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Genetics & Dysmorphology

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Genetics is a post-modern science, the applications of which are critical to all stages of life and to all manner of disease. Many new technologies in molecular biology and biochemistry are allowing better understanding of the mechanisms inherent in genetic disorders, and have led to new and better diagnostic tests and management options. However, some of these technologies and terms are unfamiliar to the clinician in practice. To best cover this complex and varied subject, this chapter contains two major parts. The first part serves as an introductory key, which reviews the basic principles of genetics. It starts from foundations of genetic diagnosis, and outlines basic knowledge of cytogenetics and molecular biology. It is then followed by a review of the principles of inherited human disorders, including different etiologies of genetic disorders, and finally a discussion of dysmorphology and teratology. The second part introduces common clinical disorders and includes descriptions of the diseases, with discussion of pathogenesis, diagnosis, and management.

■ PRINCIPLES OF GENETICS

FOUNDATIONS OF GENETIC DIAGNOSIS

CYTOGENETICS

Cytogenetics is the study of genetics at the chromosome level. Chromosome anomalies occur in 0.4% of all live births. They are a prevalent cause of mental retardation (MR) and congenital anomalies or birth defects. The prevalence of chromosome anomalies is much higher among spontaneous abortions and stillbirths.

Chromosomes

Human chromosomes consist of DNA (the blueprint of genetic material), specific proteins forming the backbone of the chromosome (called histones), and other chromatin structural and interactive proteins. Chromosomes contain most of the genetic information necessary for growth and differentiation. The nuclei of all normal human cells, with the exception of gametes, contain 46 chromosomes, consisting of 23 pairs (Figure 33-1). Of these, 22 pairs are called autosomes. They are numbered according to their size; chromosome 1 is the largest and chromosome 22 the smallest. In addition, there are two sex chromosomes: two X chromosomes in females and one X and one Y chromosome in males. The two members of a chromosome pair are called homologous chromosomes. One homolog of each chromosome pair is maternal in origin (from the

egg); the second is paternal (from the sperm). The egg and sperm each contain 23 chromosomes (haploid cells). During formation of the zygote, they fuse into a cell with 46 chromosomes (diploid cell).

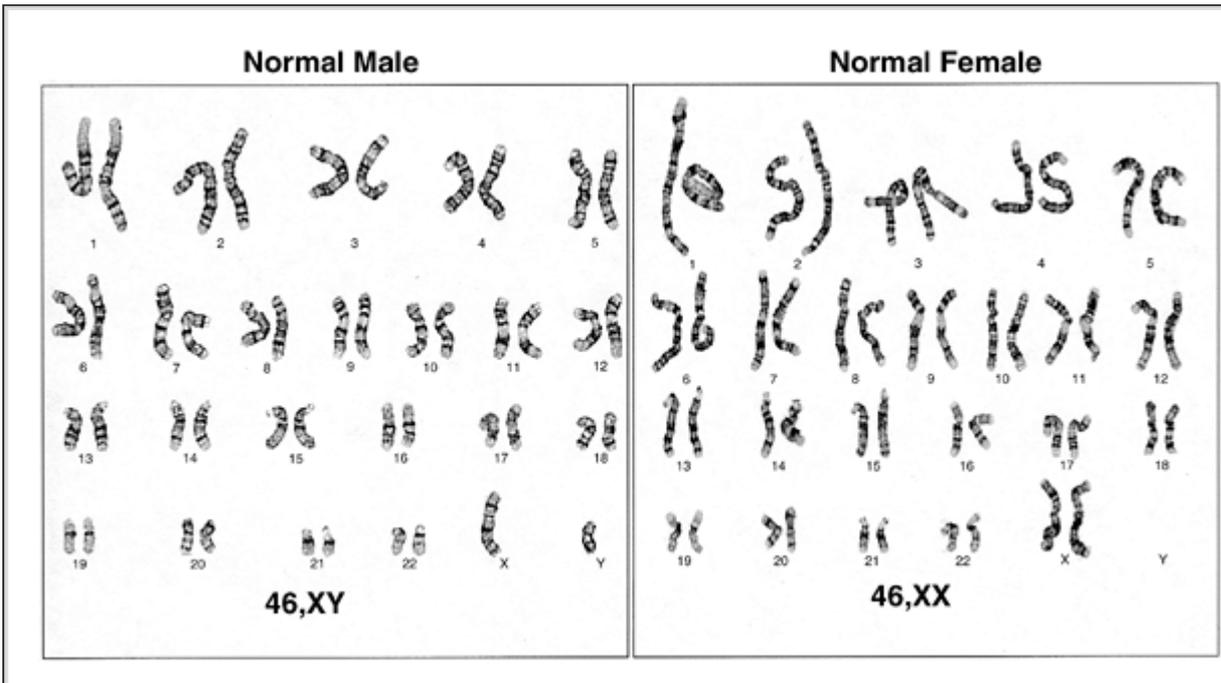


Figure 33-1. Normal male and female human karyotype. (Courtesy of Billie Carstens at CGC.)

CELL DIVISION

Cells undergo cycles of growth and division that are controlled according to their needs and functions.

Mitosis is a kind of cell division occurring in stages, during which DNA replication takes place and two daughter cells, genetically identical to the original parent cells, are formed. This cell division is typical for all somatic cells (cells other than the sperm or egg, which are called germ line cells). There are four phases of mitosis: interphase, prophase, metaphase, and anaphase (Figure 33-2). In interphase, chromosomes are long, thin, and non-visible. At this time, the genetic material is replicated. In prophase, the chromosomes are more condensed. During metaphase (the phase following DNA replication but preceding cell division), individual chromosomes can be visualized. Each arm consists of two identical parts, called chromatids. Chromatids of the same chromosome are called sister chromatids. In anaphase, the genetic material is separated into two cells.



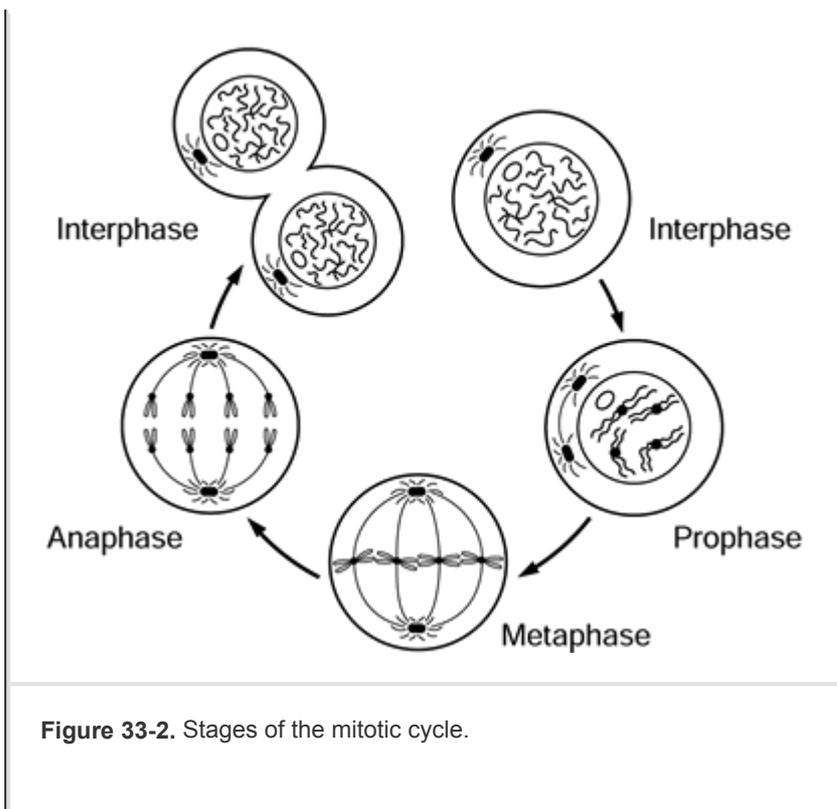


Figure 33-2. Stages of the mitotic cycle.

Meiosis (Figure 33-3), during which eggs and sperm are formed, is cell division limited to gametes. During meiosis, three unique processes take place:

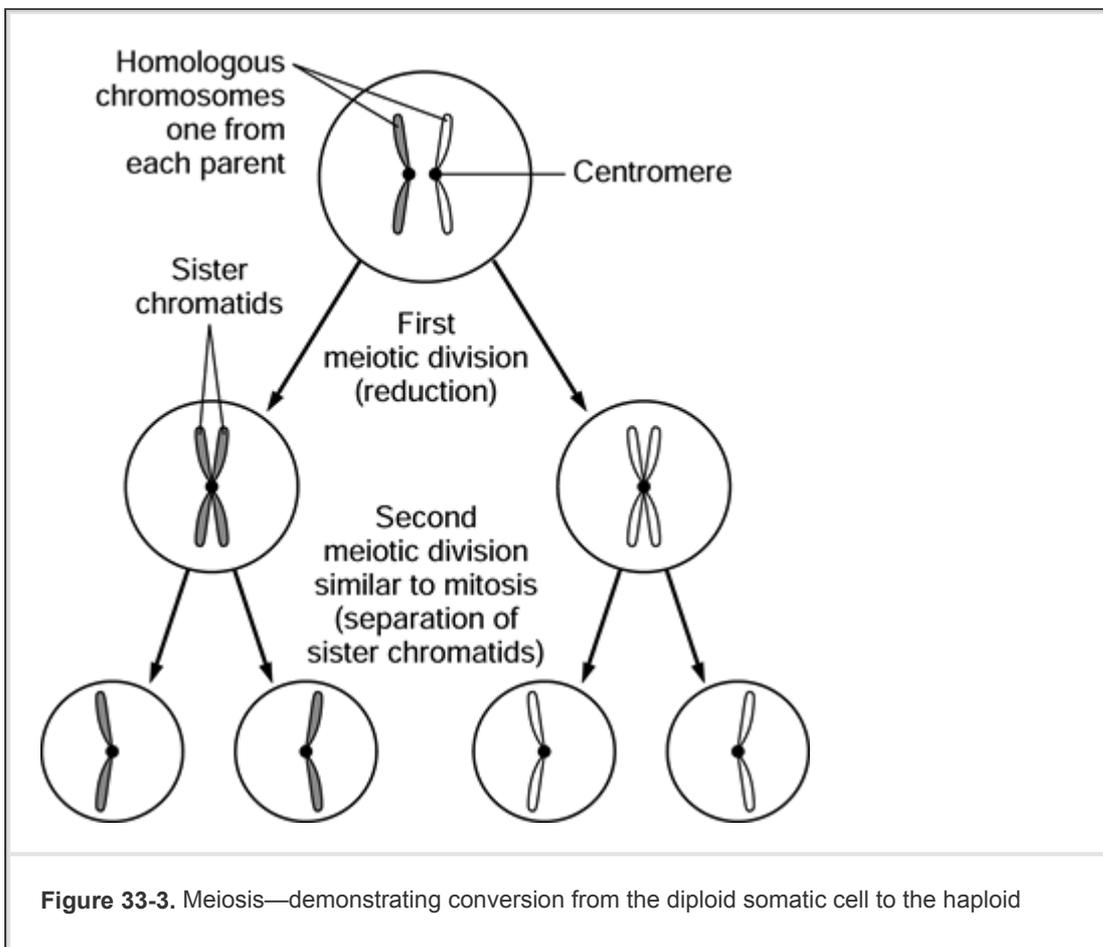


Figure 33-3. Meiosis—demonstrating conversion from the diploid somatic cell to the haploid

gamete.

1. Crossing over of genetic material between two homologous chromosomes. This is preceded by the pairing of both members of each chromosome pair, which facilitates the physical exchange of homologous genetic material.
2. Random assortment of maternally and paternally derived homologous chromosomes into the

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daughter cells. The distribution of maternal or paternal chromosomes to a particular daughter cell occurs independently in each cell.

3. Two cell divisions, the first of which is a reduction division—that is, separation between the homologous chromosomes. The second meiotic division is like mitosis, separating two sister chromatids into two genetically identical daughter cells.

Chromosome Preparation & Analysis

Chromosome structure is visible only during mitosis, most often achieved in the laboratory by stimulating a blood lymphocyte culture with a mitogen for 3 days. Other tissues used for this purpose include skin, products of conception, cartilage, and bone marrow. Chorionic villi or amniocytes are used for prenatal diagnosis. Spontaneously dividing cells without a mitogen are present in bone marrow, and historically, bone marrow biopsy was done when immediate identification of a patient's chromosome constitution was necessary for appropriate management (eg, to rule out trisomy 13 in a newborn with a complex congenital heart disease). However, this invasive test has been replaced by the availability of the FISH technique (see below).

Cells processed for routine chromosome analysis are stained on glass slides to yield a light-and-dark band pattern across the arms of the chromosomes (see Figure 33-1). This band pattern is characteristic and reproducible for each chromosome, allowing the chromosomes to be identified. Using different staining techniques, different banding patterns result: G, Q, and R banding. The most commonly used is G-banding. The layout of chromosomes on a sheet of paper in a predetermined order is called a karyotype. High-resolution chromosome analysis is the study of more elongated chromosomes in prometaphase. In such an analysis, the bands can be visualized in greater detail, allowing detection

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of smaller, more subtle chromosomal rearrangements.

Fluorescent in situ hybridization (FISH) is a powerful technique, which labels a known chromosome sequence with DNA probes attached to fluorescent dyes, thus enabling visualization of specific regions of chromosomes by fluorescent microscopy. There are many different kinds of probes, including paint probes (a mixture of sequences throughout one chromosome), sequence-specific probes, centromere probes, and telomere probes. A cocktail of differently colored probes, one color for each

chromosome, called multi-color FISH, or M-FISH can detect complex rearrangements between chromosomes. FISH can detect submicroscopic structural rearrangements undetectable by classic cytogenetic techniques and can identify marker chromosomes. (Figure 33-4). FISH also allows interphase cells (lymphocytes, amniocytes) to be screened for numerical abnormalities such as trisomy 13, 18, or 21, and sex chromosome anomalies. However, because of the possible background or contamination of the signal, the abnormality must be confirmed by conventional chromosome analysis.

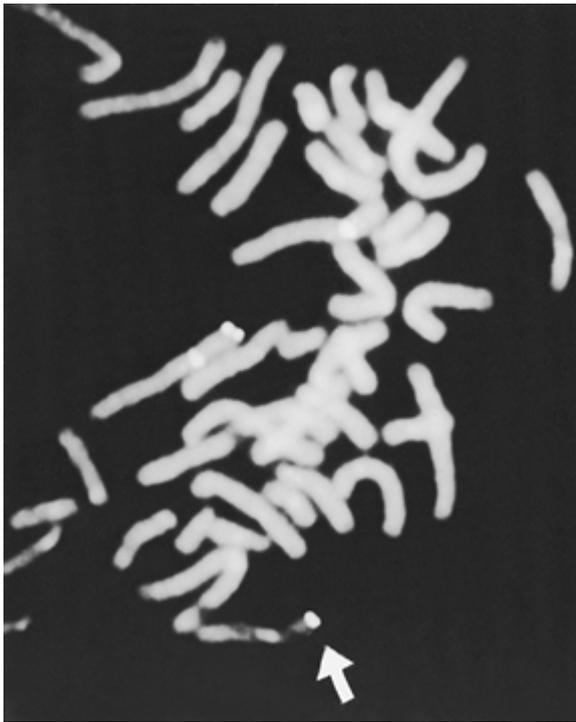


Figure 33-4. Fluorescent in situ hybridization (FISH), showing the brightly fluorescent probes of Wolf-Hirschhorn syndrome (4p deletion syndrome). One probe is hybridized to the normal location on chromosome 4; the other (arrow) documents 4/11 translocation, which was not detectable by a classic cytogenetic analysis.

Assessment of chromosome breaks and sister chromatid exchanges requires special techniques that lead to enhancement of the breaks, or special staining that allows visualization of the exchanged chromatids.

Luke S et al: FISH: Recent advances and diagnostic aspects. *Cell Vis* 1998;5:49.

Chromosome Nomenclature

Visible under the microscope is a constriction site on the chromosome called the centromere, which separates the chromosome into two arms: p, for petite, refers to the short arm, and q, the letter following p, refers to the long arm. Each arm is further subdivided into numbered bands visible using different staining techniques.

Centromeres are positioned at different sites on different chromosomes, and are used to differentiate the chromosome structures seen during mitosis as *metacentric* (p arm

and q arm of almost equal size), *submetacentric* (p arm shorter than q arm), and *acrocentric* (almost no p arm). The use of named chromosome arms and bands allows for universal communication of chromosome description. Common symbols include *del* (deletion), *dup* (duplication), *inv* (inversion), *ish* (in situ hybridization), *i* (isochromosome), *pat* (paternal origin), *mat* (maternal origin), and *r* (ring chromosome). See the next section for definitions of these terms.

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Chromosome Abnormalities

There are two types of chromosomal anomalies: numerical and structural.

ABNORMALITIES OF CHROMOSOMAL NUMBER

When a human cell has 23 chromosomes, such as human ova or sperm, it is in the haploid state (n). After conception, in cells other than the reproductive cells, 46 chromosomes are present in the diploid state ($2n$). Any number that is an exact multiple of the haploid number—eg, 46 ($2n$), 69 ($3n$), or 92 ($4n$)—is referred to as euploid. Polyploid cells are those that contain any number other than the usual diploid number of chromosomes. Polyploid conceptions are usually not viable except in a “mosaic state,” with the presence of more than one cell line in the body. (See later text for details.)

Cells deviating from the multiple of the haploid number are called aneuploid, meaning not euploid, indicating an abnormal number of chromosomes. Trisomy, an example of aneuploidy, is the presence of three of a particular chromosome rather than two. It results from unequal division, called nondisjunction, of chromosomes into daughter cells. Trisomies are the most common numerical chromosome anomalies found in humans—eg, trisomy 21 (Down syndrome), trisomy 18, and trisomy 13. Monosomies, the presence of only one member of a chromosome pair, may be complete or partial. Complete monosomies may result from nondisjunction or anaphase lag. All complete autosomal monosomies appear to be lethal early in development and only survive in mosaic forms. Sex chromosome monosomy, however, can be viable.

ABNORMALITIES OF CHROMOSOMAL STRUCTURE

There are many different types of structural chromosome anomalies. Figure 33-5 displays the formal nomenclature as well as the ideogram demonstrating chromosomal anomalies. In clinical context, the sign (+) or (-) *preceding* the chromosome number indicates increased or decreased number, respectively, of that particular whole chromosome in a cell. For example, 47,XY+21 designates a male with three copies of chromosome 21. The sign (+) or (-) *after* the chromosome number signifies extra material or missing material, respectively, on one of the arms of the chromosome. For example, 46,XX, 8q- denotes a deletion on the long arm of chromosome 8. Detailed nomenclature, such as 8q11, is required to further demonstrate a specific missing region so that genetic counseling can be provided.

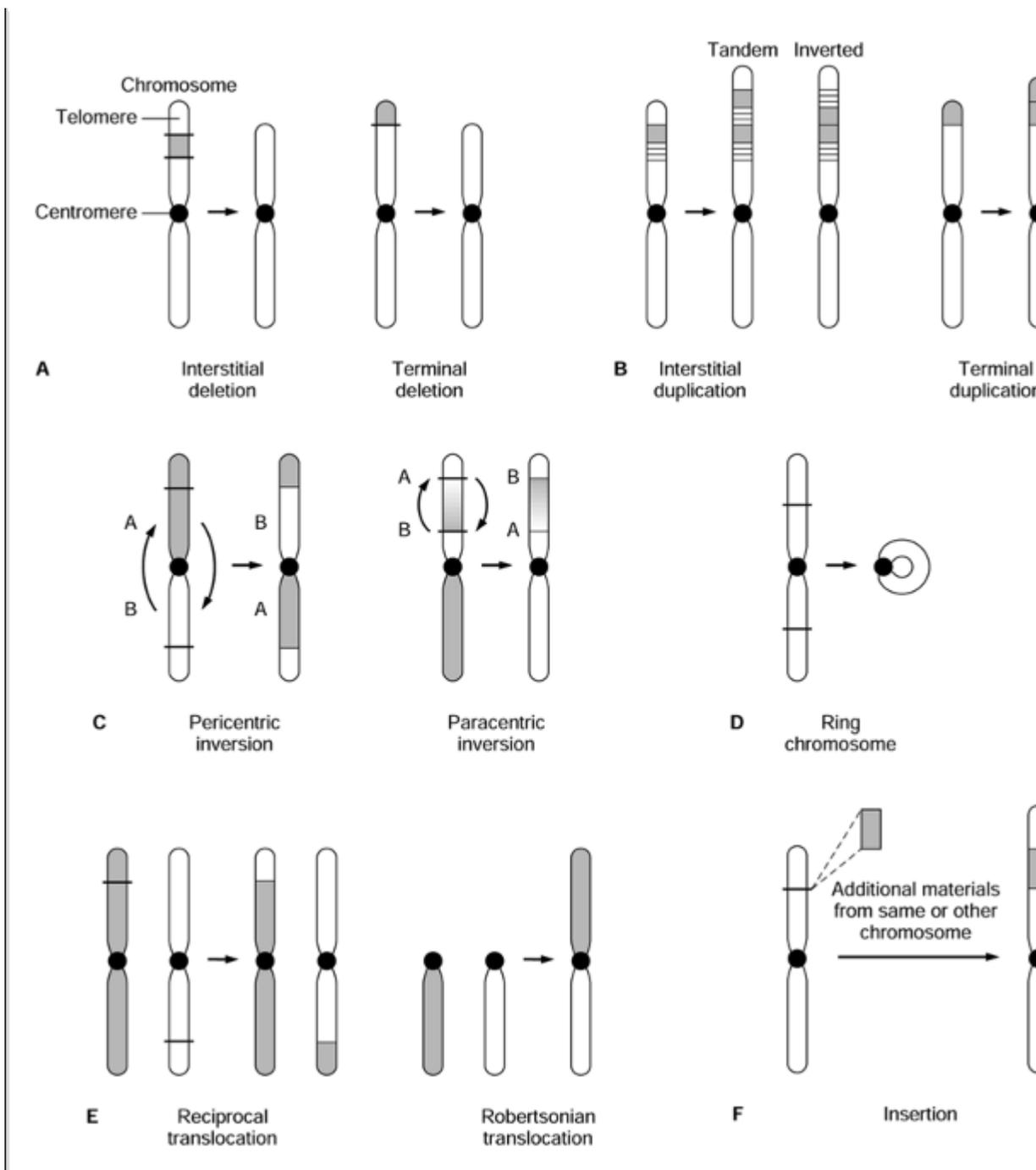


Figure 33-5. Examples of structural chromosome abnormalities: deletion, duplication, inversion, ring chromosome, translocation, and insertion.

