biochemical change in the DNA that modifies its expression. This generally includes methylation of bases or changes in chromatin structure that change DNA's availability for transcription and therefore results in decreased protein production. Epigenetic modification of some DNA is normal, but perturbations or changes in dosage of that modification have been shown to result in disorders such as some cases of Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome, and Russell-Silver syndrome. Such changes are described in more detail in those chapters.

The nomenclature for genes and gene products (proteins) can be quite confusing, despite the best efforts toward a logical approach. The names of genes are often put in italics, and these may represent an abbreviation of the name of the disorder, the name of the protein, or a function of the protein or the gene. For example, the gene causing neurofibromatosis type 1 is called *NF1*, and the protein is named neurofibromin, whereas the gene for Angelman syndrome, *UBE3A*, is named for its protein product, which is one of a family of ubiquitin-protein ligases (enzymes that are part of the protein degradation process). The gene responsible for fragile X syndrome is called *FMR1* (fragile X-linked mental retardation 1), and the protein is called FMRP (fragile X-linked mental retardation protein). Information on the genes is included in the chapters for those who are interested, but aside from genetic testing purposes, it is not critical to know the nomenclature to understand and treat the disorder.

Human genes are “packaged” into 46 **chromosomes**, of which normally 23 chromosomes are transmitted to the offspring in the egg from the mother and 23 in the sperm from the father. One pair of chromosomes, the **sex chromosomes**, differs between males and females. Females have two copies of the X chromosome, whereas males have one copy, the second sex chromosome being the Y chromosome with a largely different set of genes. The remaining 22 pairs, the **autosomes**, do not differ between males and females. The autosomes are numbered in a standard way from largest to smallest. The location of a specific gene on a chromosome is called the **locus** (the plural is **loci**). Some of the syndromes described in this book are caused by the presence of an entire extra chromosome (e.g., Down syndrome, Klinefelter syndrome) or duplication of a segment of a chromosome (e.g., some cases of Beckwith-Wiedemann syndrome). Others occur because of loss of all (e.g., Turner syndrome) or part (e.g., WAGR) of a chromosome.

The terms that clinical geneticists use to describe a body part may be unfamiliar to some readers. They have gradually evolved in a haphazard and uncoordinated manner, and have only recently been critically reviewed (Allanson et al., 2009; Biesecker et al., 2009; Carey et al., 2009; Hall et al., 2009; Hennekam et al., 2009; Hunter et al., 2009). While we have strived to use lay language wherever possible, there may be descriptive terms in these chapters that require definition. In the series of articles cited above, the reader will find preferred terms for each feature of the head and face, and hands and feet, with a definition and description of how to observe and measure (where possible) the feature. Each term is accompanied by at least one photograph.

PATTERNS OF INHERITANCE

An alteration in a gene can be dominant or recessive. A **dominant** gene mutation only needs to be present in one member of the gene pair to have a clinically evident impact. Any individual with an autosomal dominant gene mutation will have a 1 in 2 chance to pass it on to his or her child, male or female, with each pregnancy. An example is achondroplasia. In achondroplasia, the affected child frequently has two average-stature parents, indicating that the mutation occurred in the egg or sperm that was involved in the conception. This is referred to as a **new mutation** or a **de novo-mutation**. Rarely, an apparently normal couple will have more than one child with an apparently new mutation in an autosomal dominant gene. This suggests that the mutation is present in some of the cells of the germ line (gonads) but not in most other cells of the body of one parent. This is known as **germ line** (or **gonadal**) **mosaicism**. When a parent has a gonadal cell line with a dominant mutation, the recurrence risk is significantly greater than the risk for a second child with a new mutation but less than the 50% risk expected if the parent had the mutation in all cells of the body and manifested the condition. Several different dominant disorders have been documented to recur in more than one child of an unaffected parent because of germ line mosaicism. Alternately, the autosomal dominant mutation may be carried in a proportion of a parent's somatic cells as well as the germ line. In this situation, the manifestations of the condition may differ, being milder, segmental, or focal. This **somatic mosaicism** may manifest as a streaky alteration in skin pigmentation. Somatic and germ line mosaicism, at the level of the gene or chromosome, occur after conception.

An autosomal **recessive** gene mutation, when present in a single copy in an individual, will be hidden. Such a person is known as a "carrier" and will be normal. If, by chance, a person inherits an abnormal gene for an autosomal recessive disorder from both parents, there is no normal gene partner and the two altered genes will cause symptoms and signs, for example, cystic fibrosis. When each parent carries a recessive

mutation for the same disorder, the chance that they both will pass on the mutation to their child, who is then affected, is 25%.

