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INTRODUCTION

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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 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 Each chapter thus contains unpublished information based on that experience and on the author’s personal approach to management in addition to a review of published information. 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. 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.

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 is known or assumed to be the result of a single etiology. Its use implies that the group of malformations and/or physical 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 anomalies and the exclusion of others. Thus a syndrome comes to be defined by the coexistence of a small but variable number of “hallmark” anomalies, 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. 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 CHARGE association represents a simultaneous occurrence of two or more malformations that include congenital coloboma of the iris, choroid, or optic nerve, hear defects, atresia of choanae, mental and somatic retardation, male genital hypoplasia, and ear anomalies or deafness. 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 detail 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 Normal Physical Measurements* (Hall et al., 1989), *Growth References: Third Trimester to Adulthood* (Saul et al., 1998), and *Smith's Recognizable Patterns of Human Malformation* (Jones, 1997); 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 (Saul et al., 1998).

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 affected individual'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 with which many practitioners are unfamiliar. 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 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 22 for a more detailed explanation of this type of mutation.

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* (*f*ragile X-linked *m*ental *r*etardation 1), and the protein is called FMRP (*f*ragile X-linked *m*ental *r*etardation *p*rotein). 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., some cases of Prader-Willi syndrome) of a chromosome.

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 the same 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 chromosome 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 36), and Russell-Silver syndrome (Chapter 41). 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.

A new technique called molecular cytogenetics combines the technique of 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 deoxyribonucleic acid (DNA). Thus, to test whether there is a very 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 fluorescence 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 for sorting out the origin of the components of a **translocation** (structural rearrangement of chromosomal material).

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 (see Chapters 6 and 36). **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.

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.

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 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 cases 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 affected individual 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 patients 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 patient 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 knowledgeable about genetic disorders and their inheritance, can determine genetic risks, and are trained to assist in the emotional and psychological adjustments necessary 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 follow:

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In addition, important **online resources** on genetic disorders are readily available, including:

- Online Mendelian Inheritance in Man (OMIM) (www.ncbi.nlm.nih.gov/Omim) is a catalog of inherited disorders.
- GeneReviews (www.genetests.org) provides information on diagnosis, testing, and management of genetic disorders.

For those with a deeper interest, there are **electronic databases** that aid in diagnosis and provide photographs and references concerning not only common but also rare genetic disorders. These must be purchased, and include:

- London Dysmorphology Database (www.hgmp.mrc.ac.uk/lddb)
- POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) (www.possum.net.au)

A **resource of laboratories** doing specialized diagnostic testing, both clinically and for research, for genetic disorders and syndromes is:

- GeneTests (www.genetests.org) provides information on diagnosis, testing, and management of genetic disorders.

Further information on individual syndromes for practitioners or families can be obtained from other **online resources**, including:

- National Organization for Rare Diseases (NORD) (www.rarediseases.org)
- March of Dimes/Birth Defects Foundation (www.modimes.org)
- The Alliance of Genetic Support Groups (www.geneticalliance.org)