Deletion (del) (Figure 33-5a)

This refers to an absence of normal chromosomal material. It may be terminal (at the end of a chromosome) or interstitial (within a chromosome). The missing part is described using the code “del,” followed by the number of the chromosome involved in parentheses, and a description of the missing region of that chromosome, also in parentheses—eg, 46, XX, del(1)(p36.3). This chromosome nomenclature describes the loss of genetic material from band 36.3 of the short arm of chromosome 1, which results

in 1p36.3 deletion syndrome. Some more common deletions result in clinically recognizable conditions associated with mental handicaps and characteristic facial features. For example, Wolf-Hirschhorn syndrome, del(4p), results in an unusual face with "Greek-helmet" appearance; Cri-du-chat syndrome, del(5p), is typified by an unusual high-pitched cry and dysmorphic features.

Duplication (dup) (Figure 33-5b)

An extra copy of a chromosomal segment can be tandem (genetic material present in the original direction) or inverted (genetic material present in the opposite direction). A well described duplication of chromosome 22q11 causes Cat eye syndrome, resulting in iris coloboma, anal or ear anomalies.

Inversion (inv) (Figure 33-5c)

In this aberration, a rearranged section of a chromosome is inverted. It can be paracentric (not involving the centromere) or pericentric (involving the centromere).

Ring chromosome (r) (Figure 33-5d)

Deletion of the normal telomeres (and possibly other subtelomeric sequences) leads to subsequent fusion of both ends to form a circular chromosome. Ring chromosome anomalies often cause growth retardation and mental handicap.

Translocation (trans) (Figure 33-5e)

This describes the interchromosomal rearrangement of genetic material. These may be balanced (the cell has a normal content of genetic material arranged in a structurally abnormal way) or unbalanced (the cell has gained or lost genetic material as a result of chromosomal interchange). Balanced translocations may further be described as reciprocal, the exchange of genetic material between two non-homologous chromosomes, or Robertsonian, the fusion of two acrocentric chromosomes.

Insertion (ins) (Figure 33-5f)

Breakage within a chromosome at two points and incorporation of another piece of chromosomal material is called insertion. This requires three breakpoints and may occur between two chromosomes or within the same chromosome. The clinical presentation or phenotype depends on the origin of the inserted materials.

SEX CHROMOSOMAL ANOMALIES

Abnormalities involving sex chromosomes, including aneuploidy and mosaicism, are relatively common in the general population. The most common sex chromosome anomalies include 45,X (Turner Syndrome), 47,XXX, 47,XXY (Klinefelter syndrome), 47,XYY, and

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different mosaic states. (Please see later text for clinical discussion.)

MOSAICISM

Mosaicism is the presence of two or more different chromosome constitutions in

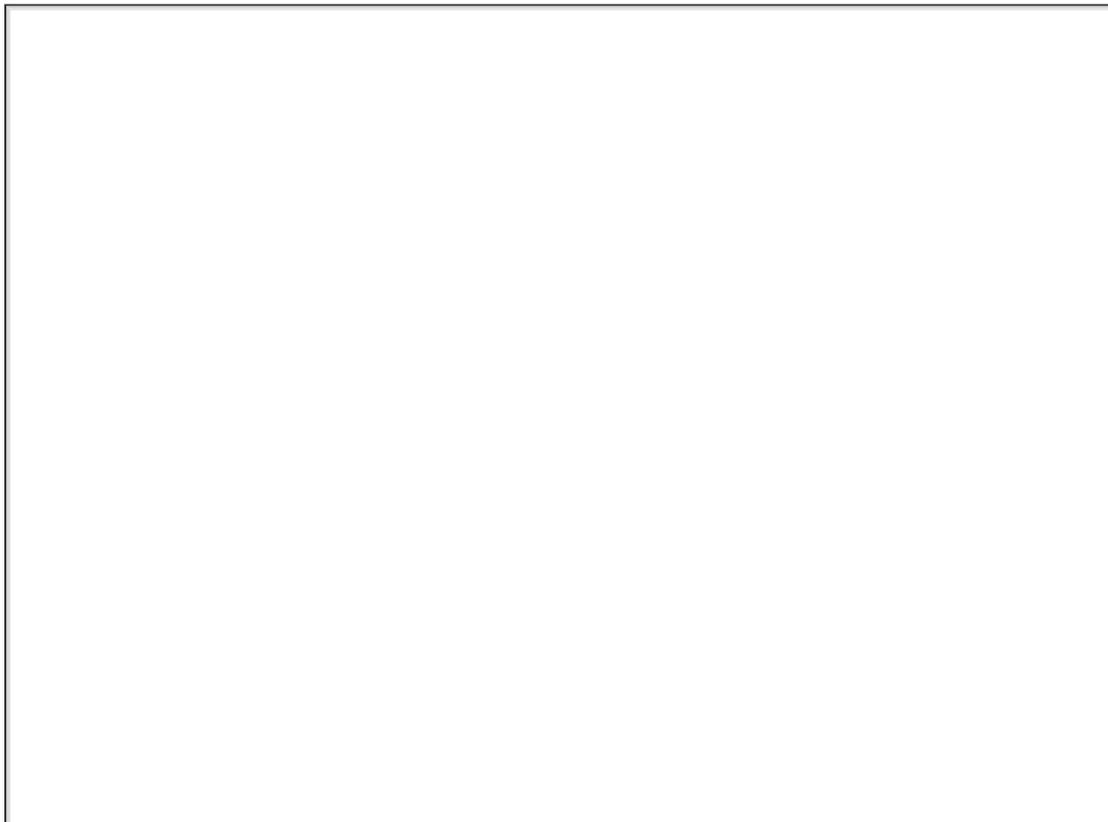
different cells of the same individual. For example, a patient may have some cells with 47 chromosomes and others with 46 chromosomes—46,XX/47,XX,+21 indicates mosaicism for trisomy 21; similarly, 45,X/46,XX/47,XXX indicates mosaicism for a monosomy and a trisomy X. Mosaicism should be suspected if clinical symptoms are milder

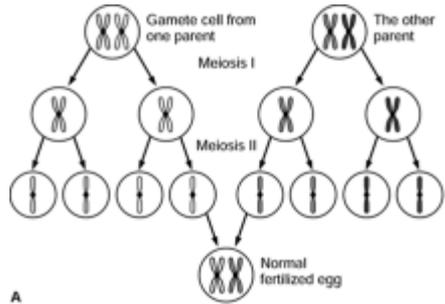
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than expected in a nonmosaic patient with the same chromosome abnormality, or if the patient's skin shows patchy or streaky hyper- or hypopigmentation. The prognosis is frequently better for a patient with mosaicism than for one with a corresponding chromosome abnormality without mosaicism. In general, the smaller the proportion of the abnormal cell line, the better the prognosis. In the same patient, however, the proportion of normal and abnormal cells in various tissues, such as skin and peripheral blood, may be significantly different. The prognosis can seldom be assessed reliably based on the karyotype in one tissue alone, such as peripheral blood. Therefore, any prognosis should be made cautiously or even be deferred.

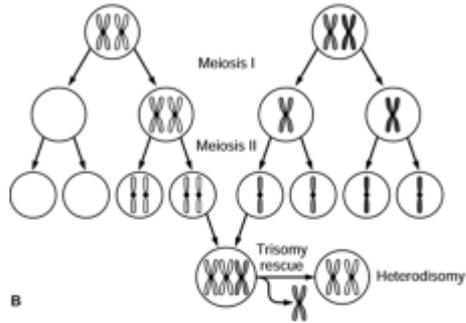
UNIPARENTAL DISOMY

Under normal circumstances, one member of each homologous pair of chromosomes is of maternal origin from the egg and the other is of paternal origin from the sperm (Figure 33-6a). In uniparental disomy (UPD), both copies of a particular chromosome pair originate from the same parent. If UPD is caused by chromosome error in the first meiotic division, both homologous chromosomes of that parent will be present in the gamete. This is called heterodisomy (Figure 33-6b). If the disomy is caused by an error in the second meiotic division, two copies of the same chromosome will be present through the mechanism of rescue, duplication, and complementation (Figure 33-6c, Figure 33-6d, Figure 33-6e). This is called isodisomy. Isodisomy may also occur as a post-fertilization error (Figure 33-6f).

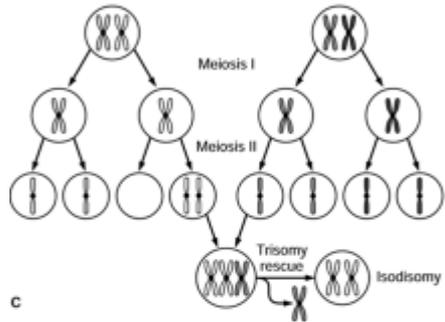




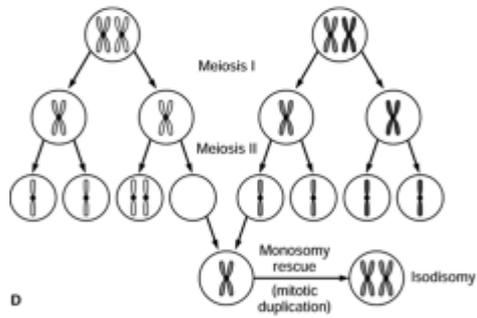
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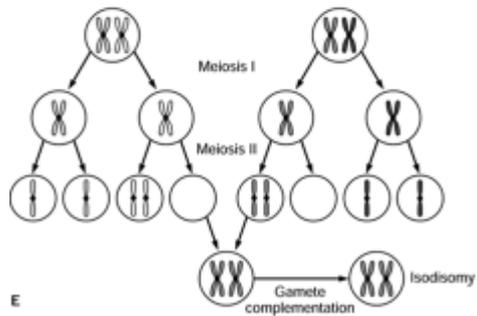
B



C



D



E

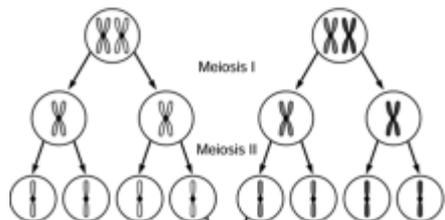


Figure 33-6. The assortment of homologous chromosomes during normal gametogenesis and uniparental disomy. **A:** Fertilization of normal gametes. **B:** Heterodisomy by trisomy rescue. **C:** Isodisomy by trisomy rescue. **D:** Isodisomy by monosomy rescue (mitotic duplication). **E:** Gamete complementation. **F:** Post-fertilization error.

A chromosomal analysis will not reveal any abnormality, but DNA analysis would reveal that the child inherited two copies of DNA of a particular chromosome from one parent without the contribution from the other parent. UPD has been documented for human chromosomes, including chromosomes 7, 11, 15, and X. It has been found in patients with Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes. In addition, cystic fibrosis with only one carrier parent (caused by maternal isodisomy) has been reported. UPD may cause severe prenatal and postnatal growth retardation. Furthermore, it is suspected that UPD of some chromosomes is lethal. The possible mechanisms for the adverse effects of UPD include possible homozygosity for deleterious recessive genes and the consequences of imprinting. (See principles of imprinting in the section, below.)

CONTIGUOUS GENE SYNDROMES

Contiguous gene syndromes result when a deletion causes the loss of genes that are adjacent to each other on a chromosome. Although many genes may be missing, the deletion may still be too small to be detected by routine karyotype. Therefore, contiguous gene syndromes are sometimes called "Microdeletion syndromes." The genes involved in these syndromes are related only through their linear placement on the same chromosome segments and do not influence each other's functions directly. Table 33-1 lists examples of the currently known contiguous gene syndromes and their associated chromosome abnormalities. In some of these syndromes—which usually occur sporadically but, in rare instances, are familial—high-resolution chromosome analysis can lead to identification of small interstitial deletions in affected individuals. In some patients with normal karyotypes, the deletion is submicroscopic and can be detected only with FISH (see Figure 33-4) or DNA analysis.

Syndrome	Abnormal Chromosome Segment
Prader-Willi/Angelman syndrome	del 15q11
Shprintzen/DiGeorge spectrum	del 22q11
Langer-Giedion syndrome	del 8q24
Miller-Dieker syndrome	del 17p13
Retinoblastoma/mental retardation	del 13q14
Beckwith-Wiedemann syndrome	11p15
Wilms tumor with aniridia, genitourinary malformations, and mental retardation	del 11p13

Table 33-1. Examples of contiguous gene syndromes.

Emanuel BS: Molecular cytogenetics: Toward dissection of the contiguous gene syndrome. *Am J Hum Genet* 1988;43:575.

CHROMOSOME FRAGILITY

It is well known that environmental factors such as radiation, certain chemicals, and viruses contribute to chromosome breaks and rearrangements. However, some well-defined autosomal recessive syndromes with DNA repair defects are associated with a greatly increased risk of chromosome aberrations, and are called chromosome instability or breakage syndromes. An example is Bloom Syndrome, characterized clinically by small stature and development of telangiectasias upon exposure to sunlight. It is caused by a defect in a DNA helicase that leads to increased somatic recombination and sister chromatid exchange. Other syndromes include the following:

- Fanconi anemia, often associated with radial ray defect, pigmentary changes, mild mental retardation, and development of pancytopenia
- Ataxia-telangiectasia (Louis-Bar syndrome), characterized by telangiectasia of the skin and eyes, immunodeficiency, and progressive ataxia, a DNA repair defect
- ICF syndrome, characterized by immunodeficiency, centromeric instability, and facial anomaly
- Roberts syndrome, characterized by growth retardation, developmental delay, limb and craniofacial anomalies
- Xeroderma pigmentosum, resulting in formation of skin lesions secondary to sun exposure
- Werner syndrome, which is associated with premature senility.

The knowledge that specific chromosome aberrations are associated with these

syndromes is often the basis for cytogenetic confirmation of their diagnosis. For example, in Fanconi anemia, after diepoxybutane (DEB) treatment, translocations between non-homologous

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so-called quadriradii and chromosomal breakage increase, which confirms the diagnosis.

CHROMOSOME ABNORMALITIES IN CANCER

Numerical and structural chromosome abnormalities are often identified in hematopoietic and solid-tumor neoplasms in individuals with otherwise normal chromosomes. These cytogenetic abnormalities have been categorized as primary and secondary. In primary abnormalities, their presence is necessary for initiation of the cancer (eg, 13q- in retinoblastoma). Secondary abnormalities appear in somatic cells de novo only after the cancer has developed (eg, Philadelphia chromosome, t[9;22][q34;q11], in acute and chronic myeloid leukemia). Cytogenetic noise is the term used to denote a variety of random chromosome abnormalities.

The primary and secondary chromosome abnormalities are specific for particular neoplasms and can be used for diagnosis or prognosis. For example, the presence of the Philadelphia chromosome is a good prognostic sign in chronic myelogenous leukemia and indicates a poor prognosis in acute lymphoblastic leukemia. The sites of chromosome breaks coincide with the known loci of oncogenes and antioncogenes.

Heerema NA et al: Association of chromosome arm 9p abnormalities with adverse risk in childhood acute lymphoblastic leukemia: A report from the Children's Cancer Group. *Blood* 1999;94:1537.

Jones KL: *Smith's Recognizable Patterns of Human Malformation*, 5th ed. Saunders, 1996.

Martinez-Climent JA et al: Chromosomal rearrangements in childhood acute myeloid leukemia and myelodysplastic syndromes. *J Pediatr Hematol Oncol* 1999;21:91.

MOLECULAR GENETICS

The advances of molecular biology have been a major breakthrough for human genetics, because they allow for the localization, isolation, and characterization of the genes that encode protein sequences. As the Human Genome Project has moved into a post-cloning era, the function of the gene products and their interaction with one another has become the main theme of molecular genetics. Also, molecular genetics can help explain the complex underlying biology involved in human diseases.

Recombinant DNA Technology

Recombinant DNA technology was developed using restriction endonucleases, which cleave DNA at specific nucleotide sequences. A difference in DNA sequence caused by a normal variation of DNA or by a gene mutation either produces or eliminates an endonuclease recognition site, resulting in a DNA fragment of different size. Thus the number and arrangement of restriction sites (called a restriction map) are characteristic

of a given DNA sequence.

Before a DNA fragment of interest can be analyzed, multiple copies of it must be produced. This can be achieved by incorporating the human DNA fragment into a vector (ie, a DNA segment containing the means of replication and selection in bacteria). The vector-containing human DNA insert is replicated, thus producing multiple copies of the segment of interest. The source of inserts can be genomic DNA, obtained directly from cleaving of the target organism, or complementary DNA (cDNA), obtained by copying messenger RNA (mRNA) into DNA by reverse transcription.

A genomic library can be assembled by fragmenting human genomic DNA with restriction enzymes and then inserting the fragments into a vector. Such a library contains large numbers of different DNA sequences. Some of these specific DNA fragments are used to manufacture human proteins (eg, insulin, growth hormone, interferon, and blood clotting factors) for pharmacologic applications; others are used as probes, which may be thought of as DNA segment-specific, radioactively labeled reagents for mapping and diagnosis.

Molecular genetic techniques are most commonly used to look for changes in genomic DNA detected by Southern blot analysis. But a similar technique with Northern blot analysis is being used increasingly to look for RNA abnormalities. Southern blot analysis relies on the use of restriction endonucleases to cleave human genomic DNA at specific nucleotide sequences and to produce DNA fragments of different lengths. These DNA fragments are then separated by agarose gel

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electrophoresis, transferred to a membrane, and overlaid with a radioactive probe. This fragment is identified by autoradiography, and its size is determined. Recently, non-radioisotope-based hybridization became available as an alternative to radioisotopes.

The **polymerase chain reaction (PCR)** replicates fragments of DNA between predetermined primers so that sufficient DNA is obtained for characterization or sequencing in the space of a few hours. For example, 20 cycles of synthesis will amplify DNA 1 millionfold. The disadvantage of PCR is that a small contamination with foreign DNA can result in an incorrect diagnosis.

Application of Molecular Biology in Clinical Genetics and Genetic Diagnosis

Genetic diagnosis can be performed by direct detection of a mutant gene or by indirect methods. Direct detection is possible only when the gene causing the disease and the nature of the mutation are known. The advantage of a diagnostic study using the direct detection of the mutant gene is that it requires the affected individual only and need not involve the testing of other family members. Indirect detection of abnormal genes is used when the gene is known but there is extensive heterogeneity of the molecular defect between families, or when the gene responsible for a disease is unknown but its chromosome location is known.

The methods of direct DNA diagnosis include restriction analysis, single-strand conformational polymorphism (SSCP) analysis, direct sequencing with assistance of PCR, heteroduplex assay, and protein truncation assay. The molecular mechanisms causing human diseases include point mutations, deletions, and insertions, and the unstable expansion of trinucleotide repeats, which leads to genetic anticipation (see

sections above and below). Molecular assay for congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency, Duchenne muscular dystrophy, Hemophilias A and B, Lesch-Nyhan syndrome, FGFR-related craniosynostosis, cystic fibrosis, and fragile X syndrome are common examples of diseases caused by these mechanisms, for which direct DNA testing is available.

If the sequence or product of an abnormal gene cannot be studied, then the linkage analysis method may be applicable. Linkage traces the inheritance of the abnormal gene between members of a kindred. This method requires that the affected individual be studied, with parents and perhaps other relatives, both affected and unaffected.

Neurofibromatosis is an example of a disorder in which both the direct and indirect assay may be used. Because of the size and the heterogenous mutation pattern of the Neurofibromin gene, the first step usually is the protein truncation assay, which is done via in vitro translation followed by analyzing the size of the protein. However, this method detects only two thirds of affected patients, in whom a nonsense mutation exists that truncates the gene message. All other cases must rely on linkage analysis, by using markers such as a restriction fragment length polymorphism (RFLP) or, increasingly, flanking microsatellite polymorphisms. The increase in density of polymorphisms discovered over the past few years means that the presence or absence of an abnormal copy of a gene in an individual can be predicted with a high degree of confidence, if the relatives have informative polymorphisms. Microsatellite polymorphisms are being used in sibling research studies to identify the multiple genes that contribute to polygenic traits such as diabetes and obesity. They are also used increasingly to identify gene changes in tumors.