Recessive genes on the X chromosome have different consequences in males and females. A mutated recessive gene on the X will tend to have little impact in a female, because there is a second, normal copy of the gene on the second X chromosome of the pair. In contrast, in the male, a mutation of a **recessive X-linked gene** will have an impact because the genes on the Y chromosome are different from those on the X, and no second gene copy exists. That male must pass the mutated X-linked gene to all his daughters but to none of his sons, because he passes his Y chromosome to his sons. Some disorders are **X-linked dominant**, and females will also be affected. However, males are generally more severely affected in such disorders.

In certain areas of the genetic code, genes behave differently if they have been inherited from the father (**paternally inherited**) rather than from the mother (**maternally inherited**). Only one copy may be active, whereas the other is inactivated, usually by a process of methylation. These genes, whose action differs depending on the parent of origin, are said to be **imprinted**. More can be learned about this phenomenon in the chapters on the imprinted disorders Angelman syndrome (Chapter 6), Beckwith-Wiedemann syndrome (Chapter 10), Prader-Willi syndrome (Chapter 42), and Russell-Silver syndrome (Chapter 48). A more detailed account of patterns of inheritance, imprinting, and mosaicism can be found in any standard text of human or medical genetics, such as those listed under **Additional Resources** below.

GENETIC TESTING

Several terms used in this book in describing genetic tests are likely to be unfamiliar to some readers. For some disorders, the appropriate test is a **chromosome analysis** (or **karyotype**, which is an ordered display of an individual's chromosomes). Chromosomes are analyzed by special staining techniques that result in visibility of dark and light bands, which are designated in a very standardized way from the centromere, or major constriction. The short arm of the chromosome is called "p," the long arm is called "q," and bands are numbered up from the centromere on the p arm and down from the centromere on the q arm. Each band is further subdivided according to areas within the bands or between them. Thus, the deletion found in velocardiofacial syndrome is in the first band of the q arm of chromosome 22, and is designated del22(q11.2). A standard chromosome analysis has at least 450 bands, which is quite adequate for numerical chromosome anomalies. For some disorders, however, the anomaly cannot be seen reliably on standard chromosome analysis and requires special handling while being processed

called **high-resolution banding**. An alternative term, **prometaphase banding**, is used because the cell growth during culturing is adjusted to maximize the number of cells in prometaphase, where the chromosomes are much less condensed and thus longer, rather than in metaphase, where cell growth is stopped in standard chromosome studies. High-resolution banding often has 550 to 800 bands, and allows much more detailed analysis.

Another technique combines chromosome analysis with the use of fluorescence-tagged molecular markers (called probes) that are applied after the chromosome preparation is produced. This method is called **fluorescence *in situ* hybridization**, or **FISH**, and relies on the phenomenon of hybridization (intertwining) of complementary pieces of DNA. Thus, to test whether there is a small deletion (called a **microdeletion**) that is not visible using chromosome analysis alone, a fluorescence-tagged DNA probe complementary to the deleted material is applied to the chromosome preparation. If the chromosome material is present in the normal amount, a fluorescent signal will be visible at that site under the fluorescence microscope; if the normal chromosome material is absent (deleted), there will be no fluorescent signal. FISH is a very powerful tool not only for diagnosing relatively common microdeletion or **microduplication** disorders but also for identifying the origin of extra chromosome material that cannot be identified by inspection alone and sorting out the origin of the components of a **translocation** (structural rearrangement of chromosomal material).

Smaller deletions and duplications are being more frequently identified by a newer technique called **array comparative genomic hybridization** (commonly abbreviated to **array CGH**, or just **CGH**). This is a novel diagnostic tool that merges traditional chromosome analysis with molecular diagnostics. Array CGH detects abnormalities by comparing DNA content from two differently labeled genomes, which allows for sensitive and specific detection of single copy number variations of submicroscopic chromosomal regions throughout the entire human genome.

Other types of genetic testing rely exclusively on molecular diagnostic methodologies. **Polymerase chain reaction (PCR)** is a powerful technique for amplifying, thus making many, many copies of a segment of DNA so that it can be analyzed. PCR is used for many genetic disorders with a recurring mutation (such as achondroplasia) or a finite number of common mutations. It can also be used to identify the presence of alterations in the normal methylation pattern in imprinted disorders. **Southern blot** techniques are more time consuming; they involve breaking DNA into small pieces using restriction enzymes and then separating them out using gel electrophoresis and analyzing whether there is a deviation in the distance that a segment of the DNA travels on the gel, indicating that its size is different from usual. Both PCR and Southern blotting usually involve the use of **DNA markers**, or **probes**. These are small

segments of DNA complementary to an area of interest. One special type of probe takes advantage of the fact that DNA normally contains many runs of repeated base pairs, such as CACACACACA. . . , which are usually located between genes and have no phenotypic consequences. These are called **microsatellites**. Such runs occur normally throughout the genome, and the number of repeats is inherited like a genetic trait. There are vast variations in the exact number of repeated doublets, which can be "counted" by molecular techniques and which represent polymorphisms or variants. These so-called **microsatellite markers** form the basis for paternity testing and are also used for diagnostic testing of neighboring genes or the genes within which they occur, although they are not the mutation of the relevant gene that causes disease.