Application of Molecular Biology in Prevention of Human Diseases

Recombinant DNA technology has the potential for preventing genetic disease by facilitating the detection of carriers of defective genes and permitting prenatal diagnosis. Family studies can also clarify the mode of inheritance, thus allowing more accurate determination of recurrence risks and appropriate options. For example, differentiation of gonadal mosaicism from decreased penetrance of a dominant gene has important implications for genetic counseling. In the past, the diagnosis of a genetic disease characterized by late onset of symptoms (eg, Huntington disease) could not be made prior to the appearance of clinical symptoms. In some inborn errors of metabolism, diagnostic tests (eg, measurement of enzyme activities) could be conducted only on inaccessible tissues. Gene identification techniques can enormously enhance the ability to diagnose symptomatic and presymptomatic individuals, and heterozygous carriers of the gene, and conduct prenatal diagnosis. However, presymptomatic DNA testing is associated with psychological, ethical, and legal implications and therefore should be used only with informed consent.

Application of Molecular Biology to Treat Human Diseases

A normal gene introduced into an individual affected with a serious inherited disorder during embryonic life (germ line therapy) in principle has the potential to be transmitted to future generations, whereas its introduction into somatic cells (somatic therapy) affects only the recipient. Experimental gene therapy by bone marrow transplantation is being tried for adenosine deaminase deficiency. Recombinant enzyme replacement had

been successfully applied in treating the nonneurologic form

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of Gaucher disease and some types of lysosomal storage disease.

Korf B: Molecular medicine: Molecular diagnosis. (Two parts.) N Engl J Med 1995;332:1218,1499.

PRINCIPLES OF INHERITED HUMAN DISORDERS

MENDELIAN DISORDERS

Traditionally, autosomal single gene disorders follow the principles explained by Mendel's observations. To summarize, the inheritance of genetic traits through generations relies upon segregation and independent assortment. **Segregation** is the process through which gene pairs are separated during gamete formation. Each gamete receives only one copy of each gene (allele). **Independent assortment** refers to the idea that the segregation of different alleles occurs independently.

Victor McKusick's catalog, *Mendelian Inheritance in Man*, lists more than 10,000 entries in which the mode of inheritance is presumed to be autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive and Y-linked. Single genes at specific loci on one or a pair of chromosomes cause these disorders. Understanding of inheritance terminology is helpful in approaching Mendelian disorders. Analysis of the pedigree and the pattern of transmission in the family, identification of a specific condition, and knowledge of that condition's mode of inheritance usually allows for explanation of the inheritance pattern.

Terminology

Several terms are important in understanding heredity patterns. These are listed below:

Dominant and Recessive

As defined by Mendel, concepts for dominant and recessive refer to the *phenotypic expression* of alleles and are not intrinsic characteristics of gene loci. Therefore it is inappropriate to discuss "a dominant locus,"

Genotype

This means the genetic status—ie, the alleles an individual carries.

Phenotype

Phenotype is the expression of an individual's genotype and may be modified by environment— ie, the structural or functional nature of an individual (appearance, physical features, organ structure, biochemical, physiologic nature).

Pleiotropy

This refers to the phenomenon whereby a single mutant allele can have widespread effects or expression in different tissues or organ systems. In other words, an allele may produce more than one effect on the phenotype. For example, Marfan syndrome has findings in different organ systems (skeletal, cardiac, ophthalmologic, etc.) due to a

single mutation within the fibrillin gene.

Penetrance

Penetrance refers to the proportion of individuals with a particular genotype that express the same phenotype. Penetrance is a proportion that ranges between 0 and 1.0 (or 0 and 100%). When 100% of mutant individuals express the phenotype, penetrance is *complete*. If some mutant individuals do not express the phenotype, penetrance is said to be *incomplete* or *reduced*. Dominant conditions with incomplete penetrance, therefore, are characterized by “skipped” generations with unaffected, obligate gene carriers.

Expressivity

This term refers to the variability in degree of phenotypic expression (severity) seen in different individuals with the same mutant genotype. Expressivity may be extremely variable or fairly consistent, both within and between families. Intrafamilial variability of expression may be due to factors such as epistasis, environment, true anticipation, presence of phenocopies, mosaicism, and chance (stochastic factors). Interfamilial variability of expression may be due to the above factors as well, but may also be due to allelic or locus genetic heterogeneity.

Genetic Heterogeneity

A number of different genetic mutations may produce phenotypes that are identical or similar enough to have been traditionally considered as one diagnosis. The conditions of “anemia” and “mental retardation” are examples of this. There are two types of genetic heterogeneity, *allelic heterogeneity* and *locus heterogeneity*.

Locus heterogeneity

This describes a phenotype caused by mutations at more than one genetic locus—ie, mutations at different loci cause the same phenotype or a group of phenotypes that appear similar enough to have been previously classified as a single disease, clinical “entity,” or diagnostic spectrum. An example would be Sanfilippo syndrome (MPS III A, B, C, and D) where the same phenotype is produced by four different enzyme deficiencies.

Allelic heterogeneity

This term is applied to a phenotype caused by more than one genetic mutation at the same gene locus—ie, different mutations at a single gene locus. As an example, cystic fibrosis may be caused by many different genetic changes, such as homozygosity for the common $\Delta F 508$ mutation, or $\Delta F 508$ and a R117H mutation. The latter example represents compound heterozygosity.

Phenotypic Heterogeneity or “Clinical Heterogeneity”

This term describes the situation in which more than one phenotype is caused by different allelic mutations at a single locus. An example of phenotypic

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heterogeneity includes different mutations within the Collagen II gene causing

hypochondrogenesis, Kniest dyplasia, spondyloepiphyseal dysplasia congenita, and some cases of Stickler syndrome. Furthermore, different mutations in the fibroblast growth factor receptor 2 (FGFR2) gene can cause different craniosynostosis disorders, including Crouzon syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, and Apert syndrome. These syndromes are clinically distinguishable and are due to the presence of a variety of genetic mutations within single genes.

Homozygous

A cell or organism that has identical alleles at a particular locus is said to be homozygous. For example, in an autosomal recessive disorder, the gene copies from both parents have to be inactivated to manifest the disease.

Heterozygous

A cell or organism that has nonidentical alleles at a genetic locus is said to be heterozygous. In autosomal dominant conditions, one copy of the gene pair is inactivated, while the other is functional, resulting in a disease state. An individual who is heterozygous for a recessive disorder will not manifest symptoms.

Online Mendelian Inheritance in Man (<http://www3.ncbi.nlm.nih.gov/Omim/>)

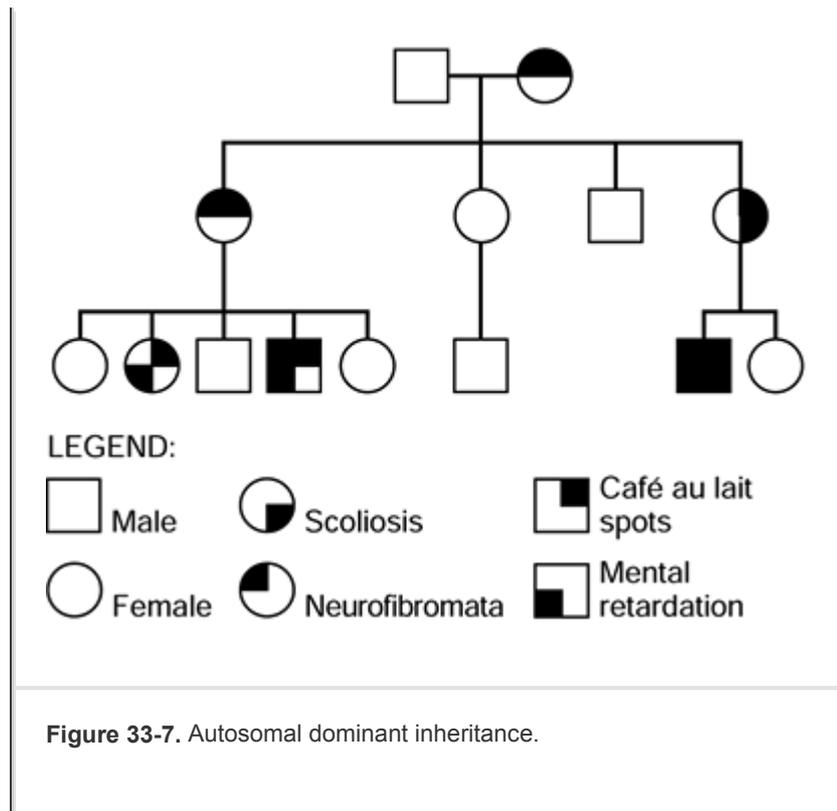
Hereditary Patterns

Autosomal Dominant Inheritance

Autosomal dominant inheritance has the following characteristics:

1. Affected individuals in the same family may experience variable expressivity.
2. Nonpenetrance is common, and the penetrance rate varies for each dominantly inherited condition.
3. Both males and females can pass on the abnormal gene to children of either sex, although the manifestations may vary according to sex. For example, baldness is a dominant trait but affects only males. In this case, the trait is said to be sex-limited.
4. Dominant inheritance is typically said to be vertical, that is, the condition passes from one generation to the next in a vertical fashion (Figure 33-7).





5. In some cases, the family history seems to be completely negative, and the patient appears to be the first affected individual. This spontaneous appearance may be caused by a new mutation. In some disorders, which tend to be more severe (eg, achondroplasia) and therefore may decrease the reproductive fitness, there is a high rate of new mutations. The mutation rate varies with each dominant condition, and in some cases the mutation rate increases with advancing paternal age. There are, however, several other possible explanations for a negative family history: (a) Nonpaternity. (b) Decreased penetrance or mild manifestations in one of the parents. (c) Germ line mosaicism (ie, mosaicism in the germ cell line of either parent), in which case the risk of recurrence increases. Germ line mosaicism may mimic autosomal recessive inheritance, because it leads to situations in which two children of completely normal parents are affected with a genetic disorder. The best example of this is osteogenesis imperfecta type II. Laboratory studies have documented germ line mosaicism by finding that only one allele of the paired collagen genes is abnormal in the severe form instead of both, as would be expected in a recessive disease. The recurrence risk in this form of osteogenesis imperfecta is 7%. (d) The abnormality present in the patient may be a phenocopy, or it may be a similar but genetically different abnormality with a different mode of inheritance.
6. As a general rule, dominant traits are more often related to structural abnormalities of protein, as for example in the Marfan syndrome.
7. For a parent who is affected, the risk of each offspring to inherit the abnormal dominant gene is 50%, or 1:2. This is true whether the gene is penetrant or not in the parent, and the severity in the offspring is not related to the severity in the affected parent. In some disorders, it may be related to the sex of the parent transmitting the gene. For

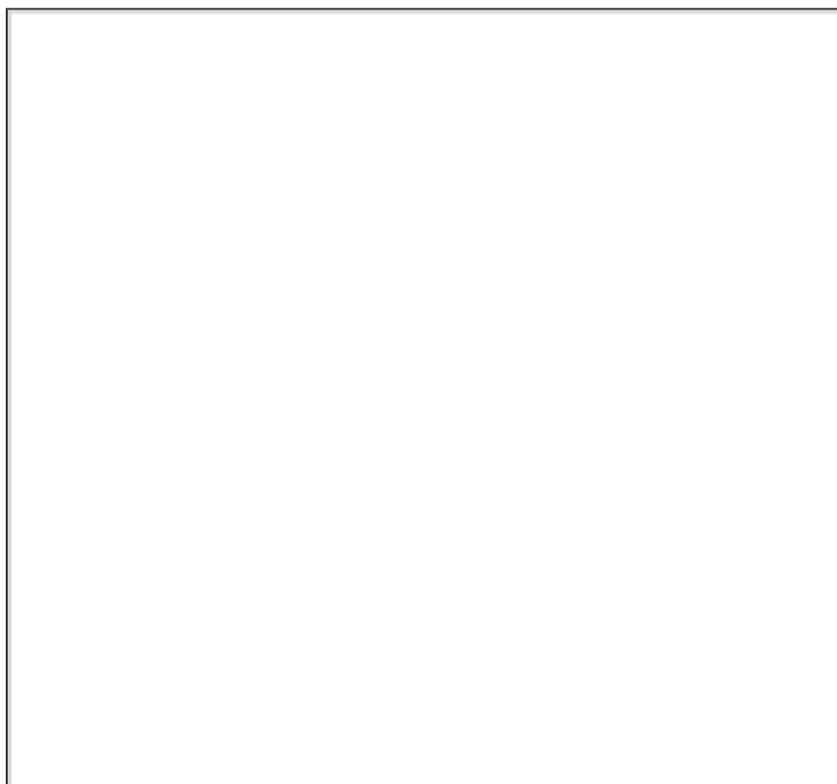
example, if the gene for myotonic dystrophy is passed through the mother, there is a 10–20% chance that the child (regardless of sex) may have a severe congenital form of the disease. Conversely, if the gene for Huntington disease is passed through the father, there is a 5–10% possibility that the offspring may have the severe, rigid juvenile form. This has been attributed to imprinting, although we know in these two conditions that it is associated with expansion of the triplet repeats (see Genetic Anticipation section, below). If an abnormality represents a new mutation of a dominant trait, the parents of the affected individual run a low risk during subsequent pregnancies, but the risk for the offspring of the affected individual is 50%.

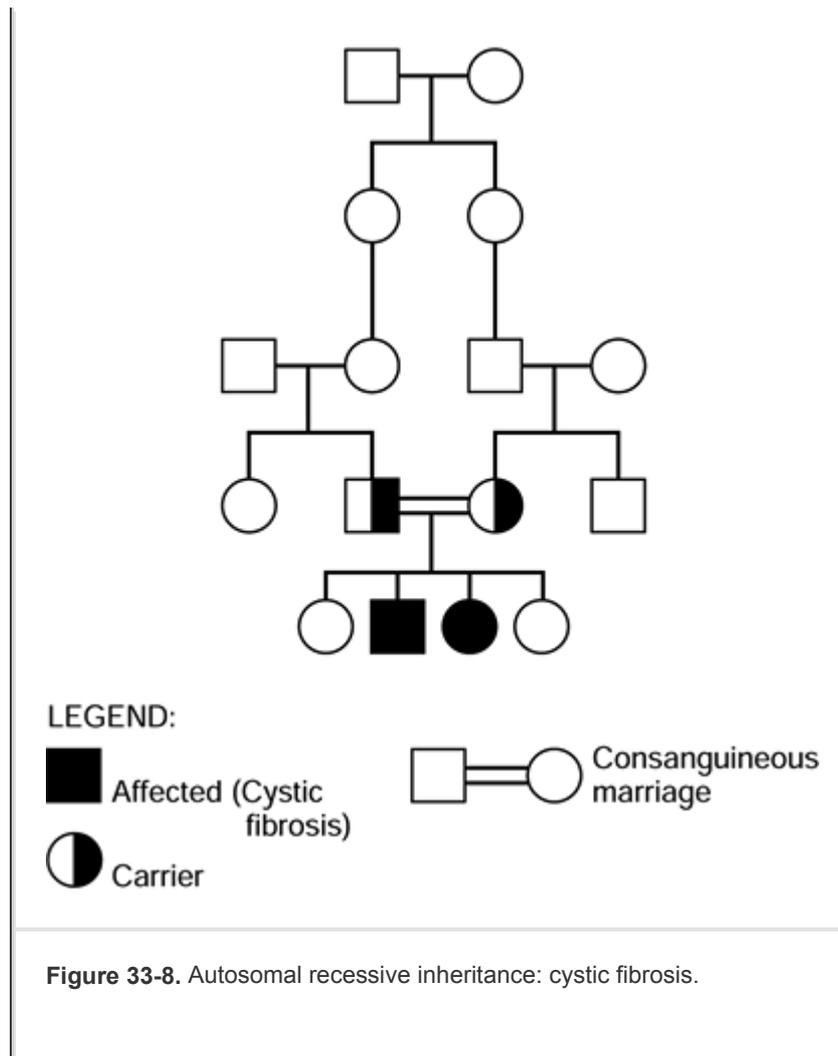
8. Prevention options available for future pregnancies include prenatal diagnosis, artificial insemination, or egg donation, depending on which parent has the abnormal gene.

Autosomal Recessive Inheritance

Autosomal recessive inheritance also has some distinctive characteristics:

1. There is less variability among affected persons. Parents are carriers and are clinically normal. (There are exceptions to this rule, however. For example, sickle cell disease is considered recessive. Under normal circumstances, carriers—those with the sickle cell trait—are normal but may become symptomatic if they become hypoxic.)
2. Males and females are affected equally.
3. Inheritance is horizontal; siblings may be affected (Figure 33-8).





4. Recessive conditions are usually rare; the rarer the condition, the more likely it is that consanguinity is present. Conversely, if a child whose parents are related presents with an unrecognized abnormality, a recessive condition must be suspected.
5. The family history is usually negative, with the exception of siblings. However, in common conditions such as cystic fibrosis, there may be an affected second- or third-degree relative.
6. Recessive conditions are frequently associated with enzyme defects.
7. The recurrence risk for parents of an affected child is 25%, or 1:4 for each pregnancy. The gene carrier frequency in the general population can be used to assess the risk of having an affected child with a new partner, for unaffected siblings, and for the affected individuals themselves.
8. In rare instances, a child with a recessive disorder and a normal karyotype may have inherited both copies of the abnormal gene from one parent and none from the other. This uniparental disomy was first described in a girl with cystic fibrosis and growth retardation. This phenomenon is of unknown frequency, but it is more likely to be present in a child with several autosomal recessive conditions or in a patient with unexpected and seemingly unrelated abnormalities or severe growth

retardation. Molecular testing can confirm the presence of uniparental disomy. The recurrence risk is obviously lower in such a situation, although the factors predisposing to uniparental disomy are not known. Maternal age may play a role in these situations.

9. Options available for future pregnancies include prenatal diagnosis in many cases, and artificial insemination.

X-Linked Inheritance

When a gene for a specific disorder is on the X chromosome, the condition is said to be X-linked, or sex-linked. Females may be either homozygous or heterozygous, because they have two X chromosomes. Males, by contrast, have only one X, and a male is said to be hemizygous for any gene on his X chromosome. The severity of any disorder is greater in males than in females (within a specific

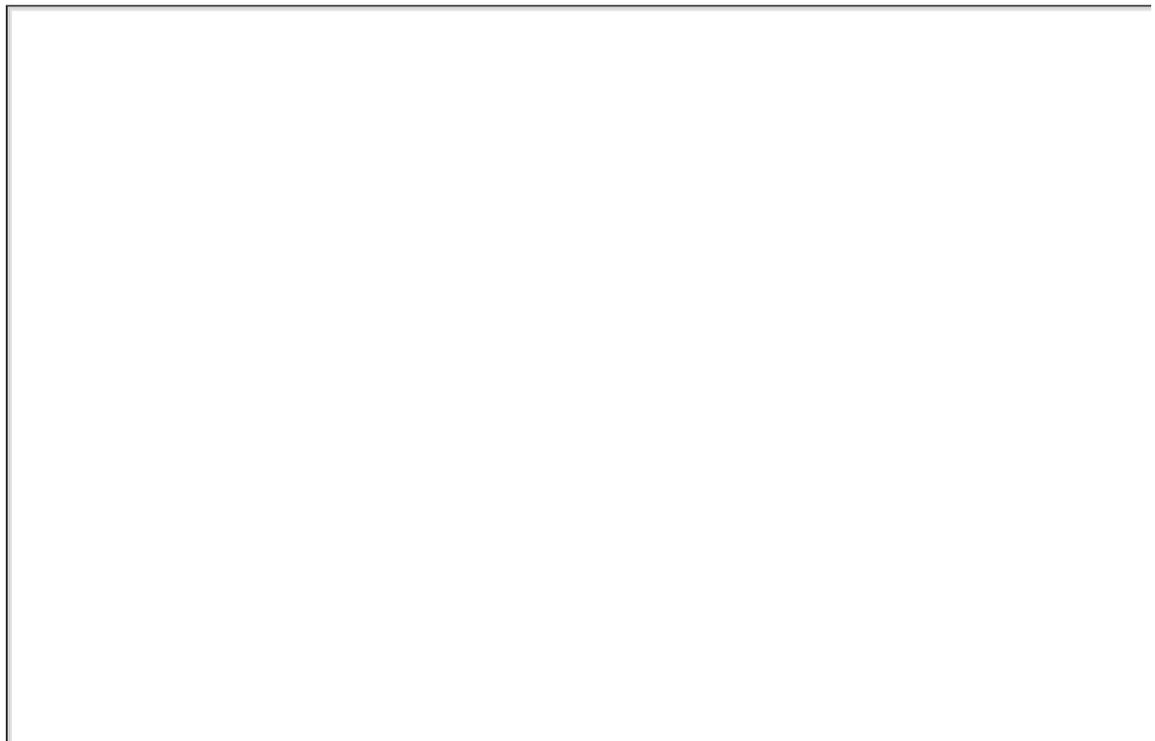
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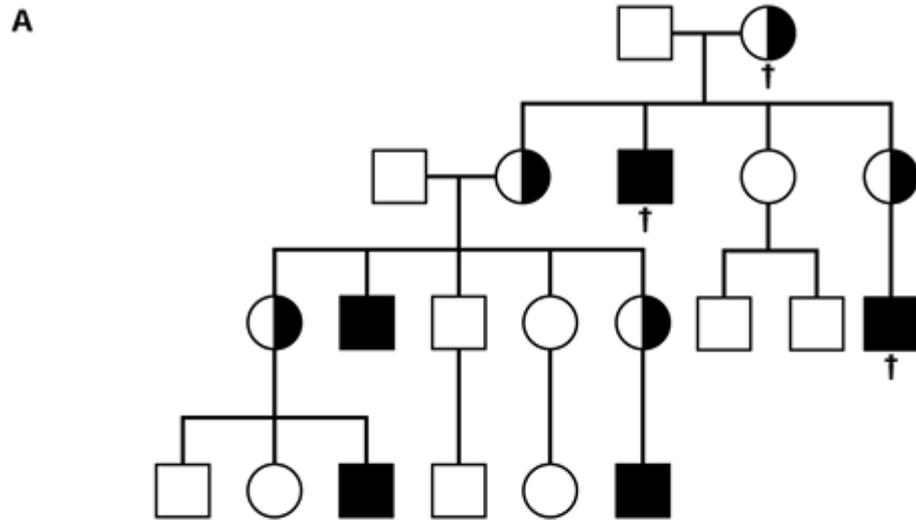
family). According to the Lyon hypothesis, because one of the two X chromosomes in each cell is inactivated, and because this inactivation is random, the clinical picture in females depends on the percentage of mutant versus normal alleles inactivated. The X chromosome is not inactivated until about 14 days of gestation, and parts of the short arm remain active throughout life.

X-Linked Recessive Inheritance

The following features are characteristic of X-linked recessive inheritance:

1. Males are affected, and heterozygous females are either normal or have mild manifestations.
2. Inheritance is diagonal through the maternal side of the family (Figure 33-9a).





LEGEND:

■ Duchenne-muscular dystrophy

◐ Carrier

† Deceased

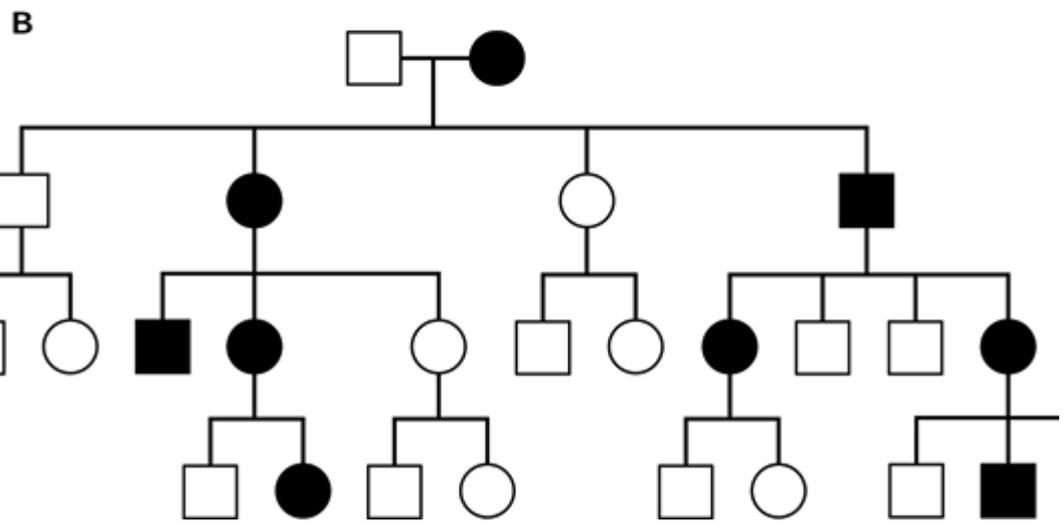


Figure 33-9. A: X-linked recessive inheritance. B: X-linked dominant inheritance.

3. A female carrier has a 50% chance that each daughter will be a carrier and a 50% chance that each son will be affected.
4. All of the daughters of an affected male are carriers, and none of his sons are affected. Because a father can give only his Y chromosome to his sons, male-to-

male transmission excludes X-linked inheritance except in the rare case of uniparental

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disomy, in which a son receives both the X and the Y from his father.

5. The mutation rate is high in some X-linked disorders, particularly when the affected male dies or is so incapacitated by the disorder that reproduction is unlikely. In such instances, the mutation is thought to occur in the propositus in one-third of cases, in the mother in one-third of cases, and in earlier generations in one-third of cases. For this reason, genetic counseling may be difficult in families with an isolated case.
6. On rare occasions, a female may be fully affected. Several possible mechanisms may account for a fully affected female: (a) unfavorable lyonization; (b) 45,X karyotype; (c) homozygosity for the abnormal gene; (d) an X-autosome translocation, or other structural abnormality of one X chromosome, in which the X chromosome of normal structure is preferentially inactivated; (e) uniparental disomy; and (f) nonrandom inactivation, which may be controlled by an autosomal gene.

X-Linked Dominant Inheritance

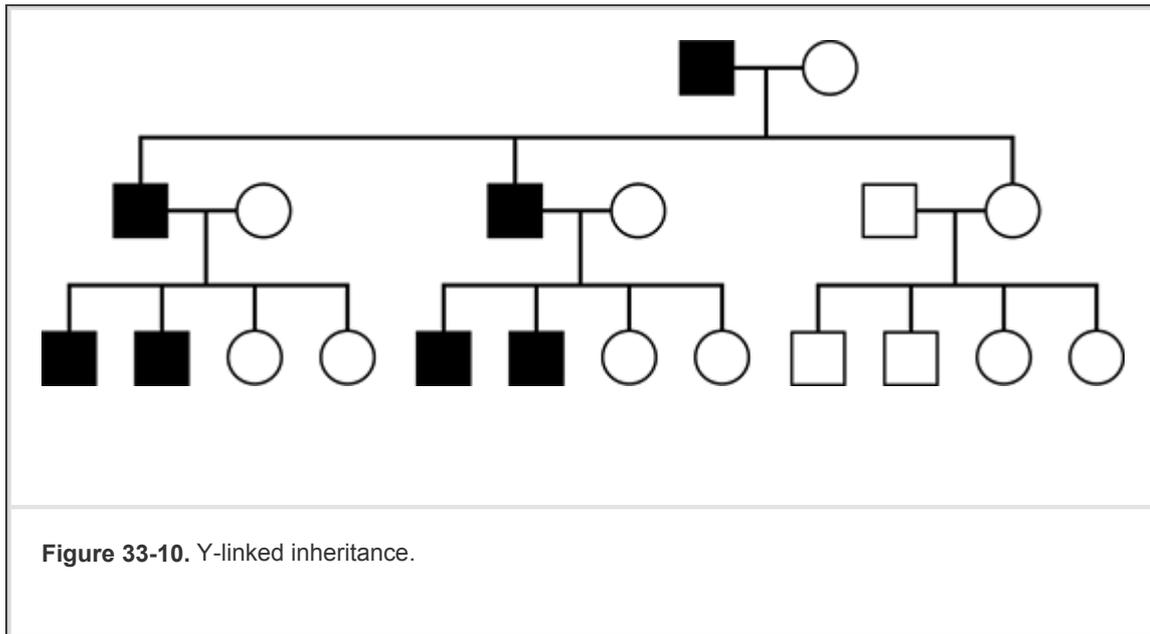
The X-linked dominant inheritance pattern is much less common than the X-linked recessive type. Examples include incontinentia pigmenti and hypophosphatemic or vitamin D-resistant rickets.

1. The heterozygous female is symptomatic, and the disease is twice as common in females because they have two X chromosomes that can have the mutation.
2. Clinical manifestations are more variable in females than in males.
3. The risk for the offspring of heterozygous females to be affected is 50% regardless of sex.
4. All of the daughters but none of the sons of affected males will have the disorder. (Figure 33-9b)
5. Although a homozygous female is possible (particularly in an inbred population), she would be severely involved. All of her children would also be affected but more mildly.
6. Some disorders (eg, incontinentia pigmenti) are lethal in males (and in homozygous females). Affected women have twice as many daughters as sons and an increased incidence of miscarriages, because affected males will be spontaneously aborted. A 47,XXY karyotype has allowed affected males to survive.

Y-Linked Inheritance

Also known as "Holandric" inheritance, these conditions are caused by genes located on the Y chromosome. These conditions are relatively rare with only about 40 entries

listed in McKusick's catalog. Male-to-male transmission is seen in this category, with all sons of affected males being affected and no daughters or females being affected. Figure 33-10 shows a typical Y-linked inheritance pedigree.



MULTIFACTORIAL INHERITANCE

Many common attributes, such as height, are familial, and are the result of the actions of multiple rather than single genes. Inheritance of these traits is described as **polygenic** or **multifactorial**. The latter term recognizes that environmental factors such as diet also contribute to these traits. As they begin to dissect the genetics of these traits in humans, geneticists are finding that multiple genes are often expressed in hierarchies in which the action of a small number of genes, 2 or 3, explains much of the variation observed within affected populations.

Studies of twins have proven useful in determining the relative importance of genetic versus environmental factors in the expression of polygenic traits. If genetic factors are of little or no importance, then the concordance between monozygotic and dizygotic twins should be the same. (Dizygotic twins are no more genetically similar to each other than to other siblings.) If an abnormality is completely genetic, the concordance between identical twins should be 100%. In polygenic conditions, the concordance rate for identical twins is higher than that seen in dizygotic twins but still not

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100%, indicating both genetic and environmental factors.

Many disorders and congenital abnormalities that are clearly familial but do not segregate as mendelian traits (e.g. autosomal dominant, recessive, etc.) show polygenic inheritance. For the most part, these conditions become manifest when thresholds of additive gene actions or contributing environmental factors are exceeded. Many common disorders ranging from hypertension, stroke, and thrombophlebitis to behavioral traits such as alcoholism demonstrate multifactorial (polygenic) inheritance. There are also common birth defects including isolated congenital heart disease, cleft lip and palate, and neural tube defects, which demonstrate polygenic inheritance. Neural tube defects provide a good model for how identification of both environmental

and genetic contributions to multifactorial traits can lead to preventive measures.

Polygenic or multifactorial inheritance has several distinctive characteristics:

1. The risk for relatives of affected persons is increased, and the risk is higher for first-degree relatives (those who have 50% of their genes in common) and lower for more distant relations, although the risk for the latter is higher than for the general population (Table 33-2).

Anencephaly and spina bifida: Incidence (average) 1:1000	
One affected child:	2-3%
Two affected children:	10-12%
One affected parent:	4-5%
Hydrocephalus: Incidence 1:2000 newborns	
Occasional X-linked recessive	
Often associated with neural tube defect	
Some environmental etiologies (eg, toxoplasmosis)	
Recurrence risk, one affected child	
Hydrocephalus:	1%
Some central nervous system abnormality:	3%
Non-syndromic cleft lip and/or palate: Incidence (average) 1:1000	
One affected child:	2-4%
One affected parent:	2-4%
Two affected children:	10%
One affected parent, one affected child:	10-20%
Non-syndromic cleft palate: Incidence 1:2000	
One affected child:	2%
Two affected children:	6-8%
One affected parent:	4-6%
One affected parent, one affected child:	15-20%
Congenital heart disease: Incidence 8:1000	
One affected child:	2-3%
One affected parent, one affected child:	10%
Clubfoot: Incidence 1:1000 (male:female = 2:1)	
One affected child:	2-3%
Congenital dislocated hip: Incidence 1:1000 (female > male) with marked regional variation	
One child affected:	2-14%
Pyloric stenosis: Incidence, males: 1:200; females: 1:1000	
Male index parent	
Brothers	3.2%
Sons	6.8%
Sisters	3.0%
Daughters	1.2%
Female index patient	
Brothers	13.2%
Sons	20.5%
Sisters	2.5%
Daughters	11.1%

Table 33-2. Empiric risks for some congenital disorders.

2. The recurrence risk varies with the number of affected family members. For

example, after one child is born with a neural tube defect, the recurrence risk is 2–3%. If a second affected child is born, the risk for any future child increases to 10–12%. This is in contrast to single-gene disorders, in which the risk is the same no matter how many family members are affected.

3. The risk is higher if the defect is more severe. In Hirschsprung disease, another polygenic condition, the longer the aganglionic segment, the higher the recurrence risk.
4. Sex ratios may not be equal. If a marked discrepancy exists, the recurrence risk is higher if a child of the less commonly affected sex has the disorder. This assumes that more genetic factors are required to raise the more resistant sex above the threshold. For example, pyloric stenosis is more common in males. If the first affected child is a female, the recurrence risk is higher than if the child is a male.
5. The risk for the offspring of an affected person is approximately the same as the risk for siblings, assuming that the spouse of the affected person has a negative family history. For many conditions, however, assortative mating, “like marrying like,” adds to risks in offspring.

NONMENDELIAN INHERITANCE

Imprinting

Although the homologs of chromosome pairs may appear identical on routine karyotype analysis, it is now known that the parental origin of each homolog can effect which genes are actually transcribed and which are inactivated. The term imprinting refers to the process

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by which there is preferential transcription of certain genes depending on the parental origin (ie, which homolog—maternal or paternal) the gene is located on. Certain chromosomes, particularly chromosome X, and the autosomes 15, 11, and 7, have imprinted regions where certain genes are only read from one homolog (ie, either the maternal or paternal allele) under normal circumstances, and the gene on the other homolog is normally inactivated. Errors in imprinting may arise because of uniparental disomy (where a copy from one parent is missing), by a chromosomal deletion causing loss of the gene normally transcribed, or by mutations in the imprinting genes that normally code for transcription or inactivation of other genes downstream. A good example of how imprinting may effect human disease is Beckwith-Wiedemann syndrome (BWS), the gene that is located on chromosome 11p15.

Hall JG: Genomic imprinting: Nature and clinical relevance. *Annu Rev Med* 1997;48:35.

Li M et al: Overgrowth syndromes and genomic imprinting: From mouse to man. *Clin Genet* 1998;53:165.

Genetic Anticipation

Geneticists coined the term anticipation to describe an unusual pattern of inheritance in which symptoms became manifest at earlier ages and with increasing severity as traits

are passed to subsequent generations. Mapping of the genes responsible for these disorders led to the discovery that certain repeat sequences of DNA at disease loci were not stable when passed through meiosis. Repeated DNA sequences, in particular triplets (eg CGG, CAG) tended to increase their copy number. As these runs of triplets expanded they eventually affected the expression of genes and produced symptoms. Curiously, all the disorders undergoing triplet repeat expansion so far detected produce neurological symptoms. Most are progressive. In general, there is a rough correlation with the size of the triplet expansion and the timing and severity of symptoms. The reasons for the meiotic instability of these sequences are not yet understood. The mechanisms appear to involve interactions between DNA structure (eg, formation of hairpin loops) and replication enzymes (DNA polymerase complexes) during meiosis.

Triplet repeat instability can modify the inheritance of autosomal dominant, autosomal recessive, and X-linked traits (see page 1041 of this chapter for clinical descriptions of triplet instability disorders). Autosomal dominant disorders include several spinal cerebellar atrophies, Huntington disease, and myotonic dystrophy. Unstable triplet repeat expansion contributes to at least one autosomal recessive disorder, Friedreich's ataxia. The most common X-linked disorder demonstrating triplet repeat instability and expansion is fragile X syndrome.

Mitochondrial Inheritance

Mitochondrial DNA is double-stranded, circular, and smaller than nuclear DNA, and is found in the cytoplasm. It codes for enzymes involved in oxidative phosphorylation, which generates adenosine triphosphate (ATP). During the last decade of the 20th century, enormous advances in technology and improved clinical documentation have led to a better understanding of the interesting disorders caused by mutations in mitochondrial DNA (mtDNA). It was initially appreciated that these unusual disorders seemed to be transmitted only by female members of a family and affected a high proportion of offspring, both male and female. Mitochondrial disorders have the following characteristics:

1. They show remarkable phenotypic variability.
2. They are maternally inherited, because only the egg has any cytoplasmic material.
3. In most mitochondrial disorders, cells are heteroplasmic. That is, all cells contain both normal and mutated or abnormal mtDNA. The proportion of normal to abnormal mtDNA in the mother's egg seems to determine the severity of the offspring's disease and the age at onset in most cases.
4. Those tissues with the highest ATP requirements—specifically, central nervous system (CNS) and skeletal muscle—seem to be most susceptible to mutations in mtDNA.
5. There is an increase in somatic cell mtDNA mutations and a decline in oxidative phosphorylation function with age. This explains the later onset of some of these disorders and may indeed be a clue to the whole aging process.

Mitochondrial disorders have been associated with deletions or duplications in

mitochondrial DNA. Large deletions are usually sporadic, but smaller deletions may be secondary events due to defects in dominantly inherited nuclear genes. Mitochondrial dysfunction may also be caused by mutations in nuclear genes encoding mitochondrial proteins, and can be inherited as dominant, recessive, or X-linked traits. Because of the difficulty in diagnosing mitochondrial disorders and the variability of the clinical course, it is often difficult to calculate specific recurrence risks.

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FAMILY HISTORY AND PEDIGREE

The first step in the collection of information regarding the genetics of a syndromic diagnosis is the construction of a family tree or pedigree. Underused by most medical personnel, the pedigree is a valuable record of genetic and medical information, which is much more useful in visual form than in list form. Tips for pedigree preparation include the following:

- Give simple instructions to the patient regarding the information desired.
- Use clearly defined symbols with a key for interpretation.
- Identify the informant, the historian, and the date of the interview.
- Start in the middle of the page to allow enough room for expansion.
- Start with the proband—the patient's siblings and parents.
- Always ask about consanguinity. Sometimes the question “Are you (the parents) related by blood?” will result in laughter but often yields potentially useful clues suggesting autosomal recessive inheritance. Ask for details such as place of birth, size of towns, and the presence of consanguinity. (These help to define recessive conditions and may increase suspicion of certain diseases more frequently in particular ethnic backgrounds.)
- Obtain the maiden names of women in the family (particularly helpful for X-linked conditions).
- Obtain data from both sides of the family.
- Ask about spontaneous abortions, stillbirths, infertility, children relinquished for adoption, and deceased individuals. Such details are essential for understanding conditions that are lethal or are associated with reproductive losses.
- Even if the disease in question appears to be coming from one side of the family, always get the basic facts about the other side of the family as well. Sometimes unrelated data may be very important in interpreting the family's overall situation. In addition, obtaining data from both sides may avoid an inference of blame being placed on one family member.

In the course of taking the family history, one may find information that is not relevant in elucidating the cause of the patients' problem but may indicate a risk for other important health concerns. Such information should be appropriately followed and addressed. Such conditions that may arise are an overwhelming family history of early onset breast and ovarian cancer, multiple pregnancy losses necessitating chromosome

analyses, or symptoms of hemochromatosis, the common treatable disorder of iron metabolism.

DYSMORPHOLOGY AND HUMAN EMBRYOLOGY

With advances in perinatal medicine and treatment of infectious diseases, birth defects have now become the leading cause of death in the neonatal period and first year of life. Birth defects are evident in 2–3% of newborns and will be detected in 7% of the adult population. The scientific investigation of the origins of birth defects is called teratology. Dysmorphology is its clinical arm.

MECHANISMS

Developmental Genetics

Most birth defects are multifactorial: They result from miscommunication between genetic processes and the environments in which they unfold. Specific causes of maldevelopment can be identified in about 30% of cases, but advances in developmental biology and human genetics promise better understanding. Single-gene mutations and chromosomal abnormalities cause approximately 25% of birth defects. Specific genes or chromosomal loci have now been identified for many recurring phenotypes, or syndromes.

Among the most fundamental genetic programs in cells are those that regulate cell division, proliferation, and those that program cell death, or apoptosis. Both proliferation and apoptosis are very active in embryogenesis. The balance between these processes is easily disrupted and imbalances in regulation of cell cycles are an important determinant of birth defects.

Morphogenic processes and the genes that regulate them have been highly conserved through evolution. Thus experiments in lower organisms such as *Drosophila* (fruit flies) can be highly relevant to humans, because mutations producing abnormal development in less complex organisms identify candidate genes for human birth defects. Among the better examples of this connection are *pax* genes, involved in eye development in *Drosophila*. Mutations in one of these genes, *Pax 6*, produces “small eye” in mice, and aniridia and other anterior chamber eye abnormalities in humans.

Developmental biology is also taking advantage of two powerful technical advances: in situ hybridization for visualizing the expression of genes in embryos, and the production of transgenic animals in which genes of interest can be “knocked out” in order to determine their contributions to development. These techniques have uncovered, for example, very important regulatory pathways,

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such as the Hedgehog signaling pathway, which affects morphogenesis in organs as diverse as limbs, the heart, and the CNS. Human mutations in one of these evolutionally conserved genes, *Sonic Hedgehog*, can result in holoprosencephaly, a severe birth defect in which the CNS fails to complete hemispheric division.