Multiplex ligation-dependent probe amplification (MLPA) is a newer sensitive technique for relative quantification of up to 50 different nucleic acid sequences in a single reaction. It is a variation of the polymerase chain reaction that permits multiple targets to be amplified with only a single primer pair. Each probe consists of two oligonucleotides that recognize adjacent target sites on the DNA, one of which is fluorescently labeled. Only when both probe oligonucleotides are hybridized to their respective targets, can they be ligated into a complete probe, and the relative fluorescence can be measured. It is routinely used for copy number analysis in various syndromes and diseases to detect an abnormal number of chromosomes, gene deletions, duplications, or expansions, and methylation abnormalities.

Markers can even be used when the precise gene or mutation is unknown, through a process called **linkage analysis**. This is a gene-hunting technique that uses linked (neighboring) markers to trace patterns of heredity in families in which more than one individual is affected with a disorder in an effort to identify whether a child inherited the chromosome with the relevant marker near a co-inherited disease-causing gene. Although this often does not represent identification of the disease gene itself, it can be very reliable within families with multiple affected and unaffected members, particularly when the disease gene or mutation is unknown. The closer the marker is to the gene of interest, the more accurate the result because proximity reduces the likelihood of crossing over. The disadvantage is that the technique requires DNA from several affected and unaffected family members.

The nomenclature for markers is a bit more uniform than that for genes. Markers are indicated by the letter D (standing for DNA), followed by the number of the chromosome they are on, followed by the letter S (standing for single copy) and the number representing the numerical order in which they were identified. Thus, D15S10 was the 10th marker to be identified on chromosome 15. This designation gives no hint as to which gene it is in or near, or where on the chromosome it maps. Increasingly, geneticists are moving away from

using this nomenclature and instead identifying the genes. The nomenclature for mutations is complex and beyond the scope of this book.

The methodology for genetic testing has become highly technical and complex, and is beyond the scope of this book. The interested reader is referred to the list of glossaries at the end of this chapter. The most accessible, detailed, and current of these glossaries is to be found online at the GeneTests web site (www.genetests.org).

ROLE OF THE MEDICAL GENETICIST AND GENETIC COUNSELOR

Many syndromes are relatively rare, and any individual physician may have limited personal experience. Medical geneticists, on the other hand, frequently have considerable experience of many affected individuals and have ready access to additional information through the genetics literature and specialized databases. The myriad manifestations of each of the syndromes included in this book often require the care of many diverse specialties. The geneticist can assist in diagnosis, testing, and counseling of affected individuals and their family as a consultant to the nongenetics physician and can orchestrate coordination of care to focus on the whole child or adult. The role of the geneticist extends beyond the individual child to involve the care and well-being of the entire family. The primary care physician is encouraged to consult medical geneticists to assist in the management of individuals with multiple anomaly syndromes.

An important facet of the care of individuals with syndromes and their families is genetic counseling. This is the provision of nondirective information about the diagnosis and its implications not only for the individual (prognosis) but also for the family (reproductive risks and options). It includes knowledge of the inheritance pattern, likelihood of recurrence in a future pregnancy, and prenatal diagnostic options. Referral to relevant community resources, such as patient support groups, brochures, and web sites and financial, social, and educational services, can also be made during this process. Assisting the individual and/or family to understand the condition and its impact, provide optimal care, and adapt to the existence of a chronic and complex disorder are all part of the process of genetic counseling. Adjustment to a new diagnosis may put considerable strain on a family, and emotional support for the family by care providers is paramount. Genetic counseling is usually provided by medical geneticists or by genetic counselors, who are Masters-prepared professionals who are knowledgeable about genetic disorders and their inheritance, can determine genetic risks, and are trained to assist in the emotional and psychological adjustments necessitated for optimal outcome.

ADDITIONAL RESOURCES AND WEB SITES

Additional information concerning the included disorders, as well as explanations of inheritance information and diagnostic testing, may be found in **standard texts** on genetics and genetic disorders. A few particularly useful **texts and references** in this context are listed below.

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