Cellular Interactions

The picture emerging from genetic studies of morphogenesis is one of a hierarchy of gene expression during development. Morphogenesis begins with expression of genes

encoding transcription factors. These proteins bind to DNA in undifferentiated embryonic cells and recruit them into developmental fields, groups of cells primed to respond to specific signals later in development. This recruitment also establishes spatial relationships and orients cells with respect to their neighbors. As fields differentiate into identifiable tissues (eg, ectoderm, mesoderm, endoderm), cellular proliferation, migration, and further differentiation are mediated through genes encoding proteins that send signals through interactions with other proteins (receptors).

Products of these genes include growth factors and their receptors, cellular adhesion molecules, and extracellular matrix proteins that both provide structure and localize signals for further differentiation. Patterns in which fields of primed cells proliferate, migrate, and then interact through locally expressed growth factors and receptors occur repeatedly in mammalian development. Within these interactions are clues to understanding not only many human birth defects but also cancer. The genes that organize cell proliferation and differentiation during development are often precisely those that are knocked out or amplified by carcinogenic mutations.

Epigenetic Regulation

Although development is regulated by genes, it is initiated and sustained by nongenetic processes. Epigenetic events are points of interaction between developmental programs and the physicochemical environments in differentiating cells. Genetic imprinting and DNA methylation are examples of epigenetic processes that affect development. Certain genes important in regulation of growth and differentiation are themselves regulated by chemical modification which occurs in specific patterns in gametes. For example, genes that are methylated are “turned off,” and not transcribed. The pattern of which genes are methylated may be determined or affected by the sex of the parent of origin (imprinting—see above). Expression of imprinted genes may sometimes be limited to specific organs ie, (the brain), and imprinting may be relaxed and methyl groups lost as development progresses. Disruption of imprinting is now recognized as contributing to birth defect syndromes (described later in this chapter).

Environmental Factors

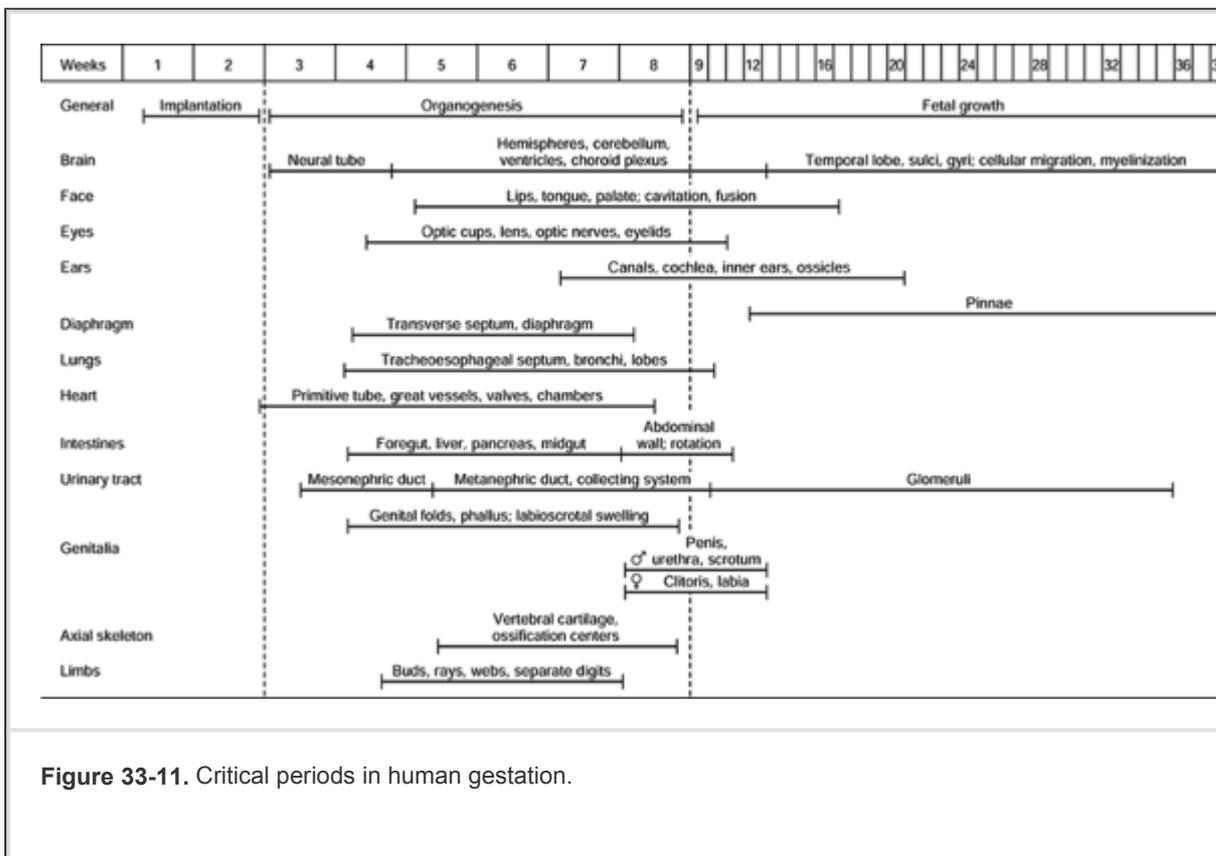
The effects of exogenous agents during development are also mediated through genetically regulated pathways. At the cellular level, environmental effects occur because xenobiotics (compounds foreign to nature), either interact with signaling pathways or receptors and misdirect morphologically important cellular functions, or they are cytotoxic and lead to cell death in excess of the usual developmental program.

In general, drug receptors expressed in embryos and fetuses are the same molecules that mediate effects in adults. However, because differentiation pathways are active, and embryonic and fetal physiology differs from that of mature organisms, pharmacologic effector systems may be different.

To affect human embryonic and fetal tissues, xenobiotics must traverse the placenta. The human placenta is a relatively good barrier against microorganisms, but it is substantially less effective at excluding drugs and chemicals. The physicochemical properties (eg, molecular size, solubility, charge) that allow foreign chemicals to be absorbed into the maternal circulation also allow them to cross the placenta. Xenobiotic metabolism occurs in the human placenta, but the placenta is better able to metabolize

steroid hormones and low-level environmental contaminants than drugs.

The timing of xenobiotic exposure is an important determinant of its effects. Individual organs express so-called critical periods of development, during which they are particularly susceptible to maldevelopment, if their programs for differentiation are disrupted or unbalanced. Figure 33-11 shows critical periods of development for several organs. These periods are not confined to early gestation. Note, for instance, that the developing brain is susceptible to toxicity throughout pregnancy.



Prescribed and over-the-counter drugs that reach pharmacologically active levels in maternal blood will, in general, equilibrate to the same levels across the placenta. Agents known to produce cytotoxicity in adults are therefore likely to be teratogenic. Abused substances achieve pharmacologically and toxicologically active levels on both sides of the placenta. Because they are frequently toxic to adults, they will be predictably toxic to embryos and fetuses. Drugs generally safe in adults will be generally safe for fetuses, but depending on specific drug-effector actions, some risk for abnormal development must always be considered. Risk assessment requires continuous monitoring of populations exposed to drugs during pregnancy.

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Effects of environmental contaminants on the embryo and fetus are also dose-dependent. Thus the level of exposure frequently becomes the primary determinant of risk. In general, exposures producing symptoms in mothers can be assumed to be potentially toxic to the fetus.

Mutagens in the environment may be a special problem. Experiments at high levels of exposure indicate that mutagenic agents are also teratogenic. Specific phenotypes,

however, are difficult to predict. Mutations induced in embryonic tissues result in mosaicism. These changes may not be visible but can contribute to diseases such as cancer later in life. DNA damage in developing cells can switch them into apoptotic pathways and may therefore have more immediate effects. The extent of this problem for humans is incompletely understood. Maternal exposure to mutagenic chemotherapy is predictably associated with abnormalities of fetal growth or birth defects. Evidence is also accumulating that transplacental exposures to environmental mutagens may affect brain growth. Not all transplacental pharmacologic effects are toxic. There is increasing potential for therapeutic transplacental uses of drugs in pregnancy. For example, folic acid supplementation can lower risks for birth defects such as spina bifida, and maternally administered corticosteroids induce fetal synthesis and secretion of surfactants prior to delivery.

MECHANICAL FACTORS

Much of embryonic development and all of fetal growth occur normally with the conceptus surrounded by amniotic fluid. The low pressure and the space provided by this fluid is critical for the development of most organs. Disruption of the formation or integrity of placental membranes for whatever reason can lead to major, usually lethal, distortion of the embryo (early amnion disruption sequence) or to deformation or even amputation of fetal extremities (amniotic band sequence).

Fetal movement is also important for morphogenesis. Normal movement is necessary for normal development of joints and is the principal determinant of folds and creases present at birth in the face, hands, feet, and other areas of the body. In the presence of fetal muscle weakness, for instance, developing joints conform to fetal position and shape of the uterus. Clubfoot, an etiologically heterogeneous condition in which the foot is malpositioned at birth, more often results from mechanical constraint secondary to intrauterine crowding, decreased muscle strength or tone, or abnormal neurologic function than from primary skeletal maldevelopment.

Lung and kidney development are particularly sensitive to mechanical forces. Constriction of the chest through maldevelopment of the ribs, lack of surrounding amniotic fluid, or lack of movement (fetal breathing) leads to varying degrees of pulmonary hypoplasia in which lungs are smaller than normal and develop fewer alveoli. Mechanically induced pulmonary hypoplasia is a common cause of respiratory distress at birth and may be lethal. Cystic renal dysplasia commonly accompanies birth defects that obstruct ureters or outflow from the bladder. In such cases, as the kidneys become functional, urinary pressure within obstructed collecting systems increases and is propagated back into developing tissues. This is a good example of how distortion of cell surface interactions and malalignment of extracellular matrix may lead to abnormal histogenesis. Developing kidneys exposed for long periods to increased internal pressures eventually become nonfunctional.

PRENATAL DIAGNOSIS

To investigate fetal growth and development, prenatal visits should be noted and, with the aid of the obstetric wheel, a record should be made of the patterns of fetal growth, the onset of fetal movement (usually at 16 weeks), and the mother's perceptions of fetal movements. Normal fetal movement is usually strong enough to discomfort the mother and be visible to the father. Abnormal fetal movement may indicate neuromuscular

dysfunction or fetal constraint. A history of decreased fetal movement will often distinguish neuromuscular abnormalities (which result in a low Apgar score) from intrapartum events (which depress the infant).

Abnormal patterns of uterine growth may also provide clues to fetal function. Increased uterine size may indicate accumulation of amniotic fluid (hydramnios). Fluid may accumulate if the fetus fails to swallow as a result of a neuromuscular disorder, obstruction of the fetal esophagus or proximal small bowel, or fetal heart failure. Hydramnios is also associated with diabetes and high-output renal failure in the fetus. Lack or delay of uterine growth may reflect fetal growth directly or may be a sign of too little amniotic fluid (oligohydramnios). Amniotic fluid may be lost through premature rupture of membranes with or without formation of amniotic bands, or it may be the result of compromised function of fetal kidneys. The mother should be questioned about loss or leakage of amniotic fluid, which may have been mistaken for a vaginal discharge.

The history should also include details about the onset and progression of labor. Breech presentation at term may indicate a uterine anomaly or abnormality of the fetal CNS. Placental pathology should also be reviewed.

CLINICAL DYSMORPHOLOGY

Classification of dysmorphic features is beginning to reflect better understanding of mechanisms of maldevelopment. However, much of the nomenclature used to

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describe abnormal development remains historical, and reflects the fact that many patterns of birth defects were recognized prior to any understanding of their molecular biology.

Birth defects are referred to as malformations when they result from altered genetic or developmental processes. When physical forces interrupt or distort morphogenesis, their effects are termed **disruptions** and **deformations**, respectively. The term **dysplasia** is used to denote abnormal histogenesis. Malformations occurring together more frequently than would be expected by chance alone, whether within a currently recognized developmental field or not, may be classified as belonging to **associations**. Those in which the order of maldevelopment is understood may be referred to as **sequences**. For example, Robin sequence is used to describe cleft palate that has occurred because poor growth of the jaw (retrognathia) has displaced the tongue and prevented posterior closure of the palate. **Syndromes** are simply recurrent patterns of maldevelopment.

Evaluation of the Dysmorphic Infant

Physicians caring for infants with birth defects must frequently provide care and make accurate diagnoses under conditions of great stress. The extent of an infant's abnormalities may not be immediately apparent, and parents who feel grief and guilt are often desperate for information. As with any medical problem, however, the history and physical examination provide most of the clues to diagnosis. Special aspects of these procedures are outlined below.

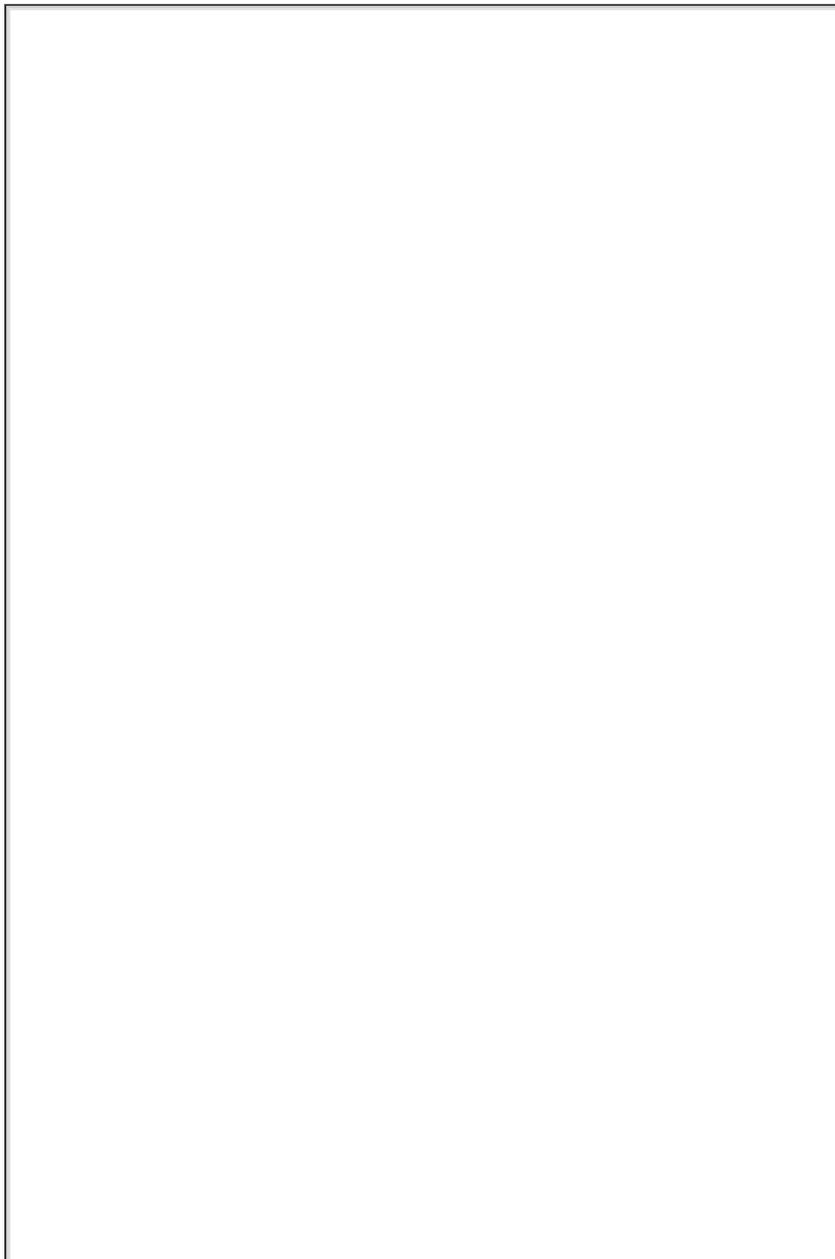
HISTORY

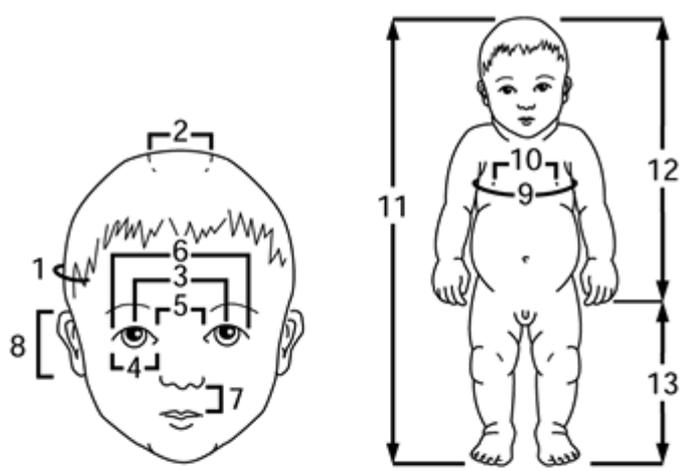
Environmental, family, and pregnancy histories may contain important clues to the diagnosis. Parental recall after delivery of an infant with an anomaly is better than recall after a normal birth. An obstetric wheel can help document gestational age and events of the first trimester: the last menstrual period, the onset of symptoms of pregnancy, the date of diagnosis of the pregnancy, the date of the first prenatal visit, and the physician's impressions of fetal growth at that time.

Family histories should always be included and may provide important clues to genetic etiology of the infant's issues. Finally, an environmental history that includes descriptions of parental habits, their work, and the home should be obtained.

PHYSICAL EXAMINATION

Meticulous physical examination is crucial for accurate diagnosis in dysmorphic infants and children. In addition to the routine procedures described in Chapter 1, special attention should be paid to the neonate's physical measurements (see Figure 33-12). Photographs are helpful and should include a scale of measurements for reference.





Measurement	Range (cm)	
	Term (38–40 weeks)	Preterm (32–33 weeks)
1 Head circumference	32–37	27–32
2 Anterior fontanelle $\left(\frac{L-W}{2}\right)$	0.7–3.7	...
3 Interpupillary distance	3.3–4.5	3.1–3.9
4 Palpebral fissure	1.5–2.1	1.3–1.6
5 Inner canthal distance	1.5–2.5	1.4–2.1
6 Outer canthal distance	5.3–7.3	3.9–5.1
7 Philtrum	0.6–1.2	0.5–0.9
8 Ear length	3–4.3	2.4–3.5
9 Chest circumference	28–38	23–29
10 Internipple distance*	6.5–10	5–6.5
11 Height	47–55	39–47
12 Ratio $\frac{\text{Upper body segment}}{\text{Lower body segment}}$	1.7	...
14 Hand (palm to middle finger)	5.3–7.8	4.1–5.5
15 Ratio of middle finger to hand	0.38–0.48	0.38–0.5
16 Penis (pubic bone to tip of glans)	2.7–4.3	1.8–3.2

*Internipple distance should not exceed 25% of chest circumference.

Figure 33-12. Neonatal measurements.

IMAGING & LABORATORY STUDIES

Radiologic and ultrasonographic examinations can be extremely helpful in the evaluation of dysmorphic infants. In general, films of infants with apparent limb or skeletal anomalies should include views of the skull and

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all of the long bones in addition to frontal and lateral views of the axial skeleton. Chest and abdominal films should be obtained when indicated. The pediatrician should consult a radiologist for further workup. Nuclear scans and imaging by CT, MRI, and ultrasonography are all useful diagnostic tools, but their interpretation in the presence of birth defects may require considerable experience.

Cytogenetic analysis provides specific diagnoses in approximately 5% of dysmorphic infants who survive the newborn period. Chromosome abnormalities are recognized in 10–15% of infants who die. Karyotypes can be determined rapidly through analysis of cells in bone marrow, and through use of FISH. These allow limited interpretation and should always be accompanied by complete analysis of cultured cells. Any case requiring rapid diagnosis should be discussed with an experienced dysmorphologist. A normal karyotype does not rule out the presence of significant genetic disease.

PERINATAL AUTOPSY

When a dysmorphic infant dies, postmortem examination can provide important diagnostic information and should include sampling of tissue for cytogenetic analysis. The pediatrician and the pathologist should consider whether samples of blood, urine, or tissue should be obtained for metabolic analyses.

X-ray studies should be done whenever limb anomalies or disproportionate growth is present. Placental as well as fetal tissue can be used for viral culture. The pediatrician should discuss the case thoroughly with the pathologist, and photographs should always be taken.

Thorogood P: *Embryos, Genes and Birth Defects*. Wiley, 1997.

■ CLINICAL FEATURES OF COMMON GENETIC DISORDERS

CHROMOSOMAL DISORDERS: ABNORMAL NUMBER

ANEUPLOIDY

Trisomy 21 (Down Syndrome)

Down syndrome occurs in about 1:600 newborns; however, the incidence is greater among children of mothers over age 35 years. Mental retardation is characteristic of Down syndrome, with typical intelligence quotients (IQs) between 20 and 80 (mostly between 45 and 55). The principal physical findings include a small, brachycephalic head, characteristic facies (upslanting palpebral fissures, epicanthal folds, midface hypoplasia, and small, dysplastic pinnae) and other dysmorphic features. About one third to one half of children with Down syndrome have congenital heart disease, most often an endocardial cushion defect or other septal defect. Anomalies of the GI tract

are seen in about 15% of cases, including esophageal and duodenal atresias. Generalized hypotonia is common. Sexual development is retarded, especially in males, who are usually sterile. The affected newborn may have prolonged physiologic jaundice, polycythemia, and a transient leukemoid reaction. Later, there is an increased tendency for thyroid dysfunction, hearing loss, celiac disease and atlanto-occipital instability. Leukemia is 12–20 times more common in Down syndrome than in unaffected children.

Trisomy 18 Syndrome

The incidence of trisomy 18 syndrome is about 1:4000 live births, and the ratio of affected males to females is approximately 1:3. Trisomy 18 is characterized by prenatal and postnatal growth retardation which is often severe; hypertonicity; dysmorphic features, including a characteristic face (Figure 33-13) and extremities (overlapping fingers and rockerbottom feet);² and congenital heart disease (often ventricular septal defect or patent ductus arteriosus). Complications are related to associated birth defects. Death is often caused by heart failure or pneumonia and usually occurs in infancy or early childhood, although a small percentage of patients reach adulthood. Surviving children show significant developmental delay and mental retardation.



Figure 33-13. Child with trisomy 18. (For details, see Jones KL: *Smith's Recognizable Patterns of Human Malformation*, 5th ed. Saunders, 1996.)

Trisomy 13 Syndrome

The incidence of trisomy 13 is about 1:12,000 live births, and 60% of affected individuals are female. The mean maternal age is increased. The symptoms and signs include prenatal and postnatal growth deficiency (although, unlike trisomy 18, infants may have a normal birth weight), CNS malformations, arrhinencephaly, eye malformations (anophthalmia, colobomas), cleft lip and palate, polydactyly or syndactyly, and congenital heart disease (usually ventricular septal defect). The facies of an infant with trisomy 13 is shown in Figure 33-14. Surviving children demonstrate failure to thrive, developmental retardation, apneic spells, seizures, and deafness. Death usually occurs in early infancy or by the second year of life, commonly as a

result of heart failure or infection.



Figure 33-14. Child with trisomy 13. (For other abnormal findings, see Jones KL: *Smith's Recognizable Patterns of Human Malformation*, 5th ed. Saunders, 1996.)

Treatment for aneuploidies

There is no convincing documentation of the merit of any of the forms of specific therapy that have been attempted

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in Down syndrome, ranging from megadoses of vitamins to exercise programs proposed to overcome the physical and developmental abnormalities of the syndrome. Therapy is for specific problems: surgery or drugs for heart problems, antibiotics for infections and thyroid function tests, infant stimulation programs, special education, and occupational training as required. The goal of treatment is to help affected children develop to their full potential. Parents' participation in support groups such as the local chapter of the National Down Syndrome Congress (<http://www.ndss.org>) should be encouraged.

There is no treatment, other than general supportive care, for trisomy 13 or 18. Because it is sometimes necessary to decide immediately after birth how extensive therapy should be for a severely malformed infant, trisomy 13 and 18 can be screened for in interphase nuclei of blood lymphocytes by FISH, and confirmed by direct chromosome analysis of blood or bone marrow mitoses. A support group for families of children with trisomies 13 and 18 who survive beyond infancy is called SOFT (www.trisomy.org/).

Genetic Counseling

Most parents of trisomic babies have normal karyotypes. The risk of having a child affected with a trisomy varies with maternal age. For trisomy 21, age-specific risks are 1:2000 for mothers under age 25 years; 1:200 for mothers age 35 years; 1:100 for

mothers age 40; and 1:10 for mothers over age 45 years. The recurrence risk for trisomy in future pregnancies is equal to 1:100 plus the age-specific maternal risk (for example, a 40 year old mother with a prior child with Down syndrome would have a risk of 1:100 for her age, plus 1:100 for her prior history, or 1:50). If the child has a trisomy resulting from a translocation, and the parent has an abnormal karyotype, the risks are increased.

When the mother is the carrier of a balanced 14/21 translocation, there is a 10–15% chance that the child will be affected and a 33% chance that the child will be a balanced

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translocation carrier. When the father is the carrier, there is a < 0.5% chance of having another affected child. If the child has a 21/21 translocation and one parent has the translocation, the recurrence risk is 100%.

The recurrence risks in other trisomies are analogous to those for Down syndrome. The mother's age at the time of conception and the nature of the chromosome abnormality are important in genetic counseling, which is indicated for prevention of all chromosome abnormalities. Prenatal diagnosis is available.

SEX CHROMOSOMES

Turner Syndrome (Monosomy X, gonadal dysgenesis)

The incidence of Turner syndrome is 1:10,000 females. However, it is estimated that 95% of conceptuses with monosomy X are miscarried and only 5% are liveborn. Newborns with Turner syndrome may have webbed neck, edema of the hands and feet, coarctation of the aorta, and a characteristic triangular facies. Later symptoms include short stature, a shield chest with wide-set nipples, streak ovaries, amenorrhea, absence of secondary sex characteristics, and infertility. Some affected girls, particularly those with mosaicism, have only short stature and amenorrhea, without dysmorphic features. Complications relate primarily to coarctation of the aorta, when present. Rarely, the dysgenetic gonads may become neoplastic (gonadoblastoma). The incidence of malformations of the urinary tract is increased. Learning disabilities are common, secondary to difficulties in perceptual motor integration. Patients with pseudohypoparathyroidism and Noonan syndrome have a similar phenotype to patients with Turner syndrome, but have normal chromosomes.

In Turner syndrome the identification and treatment of perceptual problems before they become problematic is very important. Teenage patients need counseling to cope with the stigma of their condition and to understand the need for hormone therapy. Estrogen replacement therapy will permit development of secondary sex characteristics and normal menstruation and prevent osteoporosis. Growth hormone therapy has been used to increase the height of affected girls. Females with 45,X or 45,X mosaicism have a low fertility rate, and those who become pregnant have a high risk of fetal wastage (spontaneous miscarriage, approximately 30%; stillbirth, 6–10%). Furthermore, their liveborn offspring have an increased frequency of chromosome abnormalities involving either sex chromosomes or autosomes, and congenital malformations. Thus prenatal ultrasonography and chromosome analysis are indicated for the offspring of females with sex chromosome abnormalities.

Klinefelter Syndrome (XXY)

The incidence of Klinefelter syndrome in the newborn population is roughly 1:1000, but it is about 1% among mentally retarded males and about 3% among males seen at infertility clinics. The maternal age at birth is often advanced. Unlike Turner syndrome, Klinefelter syndrome is rarely the cause of spontaneous abortions. The diagnosis is rarely made before puberty except as a result of prenatal diagnosis, because prepubertal boys have a normal phenotype. The characteristic findings after puberty include micro-orchidism associated with otherwise normal external genitalia, azoospermia, sterility, gynecomastia, normal to borderline IQ, diminished facial hair, lack of libido and potency, and a tall, eunuchoid build. In chromosome variants with three or four X chromosomes (XXXY and XXXXY), mental retardation may be severe, and radioulnar synostosis may be present as well as anomalies of the external genitalia and cryptorchidism. In the XXXXY cases, these findings are especially prominent, and microcephaly, short stature, and dysmorphic features also occur. In general, the physical and mental abnormalities associated with Klinefelter syndrome increase as the number of sex chromosomes increases. Males with Klinefelter syndrome require testosterone replacement therapy.

XYY Syndrome

Newborns in general are normal. Affected individuals may on occasion exhibit an abnormal behavior pattern from early childhood and may have mild retardation. Fertility may be normal. Many males with an XYY karyotype are normal. There is no treatment. Long-term problems may relate to low IQ and environmental stress.

XXX Syndrome

The incidence of females with an XXX karyotype is approximately 1:1000. Females with XXX are phenotypically normal. However, they tend to be taller than usual, and to have lower IQ's than their normal siblings. Learning and behavioral issues are relatively common. This is in contrast to individuals with XXXX, a much rarer condition causing more severe developmental issues, and a dysmorphic phenotype reminiscent of Down syndrome.

Boman UW et al: Psychological aspects of Turner syndrome. *J Psychosom Obstet Gynaecol* 1998;19:1.

Hovatta O: Pregnancies in women with Turner's syndrome. *Ann Med* 1999;31:106.

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Jones KL: *Smith's Recognizable Patterns of Human Malformation*, 5th ed. Saunders, 1996.

Linden MG, Bender BG, Robinson A: Sex chromosome tetrasomy and pentasomy. *Pediatrics* 1995;96:672.

Smyth CM et al: Klinefelter syndrome. *Arch Intern Med* 1998;158:1309–14.

MOSAICISM

Although most cases of severe chromosomal abnormality such as trisomy are lethal, some individuals may survive if the abnormality exists in mosaic form (ie, the patient

has a mixture of trisomic and normal cells). Two disorders with this condition include:

Trisomy 8 Syndrome

More than 100 cases of this condition have been reported. The phenotype is variable, but includes mildly dysmorphic features (deep-set eyes, hypertelorism, prominent pinnae, high arched or cleft palate), skeletal, cardiac and renal malformations. Cognitively, the individuals have limitations ranging from mild to severe.

Cat-Eye Syndrome

Cat-eye syndrome is caused by an extra chromosome which is derived from a portion of chromosome 22 (the short arm, centromere and a small piece of the long arm). The phenotype consists of iris coloboma (causing the appearance of the eye lending its name to the syndrome), dysmorphic features (down-slanting palpebral fissures, malformed pinnae), and anal atresia. Other common anomalies include those of the heart, kidneys and GI tract. Intelligence is usually mildly impaired, but may be normal.

CHROMOSOMAL ABNORMALITIES: STRUCTURAL

Chromosomal abnormalities are most often present in newborns as multiple congenital anomalies in association with intrauterine growth retardation. Common aneuploid syndromes (trisomies 13, 18, and 21) have been described earlier in this chapter. There are several common chromosomal deletions producing contiguous gene syndromes recognizable in newborns. In the presence of apparently normal chromosomes, each of these conditions can be detected by FISH.

Wolf-Hirschhorn Syndrome

Also known as 4p- (deletion of 4p16), this syndrome is characterized by microcephaly and unusual development of the nose and orbits that produces an appearance suggesting an ancient Greek warrior's helmet. Association with cleft lip and palate and other major organ anomalies such as heart and renal structural anomalies and seizure disorders, are common. The majority of the patients have severe developmental delay and mental retardation. However, higher functioning individuals have been reported. There is a critical region that defines the facial features of this syndrome and is detectable by FISH.

Cri Du Chat Syndrome

Also known as 5p- (deletion of terminal chromosome 5p), this disorder is characterized by unique facial features, growth retardation, and microcephaly. Patients have an unusual cat-like cry. Most patients have major organ anomalies and significant developmental delay.

Williams Syndrome

This, a contiguous gene disorder involving the elastin gene and other neighboring genes at 7q11.2, is characterized by short stature, congenital heart disease (supravalvular aortic stenosis), coarse, elfin-like facies with prominent lips, hypercalcemia or hypercalciuria in infancy, developmental delay, and neonatal irritability evolving into an overly friendly personality. Microdeletions of the elastin gene

are diagnostic through FISH testing which is widely available. However, individuals with smaller deletions require more specific probes to confirm the diagnosis. Calcium restriction may be necessary in early childhood to prevent nephrocalcinosis. Calcium determination is recommended in early infancy, and the hypercalcemia often resolves during the first year of life. The natural history includes progression of cardiac disease and predisposition to hypertension and spinal osteoarthritis in adults. Most patients have mild to moderate intellectual deficits.

Langer-Giedion Syndrome

This syndrome, also known as trichorhinophalangeal syndrome type II, is caused by a deletion on the long arm of chromosome 8 (8q24.11-q24.13). Individuals with Langer-Giedion syndrome show unusual facial features (large, bulbous nose, large ears), and develop bony abnormalities including cone-shaped epiphyses and multiple bony exostoses. The skin may be loose and redundant, resembling the connective tissue disorder, Ehlers-Danlos syndrome. Intelligence is impaired and hearing loss is common.

Aniridia-Wilms Tumor Association (WAGR)

This syndrome is caused by a deletion of the short arm of chromosome 11 (11p13). In addition to the aniridia,

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other common eye defects include cataracts and ptosis. Many patients have visual impairment. About ½ of patients develop Wilms tumor. Other anomalies include facial dysmorphism and genitourinary abnormalities. The acronym WAGR stands for **W**ilm's tumor, **a**niridia, **g**enitourinary anomalies, and **r**etardation.

Miller-Dieker Syndrome

A contiguous gene syndrome involving 17p13, this abnormality is characterized by microcephaly and severe CNS dysgenesis. The most commonly seen CNS malformation is termed *lissencephaly* ("smooth brain" as the brain is lacking its normal convolutions and gyri). An unusually developed face and forehead reflect abnormal migration of neuronal germinal matrix cells. When the affected individuals cry, there are longitudinal grooves in the forehead, which is characteristic. Mutations in the gene MDS1, which is located in the critical region, can cause isolated lissencephaly, without the full picture of Miller-Dieker. Severe cognitive and developmental delay and seizure disorders are common. In the presence of apparently normal chromosomes, FISH can detect this condition.

Smith-Magenis Syndrome

This syndrome is associated with microdeletion of 17p11, and is characterized by prominent forehead, deep set eyes, cupid-shaped upper lip, self-mutilating behavior (pulling nails, hair and putting objects into body orifices), sleep disturbance, and developmental delay. Some patients also have seizure disorders. Melatonin has proven helpful in improving the abnormal sleep patterns, and controlling the behavior. Some individuals with larger deletions involving PMP22 can present with peripheral neuropathy.

Del 22q11 Syndrome

Also known as DiGeorge syndrome, this abnormality was originally described in newborns presenting with cyanotic congenital heart disease, usually involving great vessel abnormalities; thymic hypoplasia leading to immunodeficiency; and hypocalcemia due to absent parathyroid glands. The disorder is now known to result most often from deletions of chromosome 22q11 and to be phenotypically highly variable. The less severe phenotypes include velocardiofacial syndrome (VCFS), Shprintzen syndrome, Cayler cardiofacial syndrome, and a subset of Opitz and BBB syndromes. Characteristics include mild microcephaly; palatal clefting or incompetence; speech and language delays; congenital heart disease (ventricular or atrial septal defect); buildup of tissue lateral to the nose; long, tapering fingers; and emotional lability. Midline defects such as umbilical hernia, and hypospadias can be associated anomalies. In some cases, individuals have an apparent predisposition to psychosis.

MENDELIAN DISORDERS

AUTOSOMAL DOMINANT INHERITANCE

Neurofibromatosis Type 1



Essentials of Diagnosis & TYPICAL FEATURES

Minimal diagnostic criteria require two or more of the following:

- *Six or more café au lait macules, at least 15 mm in diameter in postpubertal and 5 mm in prepubertal individuals.*
- *Two or more neurofibromas of any type or one plexiform neurofibroma.*
- *Axillary or inguinal freckling.*
- *Two or more Lisch nodules (iris hamartomas)*
- *Optic glioma*
- *Distinctive bony lesions such as sphenoid dysplasia or pseudarthrosis.*
- *An affected first-degree relative.*

GENERAL CONSIDERATIONS

Neurofibromatosis 1 is one of the most common autosomal dominant disorders, occurring in 1:3000 births and seen in all races and ethnic groups. It has a wide range of clinical manifestations. In general, the disorder is progressive, and new manifestations appear over time. Neurofibromatosis 2, characterized by bilateral acoustic neuromas, with minimal or no skin manifestations is a different disease caused by a different gene.

CLINICAL FINDINGS

Café au lait macules may be present at birth, and about 80% of individuals with neurofibromatosis 1 will have more than 6 by age 1 year. The typical skin lesion is 10-30 mm, ovoid, and smooth-bordered, but there is great variation. Neurofibromas are benign tumors consisting of Schwann cells, nerve fibers, and fibroblasts; they may be discrete or plexiform. Discrete tumors are more common and can occur at any age. They are well demarcated and can present in cutaneous, subcutaneous,

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or internal tissues. Plexiform neurofibromas are more diffuse and can invade normal tissue. They are congenital and are frequently detected during periods of rapid growth. If the face or a limb is involved, there may be associated hypertrophy or overgrowth. The incidence of Lisch nodules, which can be seen with a slit lamp, also increases with age.

Common features of affected individuals include a large head (though only a small percentage have true hydrocephalus), bony abnormalities on x-ray studies, scoliosis, and a wide spectrum of developmental problems. The most common problems in childhood are secondary to plexiform neurofibromas, and learning disabilities. Although the average IQ is within the normal range, it is lower than in unaffected family members. The learning problems seem to be specific and involve a visual perception disability that could lead to difficulties in reading and writing or to behavioral impulsivity.

DIFFERENTIAL DIAGNOSIS

Areas of hyperpigmentation can occur in other conditions (e.g., Albright, Noonan, and Leopard syndromes), but the lesions are either single or different in character. Isolated neurofibromas and familial café au lait spots as an autosomal dominant trait (fewer than six and with no other manifestations of neurofibromatosis) have been described. The relationship of such cases to classic neurofibromatosis type 1 is uncertain.

COMPLICATIONS

It is difficult to differentiate a complication from a rare manifestation of the underlying disorder. Seizures, deafness, short stature, early puberty, and hypertension occur in less than 25% of persons with neurofibromatosis. Optic glioma seems to occur in about 15% of individuals with neurofibromatosis 1. Although the tumor may be apparent at an early age, it rarely causes functional problems and is usually nonprogressive. Patients have a slightly increased risk (5% life risk) for a variety of malignancies. Other tumors may be benign but may cause significant morbidity and mortality because of their size and location in a vital or enclosed space.

TREATMENT

The therapy is symptomatic. Neurofibromas can be removed if they cause discomfort or are a cosmetic problem. The most important part of therapy is close, ongoing follow-up. Because this disorder is progressive, affected individuals should be seen at regular intervals and have regular monitoring of height, head circumference, blood pressure, and scoliosis. Additionally, eye examinations are necessary for early detection of changes associated with aggressive optic glioma. Developmental screening as well as

other evaluations (eg, magnetic resonance imaging [MRI] scans) are done as indicated according to symptoms. Follow-up is best done in a multidisciplinary neurocutaneous clinic.

PROGNOSIS

Because there is such variability in neurofibromatosis, it is difficult to assess the prognosis. However, most affected children have only skin lesions and few other problems. Severely affected individuals are rare in the pediatric age range, and close follow-up and early intervention may ameliorate some complications.

GENETIC COUNSELING

The gene for neurofibromatosis 1 is on the long arm of chromosome 17 and seems to code for a protein similar to a tumor suppressor factor. Neurofibromatosis results from many different mutations of this gene. Approximately 50% of all cases of neurofibromatosis are caused by new mutations. Before attributing an individual case to a new mutation, however, both parents must be evaluated carefully, including a thorough examination of the skin and a slit-lamp examination to look for Lisch nodules. Recent evidence suggests that penetrance is close to 100% in those who carry the gene if individuals are examined carefully.

Gutmann DH et al: The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997;278:51.

Marfan Syndrome

Marfan syndrome is caused by mutations in genes coding for the connective tissue protein fibrillin, but laboratory detection of mutations in clinical practice remains, for the time being, difficult. Clinical diagnostic criteria have been developed that include disproportionate growth (arachnodactyly and tall stature), joint hyperextensibility, lens dislocation, and dilation of the aortic root. The latter two characteristics are considered major criteria and are diagnostic when accompanied by evidence of connective tissue involvement, usually joint hyperextensibility. The characteristic facies is long and thin, with down-slanting palpebral fissures. The palate is high arched and dentition is often crowded. The most serious associated medical problems involve the heart. Many patients with Marfan syndrome have mitral valve prolapse. A potentially life-threatening cardiac problem is progressive aortic root dilatation, which may lead to aneurysmal rupture and death.

The diagnosis of Marfan syndrome is still made on a clinical basis and many cases represent sporadic new mutations. Although the gene for fibrillin has been

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identified, there are many unique, family-specific mutations, making molecular confirmation difficult.

Medical management for patients with Marfan syndrome includes appropriate management of the ophthalmologic, orthopedic, and cardiac issues. Serial echocardiograms are indicated to diagnose and follow the degree of aortic root enlargement, which can be managed medically and surgically in more severe cases. In individuals with Marfanoid habitus and cognitive disabilities, homocystinuria should be excluded through careful metabolic testing. Another connective tissue disorder, Ehlers-

Danlos syndrome (EDS), shares some features with Marfan syndrome, including joint hyperextensibility and skin fragility. The skin is the target organ for the most significant symptoms in EDS patients. There are at least 9 forms of EDS, most inherited as dominant traits, but the biochemical causes have only been worked out for a few of the forms.

Achondroplasia

Achondroplasia is the most common form of skeletal dysplasia, like many forms of skeletal dysplasias, is inherited as a dominant condition, and is caused by a mutation in fibroblast growth factor receptor (FGFR) 3. The classic phenotype includes relative macrocephaly, midface hypoplasia, short-limbed dwarfism, and trident-shaped hands. The phenotype is apparent at birth, and may be diagnosed prenatally on ultrasound. Individuals with achondroplasia are cognitively normal. Bony overgrowth at the level of the foramen magnum may lead to progressive hydrocephalus, and may warrant neurosurgical intervention. Because of this, head circumference during infancy must be closely monitored and plotted on a diagnosis-specific head circumference chart. Serial head ultrasounds are helpful every few months. Orthopedic intervention is necessary for spinal problems including severe lumbar lordosis, and gibbus deformity. Long bone lengthening procedures, such as the *Ilizaroff* are used in some centers to increase height and upper extremity function, but their use is still controversial. Two hemizygous parents with achondroplasia have a 25% risk of having a child homozygous for FGFR 3 mutations, which is a lethal disorder.

Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI), or brittle bone disease, is a relatively common autosomal dominant disorder, caused by mutations in Type I collagen. Most patients with more severe disease represent new mutations for this disorder. There are 4 types of OI. Types I and IV are relatively mild, and generally present with increased incidence of fracturing, but otherwise a fairly normal phenotype. Type II is generally lethal in the newborn period, and is the most severe form. Formerly believed to be autosomal recessive, Type II is now thought to be caused by a new dominant mutation, with multiple cases within a family attributed to parental germ cell mosaicism. Type III is the severe form causing significant bony deformity secondary to multiple fractures. A major breakthrough in the management of OI patients has been the use of *Pamidronate*, a bisphosphonate compound, which has been reported to lead to a reduced incidence of fracture, and improvement in bone density.

Craniosynostoses Syndromes

The craniosynostosis disorders are common dominant disorders associated with premature fusion of cranial sutures. This class of disorders is now known to be caused by mutations in FGFR genes. Crouzon syndrome is the most common of these disorders, and is associated with multiple suture fusions, but with normal limbs. Common problems associated with craniosynostosis include shallow orbits leading to proptosis, midface narrowing that may result in upper airway obstruction, and hydrocephalus that may require shunting. Children with craniosynostosis undergo multiple staged craniofacial/neurosurgical procedures to address these issues. Other craniosynostosis disorders have limb as well as craniofacial anomalies, and include Pfeiffer syndrome, Apert syndrome, Jackson-Weiss syndrome, and Saethre-Chotzen

syndrome.

Treacher-Collins Syndrome

Treacher-Collins Syndrome is a dominant disorder, although more than ½ of the patients represent new mutations. This is a craniofacial disorder associated with malar and mandibular hypoplasia, malformed ears with associated hearing loss, and abnormalities of the eye including lower lid coloboma and absent lashes. There may be airway anomalies causing life-threatening problems in the newborn period. Intelligence is generally normal. This disorder has been linked to chromosome 5q32-33.2 in some families.

AUTOSOMAL RECESSIVE DISORDERS

Cystic Fibrosis

The gene for cystic fibrosis is CFTR on the long arm of chromosome 7. Approximately 1 in 22 persons are carriers. Over 600 different mutations have been identified: the most common in the Caucasian population, known as $\Delta F 508$, is a three-base deletion coding for phenylalanine.

Cloning of the gene for cystic fibrosis and identification of the mutation in the majority of cases has completely

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changed genetic counseling and prenatal diagnosis for this disorder, although the sweat chloride assay is still important in confirming the diagnosis. The American College of Medical Genetics recommends the 25-mutation assay by PCR based techniques, which can cover 85–90% of the mutations. If a mutation is found, carriers can be identified and specific prenatal diagnosis can be performed, identifying both carriers and affected fetuses. If a mutation cannot be identified, linkage analysis, DNA haplotyping, and amniotic fluid enzyme studies can be done.

The identification of the mutation in the cystic fibrosis gene has also raised the issue of mass newborn screening, because of the high frequency of this gene in the Caucasian population. Some states, such as Colorado, have offered newborn screening by trypsinogen assay, which can detect 70% of CF patients. While the argument exists for such screening (as early detection can ensure good nutritional status starting at birth, which is the key prognostic factor for the classic CF patient), newborn screening is controversial as there is no cure for CF. (For more details of medical management, please see the Pulmonology and GI chapters in this text).

Shrimpton AE et al: Cystic fibrosis mutation frequencies in upstate New York. Hum Mutat 1997;10(6):436.

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome (SLOS), a common autosomal recessive disorder, may have an incidence as high as 1:8000, and the carrier frequency may be as high as 1:31. In 1994, SLOS was shown to be caused by a metabolic error in the final step of cholesterol production. This enzyme deficiency results in low cholesterol levels, and accumulation of the precursor, 7-dehydrocholesterol. Patients with SLOS present with a characteristic phenotype including dysmorphic facial features (Figure 33-15), multiple

congenital anomalies (including defects of the CNS, heart, cleft palate, cardiac, kidneys, genitalia and limbs), hypotonia, growth failure, and mental retardation. Treatment with cholesterol can ameliorate the growth failure and lead to improvement in behavior and developmental course, although treatment does not cure this complex disorder.



Figure 33-15. Child with Smith-Lemli-Opitz syndrome, featuring bitemporal narrowing, upturned nares, ptosis, and small chin.

Sensorineural Hearing Loss (SNHL)

Nonsyndromic, recessively inherited deafness is the predominant form of severe inherited childhood deafness. There is marked genetic heterogeneity in causes of sensorineural hearing loss (SNHL), including autosomal dominant, recessive, and X-linked patterns. Of mutations known to cause SNHL, mutations of connexin 26 (CX26), a gap junction protein, are present in 49% of cases of prelingual deafness. Gap junctions are regionally specialized structures on plasma membranes of contacting adherent cells. These structures were shown to consist of cell-to-cell channels. Connexins are the proteins in the gap junctions. There are different kinds of connexins. Some mutations of connexin 26 can follow autosomal dominant inheritance, but the common mutations follow the recessive mode. Molecular testing is available.

Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder in which anterior horn cells in the spinal cord degenerate. The molecular basis for loss of these cells is incompletely understood, but the mechanism appears to involve apoptosis of neurons in the absence of the product of the *SMN 1* (Survival Motor neuron) gene located on chromosome 5q. Loss of anterior horn cells leads to progressive atrophy of

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skeletal muscle. The disorder has an incidence of approximately 1 in 12,000 with the majority of the cases presenting in infancy. Carrier frequencies approach 1 in 50 in populations with European ancestry. Three clinical phenotypes are recognized based on age of onset and rate of progression. *SMA 1* is the most devastating. Mild weakness

may be present at birth, but is clearly evident by 3 months and is accompanied by loss of reflexes. Progression of the disorder leads to fasciculations and eventual respiratory failure, usually by age 1 year. Symptoms of *SMA II* begin later; with weakness and decreased reflexes generally apparent by 2 years of age. Children affected with *SMA III* begin to become weak as they approach adolescence.

The genetics of SMA are complex and relate to duplication, deletion, and gene conversion events in the region of the *SMN 1* gene. Homozygous deletion of exon 7 is detectable in more than 90% of all forms of SMA and constitutes a genetic test by which the clinical diagnosis can be confirmed. Variability in presentation appears to involve expression of neighboring genes including a more centromeric *SMN 2* pseudogene. The presence and expression of multiple copies of *SMN 2*, and a nearly complete copy of *SMN 1*, introduces complexity into molecular genetic analysis used to detect carriers. Prenatal diagnosis is available through analysis of *SMN 1* or genetic linkage, but carrier testing in individuals not related to affected patients known to have homozygous *SMN 1* deletions is not yet available.

Metabolic Disorders

Most inborn errors of metabolism are inherited in an autosomal recessive pattern. See the previous chapter in this text on metabolic disorders for detailed explanations of these disorders.

X-LINKED INHERITANCE

Duchenne-Type Muscular Dystrophy

Duchenne muscular dystrophy (DMD) results from failure of synthesis of the muscle cytoskeletal protein, dystrophin, whose gene is located on the X chromosome, Xp12. Approximately 1 in 4,000 male children are affected. Mutations in the same gene that result in partial expression of the dystrophin protein produce a less severe phenotype, Becker muscular dystrophy (BMD). In both disorders, there is progressive degeneration of skeletal muscle. Cardiac muscle eventually also becomes involved. Boys with DMD exhibit proximal muscle weakness and pseudohypertrophy of calf muscles at age 5–6 years. Patients become non-ambulatory at around age 13. Serum CK levels are markedly elevated. Affected boys frequently die in their early 20s of respiratory failure and cardiac dysfunction. The prognosis for Becker muscular dystrophy is more variable. Although corticosteroids are useful in maintaining strength, they do not slow progression of the disorder.

The gene for dystrophin is very large and a common target for mutation. Large deletions or duplications can be detected in the gene for dystrophin in 65% of cases. Demonstration of such a mutation provides a useful genetic marker for the disorder, but diagnosis and prognosis require muscle biopsy and immunohistochemistry for the dystrophin protein.

Theoretically, one-third of DMD cases presenting with a negative family history are likely to be new mutations. When a mutation in the gene for dystrophin is detected, maternal carrier status is easily determined and work-up of the extended family is straightforward. Nonetheless, risk assessment and counseling must be approached with care since germ line mosaicism for mutations in the gene for Dystrophin occurs in approximately 15% of families. Thus, it is necessary to look for mutations in all sisters

of affected boys. If a mutation has been detected, prenatal diagnosis is routinely offered to mothers regardless of their apparent carrier status based on analysis of blood samples. Since mutations are currently not detected in approximately 35% of cases, alternative approaches that estimate carrier risks based on CK levels and utilize genetic linkage for prenatal diagnosis remain useful. Counseling and prenatal diagnosis remain difficult in some families.

Hemophilia

Hemophilia A is an X-linked, recessive, bleeding disorder caused by a deficiency in the activity of coagulation factor VIII. Affected individuals develop a variable phenotype of hemorrhage into joints and muscles, easy bruising, and prolonged bleeding from wounds. The disorder is caused by heterogeneous mutations in the factor VIII gene, which maps to Xq28. Carrier detection and prenatal diagnosis can be done by direct detection of selected mutations, especially the inversions, the most common gene change, as well as indirectly by linkage analysis. Replacement of factor VIII is done using a variety of preparations derived from human plasma or recombinant techniques. While replacement therapy is effective in most cases, 10–15% of treated individuals develop neutralizing antibodies that decrease its effectiveness.

Alport Syndrome

Alport syndrome is characterized by variable degrees of hearing loss and nephropathy. It is a clinically heterogeneous disease and at least 6 different variants have been reported. The most common type is X-linked due to

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mutations in the gene coding for the alpha chain of type IV collagen. Female carriers with Collagen IVA5 mutations may manifest mild clinical findings such as hematuria and later onset hearing loss. Affected males usually develop end stage renal disease. Molecular testing for affected males is available but no single test is available for female carriers.

Metabolic Disorders

Some important inborn errors are inherited as X-linked disorders, such as adrenoleukodystrophy. See the chapter on Metabolic Disorders in this text for more detailed descriptions.

NONMENDELIAN INHERITANCE

DISORDERS OF IMPRINTING

Beckwith-Wiedemann Syndrome

The association of macrosomia (enlarged body size), macroglossia (enlarged tongue), and omphalocele, constitutes the Beckwith-Wiedemann syndrome, now known to be related to abnormal expression of genes located at chromosome 11p15. Other associated findings include mild facial dysmorphism (hypertelorism, unusual ear creases), infantile hypoglycemia due to transient hyperinsulinemia, multiple congenital anomalies (cleft palate and genitourinary anomalies common) and increased risk for certain malignancies, especially Wilms tumor (7–10%). A growth factor gene, *IGF2* is

normally imprinted such that the maternal allele is ordinarily not expressed during intrauterine development. Chromosomal abnormalities affecting expression of this gene, such as duplication of the paternal 11p15 region, are associated with BWS. Paternal UPD leading to duplication of transcription of IGF-2 on the paternal homolog, with loss of a tumor suppressor gene (H19) normally read from the maternal homolog, may lead to the macrosomia and an increased predisposition to cancer seen in this disorder. Supporting the role of imprinting in BWS is that paternal imprinting has been documented in about 10% of BWS patients, and that about 70% of Wilm's tumors from BWS patients show loss of imprinting (LOI) of the genes coding for IGF-2 and H19. Children affected with this condition should undergo ultrasound surveillance for abdominal tumors every 3 months until they are age 7 years.

Prader-Willi Syndrome

Prader-Willi syndrome results from lack of expression of a number of imprinted genes, including SNRPn, located on chromosome 15q11. Clinical characteristics include severe hypotonia in infancy that often necessitates placement of a feeding gastrostomy tube. In older children, characteristic facies become obvious, with almond-shaped eyes, and frequent strabismus. Short stature, obesity, hypogenitalism, and small hands and feet with tapering fingers are now believed to be associated with growth hormone deficiency. Obsessive hyperphagia (usual onset 3-4 years), and type 2 (adult-onset) diabetes mellitus are common features.

Multiple chromosomal rearrangements and mutations have been reported to disrupt expression of the genes that contribute to this syndrome. Of these, deletion of paternal chromosome 15q11 is the most common, followed by maternal uniparental disomy. Molecular techniques that analyze patterns of methylation of involved DNA sequences provide a practical approach to diagnosis whenever there is clinical suspicion. But additional studies (eg, FISH) to determine the genetic mechanisms responsible are necessary in confirmed cases, for reproductive risk counseling.

Angelman Syndrome

Angelman syndrome also involves imprinting and results from a variety of mutations that inactivate a ubiquitin-protein ligase gene, UBE3A, located in the same region of chromosome 15 as SNRPn, the maternally imprinted gene involved in Prader-Willi syndrome (see above). UBE3A is paternally imprinted, and during normal development the maternal allele is expressed only in the brain. The classic phenotype includes severe mental retardation with prognathism, seizures, and marked delay in motor milestones, abnormal puppet-like gait and posturing, poor language development, and paroxysmal laughter and tongue thrusting.

Angelman syndrome is most commonly caused when sequences detectable by FISH on 15q11 are deleted from the maternal homologue. Uniparental paternal disomy 15 is the least common cause. Mutations in UBE3A cause the disorder in perhaps one fourth of cases.

With additional studies of mutations in the gene responsible for this syndrome, it is possible that its clinical description will be expanded to include less severely delayed individuals. Recurrence is possible when mothers carry mutations that are paternally imprinted and therefore silent until they are passed on as nonimprinted alleles.

UPD 7

Certain genes on chromosome 7 are now known to be imprinted. UPD 7 has been reported to cause cystic fibrosis in a child who inherited two copies of the $\Delta F 508$ deletion from one parent. That child also had

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Russell-Silver syndrome, a syndrome associated with intrauterine growth failure and dwarfism. Imprinting abnormalities and UPD may prove to be associated with growth abnormalities.

Elias ER, DeBaun MR, Feinberg AP: Beckwith-Wiedemann syndrome. In Jameson JL (editor): *Principles of Molecular Medicine*, Humana Press, 1998.

DISORDERS ASSOCIATED WITH ANTICIPATION**(Autosomal dominant) MYOTONIC DYSTROPHY**

Internists are most likely to encounter families with myotonic dystrophy, a condition characterized by muscle weakness and tonic muscle spasms (myotonia) along with hypogonadism, frontal balding, cardiac conduction abnormalities, and cataracts. It is unclear how many genes are involved in this disorder. The critical region is on chromosome 19, where an amplified trinucleotide repeat (CTG) occurs in the 3-prime untranslated region of a protein kinase gene. Normal individuals have from 5 to 30 CTG repeat copies. Repeat copies greater than 50 are meiotically unstable, but individuals carrying this number of repeats may be only mildly affected (eg, cataracts). Most individuals with repeat copies greater than 100 will have symptoms or electrical myotonia as adults. However, as copy numbers approach approximately 400, symptoms become evident in children. Expansion can progress to greater than 1000 copies and in doing so produce fetal and neonatal disease that is often lethal. As the copy numbers enlarge from generation to generation, they become more unstable through meiosis. Dramatic expansion from approximately 200 to 400 repeat copies producing mild, often clinically undetected symptoms to very large copy numbers (800–2000) associated with fetal manifestations (polyhydramnios and arthrogryposis) occur frequently when the expanded repeat copies are passed through female, but not male, meiosis. Therefore, an important component in the workup of the floppy infant is a careful neurologic assessment of the mother for evidence of weakness or myotonia. Diagnostic molecular testing which measures the number of CTG repeats is now available.

(Autosomal recessive) FRIEDREICH'S ATAXIA

Symptoms include progressive incoordination (cerebellar dysfunction) with both motor and sensory findings beginning in preadolescence and typically advancing through the teenage years. The gene involved, *FRDA*, is located on chromosome 9. Normal individuals carry 7 to 22 GAA repeats at this locus. Close to 75% of affected patients are homozygous for repeat expansions having greater than 200 copies. Point mutations in the gene also occur. Meiotic instability of this repeat sequence is more variable than are others. Contractions occur more frequently than do expansions. Relationships between genotype and phenotype are also more complex. Molecular diagnostic testing requires careful interpretation with respect to prognosis and reproductive risks.

(X-linked) FRAGILE X SYNDROME

Fragile X syndrome, present in approximately 1 in 1000 males, is the most common cause of mental retardation in males. The responsible gene is *FMR-1*, which has unstable CGG repeats at the 5' end. Normal individuals have up to 55 CGG repeats. Individuals with 55–200 CGG repeats have a *premutation*, and are generally phenotypically normal. Affected individuals with fragile X syndrome (full mutation) have greater than 200 CGG repeats, and also have hypermethylation of both the CGG expansion, and an adjacent CpG island. This methylation turns off the FMR-1 gene. DNA analysis, rather than cytogenetic testing, is the method of choice for confirming the diagnosis of fragile X syndrome.

Most males with fragile X syndrome present with mental retardation, oblong face with large ears, and large testicles, especially after puberty. Other physical signs include symptoms suggestive of a connective tissue disorder (eg, hyperextensible joints, mitral valve prolapse). Many affected individuals are hyperactive and exhibit infantile autism or autistic-like behavior. Some males with the abnormal gene are of normal phenotype.

In contrast, about one half of females with the fragile X full mutation show normal intelligence, but often evidence learning disabilities and behavioral problems. About one half of females with the full mutation have lower IQ's in the range of mental retardation, and more severe behavioral problems. Females have more mild phenotypic changes than the males. There is a difference in the clinical expression of fragile X in male and female offspring depending on which parent is transmitting the gene. The premutation can change into the full mutation only when passed through a female. Identification of the abnormal DNA amplification by direct DNA analysis can confirm the diagnosis of fragile X in an affected individual, and can detect asymptomatic gene carriers of both sexes. Therefore, DNA analysis is a reliable test for prenatal and postnatal diagnosis of fragile X syndrome and facilitates genetic counseling.

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de Vries BB et al: The fragile X syndrome. *J Med Genet* 1998; 35:579.

Pimentel MM: Fragile X syndrome. *Int J Mol Med* 1999;3:639.

DISORDERS ASSOCIATED WITH MITOCHONDRIAL INHERITANCE

According to a special Mitochondrial issue of the *Seminars in Medical Genetics*, published in the *American Journal of Medical Genetics*, Spring of 2001, there are now more than 100 known point mutations and rearrangements of mtDNA identified, which cause a large number of human diseases. Symptoms of the mitochondrial disorders are secondary to deficiency in the respiratory chain enzymes of oxidative phosphorylation, which supply energy to all cells. Mitochondrial diseases are progressive disorders with neurologic dysfunction including hypotonia, developmental delay, and seizures. Ophthalmologic issues, hearing loss, GI tract dysfunction with growth failure, renal, endocrine, cardiac and autonomic dysfunction are some of the many issues which can affect patients with mitochondrial diseases. The following disorders are three of the more common ones.

MELAS

MELAS is an acronym for Mitochondrial Encephalopathy, Lactic Acidosis, and Strokelike episodes. Symptoms occur in the pediatric age group and include recurrent episodes resembling stroke (blindness, paralysis), headache, vomiting, weakness of proximal muscles, and elevated blood lactate. (**Note:** lactate may be falsely elevated secondary to technical difficulties in obtaining the blood specimen that needs to be free-flowing, or delay in laboratory measurement.) The most common mutation causing MELAS is in the tRNA^{Leu} gene (A3243G).

MERRF

MERRF is an acronym for Myoclonus Epilepsy with Ragged Red Fibers. Children with MERRF present with a variety of neurologic symptoms including myoclonus, deafness, weakness of muscles, and seizures. Eighty percent of cases are due to a missense mutation in the mitochondrial tRNA^{Lys} gene (A8344G).

LEIGH SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY

Multiple different abnormalities in respiratory chain function lead to Leigh's disease, which is a very severe disorder associated with progressive loss of developmental milestones associated with extrapyramidal symptoms, and brainstem dysfunction. Episodes of deterioration are frequently associated with an intercurrent febrile illness. Symptoms include hypotonia, unusual choreoathetoid hand movements, feeding dysfunction with failure to thrive, and seizures. Focal necrotic lesions of the brainstem and thalamus are hallmarks on MRI scan. Mitochondrial mutations affecting the respiratory chain, especially complexes I, II and IV, and nuclear DNA mutations affecting Complex II have been identified as causing Leigh's.

DiMauro S, Schon EA: Mitochondrial DNA mutations in human disease. *Am J Med Genet* 2001;106 (#1):18–26.

Korf B: Molecular medicine: Molecular diagnosis. (Two parts.) *N Engl J Med* 1995;332:1218, 1499.

Munnich A, Rustin P 2001 Clinical Spectrum and Diagnosis of Mitochondrial disorders. *Am J Med Genet* 106 (#1):4–17.

Nehring WM et al: Clinical genetics: An overview. *J Cardiovasc Nurs* 1999;13(4):19.

Warner TT et al: Genetic counselling in mitochondrial diseases. *Curr Opin Neurol* 1997;10(5):40.

MULTIFACTORIAL INHERITANCE

CLEFT LIP & CLEFT PALATE

From a genetic standpoint, cleft lip with or without cleft palate is distinct from isolated cleft palate. The former is more common in males, the latter in females. Although both can occur in a single family, particularly in association with certain syndromes, this pattern is unusual. There is racial variation in the incidence of facial clefting. Among Asians, whites, and blacks, the incidence is 1.61, 0.9, and 0.31, respectively, per 1000 live births.

Clinical Findings

A cleft lip may be unilateral or bilateral and complete or incomplete. It may occur with a cleft of the entire palate or just the primary (anterior and gingival ridge) or secondary (posterior) palate. An isolated cleft palate can involve only the soft palate or both the soft and hard palates. It can be a V-shaped or wide horseshoe cleft. When the cleft palate is associated with micrognathia and glossoptosis (a tongue that falls back and causes respiratory or feeding problems), it is called the Pierre Robin Sequence. Among individuals with facial clefts—more commonly those with isolated cleft palate—there is an increased incidence of other congenital abnormalities. The incidence of congenital heart disease, for example, is between 1–2% in liveborn infants, but among those with Pierre Robin sequence it can be as high as 15%. Associated abnormalities should be looked for in the period immediately after birth and before surgery.

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Differential Diagnosis

A facial cleft may occur in many different circumstances. It may be an isolated abnormality or part of a more generalized syndrome. Prognosis, management, and accurate determination of recurrence risks all depend on accurate diagnosis. In evaluating a child with a facial cleft, the physician must determine if the cleft is nonsyndromic or syndromic.

NONSYNDROMIC

In the past, nonsyndromic cleft lip or cleft palate has been considered a classic example of polygenic or multifactorial inheritance. More recently, however, this mode of inheritance has been questioned, and several studies have suggested one or more major autosomal loci, both recessive and dominant or co-dominant. Empirically, however, the recurrence risk is still in the range of 2–3% because of nonpenetrance or the presence of other contributing genes.

SYNDROMIC (TABLE 33-3)

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Environmental

Maternal seizures, anticonvulsant usage (CL/CP or CP)
 Fetal alcohol syndrome (CP)
 Amniotic band syndrome (CL/CP)

Chromosomal

Trisomies 13 and 18 (CL/CP)
 Wolf-Hirschorn or 4p- syndrome (CL/CP)
 Shprintzen or 22q11.2 deletion syndrome (CP)

Single-gene disorders

Van der Woude syndrome, AD (CL/CP or CP)
 Treacher Collins syndrome, AD (CP)
 Stickler syndrome, AD (CP)
 Smith-Lemli-Opitz, AR (CP)²

Unknown etiology

Möbius syndrome (CP)
 Cornelia de Lange syndrome (CP)

¹AD = autosomal dominant.

²AR = autosomal recessive.

Table 33-3. Syndromic isolated cleft palate (CP) and cleft lip with or without cleft palate (CL/CP).

Cleft lip, with or without cleft palate, and isolated cleft palate may occur in a variety of syndromes that may be environmental, chromosomal, single-gene, or of unknown origin. Prognosis and accurate recurrence risks depend on the correct diagnosis.

Complications & Treatment

Problems associated with facial clefts include early feeding difficulties, which may be severe; recurrent serous otitis media associated with fluctuating hearing and language delays; speech problems, including hypernasality and articulation errors; and dental and orthodontic complications. Long-term management ideally should be through a multidisciplinary cleft palate clinic.

Genetic Counseling

Accurate counseling depends on accurate diagnosis and the differentiation of syndromic from nonsyndromic clefts. A complete family history must be taken, and the patient and both parents must be examined. The choice of laboratory studies is guided by the presence of other abnormalities and clinical suspicions. They may include chromosome analysis, including FISH, eye examination, and x-ray studies. When the risk for a facial cleft is known to be increased, clefts of both the lip and the palate have been sought and detected on ultrasound prenatally. Otherwise, intrauterine diagnosis of clefts is more likely to be established in syndromes in which the identification of other more serious abnormalities prompts the examiner to perform very detailed visualization of all organs.

NEURAL TUBE DEFECTS

Neural tube defects comprise a variety of malformations, including anencephaly, encephalocele, spina bifida or myelomeningocele, sacral agenesis, sacral lipomas, and

other spinal dysraphisms. Recent research suggests that the neural tube develops via closure at multiple rather than just two closure sites, and that each closure site is probably mediated by different genes and affected by different teratogens. Hydrocephalus associated with the Arnold-Chiari type II malformation commonly occurs with myelomeningocele. Sacral agenesis, also called the caudal regression syndrome, occurs more frequently in infants of diabetic mothers.

Clinical Findings

At birth, neural tube defects can present as an obvious rachischisis (open lesion), or as a more subtle skin-covered lesion associated with a fatty mass, a hemangioma, a tuft of hair, or asymmetric buttock creases. In the latter case, CT or MRI should be conducted to better define the anatomic defect. The extent of neurologic deficit depends on the level of the lesion, and may include clubfeet, dislocated hips, or total flaccid paralysis below the level of the lesion. Hydrocephalus may be apparent at birth, or may present with an increase in head circumference, irritability, and poor feeding, with vomiting shortly after the back has been repaired surgically. Neurogenic bladder and bowel are commonly seen. Other anomalies of the CNS may be present, as well as anomalies of the heart or kidneys.

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Differential Diagnosis

Neural tube defects may occur in isolation, or as part of a genetic syndrome. They may result from teratogenic exposure to alcohol or the anticonvulsant valproate. Any infant with dysmorphic features or other major anomalies in addition to the NTD should be evaluated by a geneticist, and have a chromosome analysis.

Complications & Management

Neurosurgical

Infants with an open NTD should be placed in prone position, and the lesion kept moist with sterile dressing. Neurosurgical closure should occur within 24–48 hours after birth to reduce risk of infection. The infant should be monitored closely, and a ventriculoperitoneal shunt should be inserted as soon as signs of hydrocephalus become apparent. Shunts are required in about 85% of cases of myelomeningocele. Complications of the shunt include malfunction and infection. Symptoms of the Arnold-Chiari II malformation include feeding dysfunction, abducens nerve palsy, vocal cord paralysis with stridor, and apnea. Shunt malfunction may cause an acute worsening of Chiari symptoms that may be life-threatening.

Orthopedic

The child's ability to walk varies according to the level of the lesion. Children with low lumbar and sacral lesions walk with minimal support; those with high lumbar and thoracic lesions are rarely functional walkers; and in those with midlumbar lesions the effects are variable. Orthopedic surgery is necessary to get the child upright and ambulatory, and to address foot deformities and scoliosis. Physical therapy services are indicated.

Urologic

Neurogenic bladders have variable presentations. Urodynamic studies are recommended early on to define bladder function, and management is guided by the results of these studies. Continence can be achieved in a variety of ways, including use of anticholinergic or sympathomimetic agents, clean intermittent catheterization, and a variety of urologic procedures. Renal function should be monitored regularly, and an ultrasound examination should be periodically repeated. Symptomatic infections should be treated.

Symptoms of neurogenic bowel include incontinence and chronic constipation, managed with a combination of dietary modifications, laxatives and stool softeners, and rectal stimulation. A recently developed surgical procedure called ACE (antegrade continence enema) uses the appendix to create a conduit from the upper colon to the surface at the umbilicus. An enema is then given through the conduit, cleaning out the colon from above rather than from below. Early results with respect to continence and patient satisfaction have been encouraging.

Special Issues and Prognosis:

All children requiring multiple surgical procedures (ie, patients with spina bifida or urinary tract anomalies) have a significant risk for developing hypersensitivity type I (IgE-mediated) allergic reactions to latex. For this reason, non-latex medical products are now routinely used when caring for patients with NTD's. Most individuals with spina bifida are cognitively normal, but learning disabilities are common. Individuals with encephalocele, or other CNS malformations generally have a much poorer intellectual outcome. Individuals with closed spinal cord abnormalities (eg, sacral lipomas) have more mild issues in general, and intelligence is usually normal. Problems in older patients include the development of spinal cord tethering, which usually presents with back pain, progressive scoliosis, and changes in bowel or bladder function. This often requires neurosurgical intervention. Individuals with NTDs have lifelong medical issues, which require the care of multiple medical and surgical specialists, as well as special educational and psychosocial issues requiring support for the patient and family. A good support for families is the national Spina Bifida Association (sbaa@sbaa.org), which has many local chapters.

Genetic Counseling

Recurrence risks vary according to the underlying cause, but most isolated neural tube defects are polygenic, with a recurrence risk of 2–3% for the parents in future pregnancies. The recurrence risk for siblings of the parents and siblings of the patients is 1–2%. A patient with spina bifida has a 5% chance of having an affected child. Prenatal diagnosis is available, and pregnancies can be monitored in a variety of ways. In fetuses with open neural tube defects, maternal serum alpha-fetoprotein levels measured at 16–18 weeks' gestation are elevated. Alpha-fetoprotein and acetylcholine esterase levels in amniotic fluid are also elevated. Ultrasound studies will detect approximately 90% of neural tube defects. Recent studies have shown that prophylactic folic acid can significantly lower the incidence and recurrence rate of neural tube defects, but the intake of the folic acid must start at least 3 months prior to conception and continue during the first month of pregnancy. It is now recommended that all women of childbearing age take 0.4 mg of folic acid daily. For the woman at increased

risk because of a previous child with a neural tube defect, the current recommendation is to increase folic acid intake to 4 mg daily when pregnancy is planned. Although the data are inconsistent, some evidence indicates that preconceptional folic acid supplementation may also lower the incidence of other congenital malformations such as conotruncal heart defects.

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Elias ER, Hobbs N: Spina bifida: Sorting out the complexities of care. *Contemp Pediatr* 1998;15:156

COMMON RECOGNIZABLE DISORDERS WITH VARIABLE OR UNKNOWN ETIOLOGY

The text that follows describes several important and common human malformation syndromes. The emphasis is on clinical findings that should suggest their inclusion in differential diagnoses. Likely causes, if known, are also briefly explained. The best illustrations are in *Smith's Recognizable Patterns of Human Malformation*. An excellent Internet site at the University of Kansas Medical Center can be consulted for further information (<http://www.kumc.edu/gec/support>).

Arthrogryposis Multiplex

Arthrogryposis multiplex is due to lack of fetal movement. Causes most often involve constraint, CNS maldevelopment or injury, or neuromuscular disorders. In the neuromuscular disorders, polyhydramnios is often present as a result of lack of fetal swallowing. Pulmonary hypoplasia may also be present, reflecting lack of fetal breathing. The workup will usually include brain imaging, careful consideration of metabolic disease—especially peroxisomal disorders associated with elevated very-long-chain fatty acids—neurologic consultation, and, in some cases, electrophysiologic studies and muscle biopsy. The family history should be reviewed carefully for findings such as muscle weakness or cramping, cataracts, and early-onset heart disease, suggesting myotonic dystrophy. Parents should have careful neurologic examinations that include testing for myotonia.

CHARGE Association

CHARGE association affects structures derived from rostral neural crest cells but also includes abnormal development of the eyes and midbrain. It is a sporadic condition whose etiology is not understood. The acronym CHARGE serves as a mnemonic for associated abnormalities that include **c**olobomas, **c**ongenital **h**ear disease, **c**hoanal **a**tresia, **g**rowth **r**etardation, **g**enital abnormalities (hypogenitalism), and **e**ar abnormalities.

Abnormal ear development always occurs in association with this condition. Whenever abnormal ears are encountered, careful physical assessment should follow, and ophthalmologic consultation should be considered. Facial asymmetry is a common finding. Studies of surviving patients indicate that neuronal damage due to airway and feeding complications contribute substantially to developmental delays. A number of other syndromes, some with much better prognoses, overlap with this condition. Chromosomal studies are normal but are usually necessary to distinguish this condition from other disorders. The following website of the Charge Syndrome Foundation, Inc, is

a helpful source for additional information: <http://www.chargesyndrome.org/>

Cornelia De Lange Syndrome

Cornelia de Lange syndrome is a sporadically occurring malformation syndrome whose cause remains obscure. It is characterized by severe growth retardation; limb, especially hand, reduction defects (50%); congenital heart disease (25%); and stereotypical facies with hirsutism, medial fusion of eyebrows (synophrys), and thin, downturned lips.

The course and severity are variable, but the prognosis for survival and normal development is poor. Chromosomal analysis is usually normal.

Goldenhar Syndrome

Goldenhar syndrome, also known as vertebroauriculofacial syndrome, is an association of multiple anomalies involving the head and neck. The classic phenotype includes hemifacial microsomia (one side of the face smaller than the other), with abnormalities of the pinna on the same side with associated deafness. Ear anomalies may be quite severe and include anotia. A characteristic benign fatty tumor in the outer eye, called an epibulbar dermoid, is frequently present, as are preauricular ear tags. Vertebral anomalies, particularly of the cervical vertebrae, are seen, and vertebral anomalies lower down are common. The Chiari Type I malformation (herniation of the cerebellum into the cervical spinal canal) is a common associated anomaly. Cardiac anomalies, and hydrocephalus are seen in more severe cases. Most patients with Goldenhar syndrome have normal intelligence. The cause is unknown.

Kabuki Syndrome

Kabuki syndrome is a disorder of unknown cause, characterized by a distinctive facial appearance (hypertelorism with long palpebral fissures, large pinnae), developmental delay, and hearing loss. Most cases are sporadic although a few cases with dominant transmission have been reported. Anomalies of the heart and genitourinary system are occasionally seen.

Noonan Syndrome

Noonan syndrome is an autosomal dominant disorder characterized by short stature, congenital heart disease, abnormalities of cardiac conduction and rhythm,

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webbed neck, downslanting palpebral fissures, and low-set ears. Affected children may be large at birth and have mild subcutaneous edema. The phenotype evolves with age and may be difficult to recognize in older relatives. Mild developmental delays are often present. No genes have yet been identified, but a candidate locus has been mapped to chromosome 12q.

Oligohydramnios Sequence (Potter Sequence)

This condition presents in newborns as severe respiratory distress due to pulmonary hypoplasia in association with positional deformities of the extremities, usually bilateral clubfeet, and typical facies consisting of suborbital creases, depressed nasal tip and low-set ears, and retrognathia. The sequence may be due to prolonged lack of amniotic

fluid. Most often it is due to leakage, renal agenesis, or severe obstructive uropathy.

Opitz G/BBB

Disrupted development of midline structures is a feature of several overlapping malformation syndromes, a number of them heritable. Hypertelorism (wide set eyes) is a unifying feature for these conditions, but it is the combined association of midbrain anomalies (agenesis of the corpus callosum), cardiac septal defects, and genitourinary tract anomalies, in particular, hypospadias, that has led to the recognition of a commonly disrupted midline developmental field. Current clinical genetic terminology refers to these conditions as Opitz/BBB syndrome.

In addition to malformation of midline structures, hypotonia and problems with swallowing and gastroesophageal reflux are hallmark symptoms. Mentation is usually subnormal. Many cases are sporadic, but well documented families with apparent autosomal dominant and X-linked inheritance identify the phenotype as genetically heterogeneous. Linkage studies have recently identified a candidate gene dubbed M101 on the X-chromosome. Mutations in this gene segregate with syndromic phenotypes in affected males. An additional X-chromosomal locus and an autosomal locus very close to the Shprintzen syndrome region, 22q11, are also under investigation. A number of Opitz G/BBB syndrome patients, in fact, have been shown by FISH to have deletions in this region. Additional resources include the website <http://www.gle.egsd.k12.co.us/opitz/index.html>, Opitz Family Network and the OPITZ G/BBB Family Network.

Overgrowth Syndromes

Overgrowth syndromes are becoming increasingly recognized as important childhood conditions. They may present at birth and are characterized by macrocephaly, motor delays (cerebral hypotonia), and, in many cases, asymmetry of extremities. Bone age may be advanced. The most common overgrowth syndrome is Sotos syndrome. Patients with Sotos syndrome have a characteristic facies with a prominent forehead and downslanting palpebral features. The cause of Sotos syndrome is unknown. There is a small but increased risk of cancer in patients with Sotos syndrome. Other overgrowth syndromes include Beckwith-Wiedemann syndrome, described in the section on imprinting, and two single-gene disorders called Simpson-Golabi-Behmel syndrome, and Bannayan-Riley-Ruvalcaba (BRR) syndrome. Simpson-Golabi-Behmel syndrome exhibits a Beckwith-Wiedemann-like phenotype, but with additional anomalies including polydactyly and more severe facial dysmorphism. Unlike BWS patients who have normal intelligence, patients with Simpson-Golabi often have developmental delay. It is inherited as an X-linked disorder. Patients with BRR have macrosomia, macrocephaly, and unusual freckling of the penis. They have mild developmental issues. They may develop hemangiomas/lymphangiomas, and have a predisposition to intestinal malignancies. The cause of BRR was recently found to be a mutation of the PTEN gene implicated in Cowden's syndrome, the association of intestinal polyposis with malignant potential.

Rubenstein-Taybi Syndrome

Rubenstein-Taybi Syndrome is a common genetic disorder of unknown cause, characterized by developmental delay, growth failure, and a distinctive facial

dysmorphology with microcephaly, prominent nose and small chin. Feeding problems are common. About 25% of patients have been found with a microdeletion of chromosome 16 detectable by FISH, but most patients have a normal karyotype.

Syndromic Short Stature

Short stature is an important component of numerous syndromes, or it may be an isolated finding. In the absence of nutritional deficiencies, endocrine abnormalities, evidence for skeletal dysplasia (disproportionate growth with abnormal skeletal films), or a positive family history, intrinsic short stature can be due to uniparental disomy (see above) such that only imprinted (silenced) copies of specific sequences are present. The phenotype of Russell-Silver syndrome—short stature with normal head growth (pseudohydrocephalus), normal development, and minor dysmorphic features (especially fifth finger clinodactyly)—has been associated in some cases with maternal uniparental disomy for chromosome 7.

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VACTERL Association

VACTERL association is described by an acronym denoting the association of **V**ertebral defects (segmentation anomalies), **I**mperforate **A**nus, **C**ardiac malformation (most often ventricular septal defect), **T**racheo-**E**sophageal fistula, **R**enal anomalies, and **L**imb (most often radial ray) anomalies. The disorder is sporadic and some of the defects may be life-threatening. The prognosis for normal development is good. The cause is unknown, but a high association with monozygotic twinning suggests a mechanism dating back to events perhaps as early as blastogenesis. Recently, disturbance of the sonic hedgehog pathway was suggested to be part of the mechanism for VACTERL, based on a mouse model. Careful examination and follow-up are important, because numerous other syndromes with more complicated prognoses also include features present in VACTERL association. Chromosomal studies and genetic consultation are warranted.

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PERINATAL GENETICS

TERATOGENS

Fetal Alcohol Syndrome (FAS)

Fetal alcohol syndrome results from excessive exposure to alcohol during gestation and affects 30–40% of offspring of mothers whose daily intake of alcohol exceeds 3 oz. Features of the syndrome include short stature; poor head growth (may be postnatal in onset), developmental delay, and midface hypoplasia characterized by a poorly developed long philtrum, narrow palpebral fissures, and short nose with anteverted nares. Facial findings may be subtle, but careful measurements and comparisons with standards (Figure 33-12) can be useful. Structural abnormalities occur in half of affected children. Cardiac anomalies and neural tube defects are commonly seen. Genitourinary tract anomalies are frequent. Scientists and clinicians now agree that the term *fetal alcohol effect* may be misleading and should not be applied to apparently incomplete phenotypes. Careful evaluation for other syndromes and chromosomal disorders should be included in the workup. Behavioral abnormalities in older children may or may not be directly attributable to alcohol, because psychiatric disorders, many with recognized inherited predisposition, affect a large number of women and their partners who abuse alcohol.

Maternal Anticonvulsant Effects

Anticonvulsant exposure during pregnancy is now recognized as being associated with adverse outcomes in approximately 10% of children born to women who are taking anticonvulsants. A syndrome characterized by small head circumference, anteverted nares, cleft lip and palate (occasionally), and distal digital hypoplasia was first described in association with maternal use of phenytoin but also occurs with other anticonvulsants. Risks for spina bifida are increased, especially in pregnancies exposed to valproic acid. Tegretol, felt to be less teratogenic than other anticonvulsants, has been associated with a characteristic dysmorphic facial appearance and developmental issues.

Retinoic Acid Embryopathy

Vitamin A and its analogs are potent morphogens that interact with specific receptors and therefore have considerable teratogenic potential. Developmental toxicity occurs in approximately one third of pregnancies exposed in the first trimester to the synthetic retinoid isotretinoin, commonly prescribed to treat acne. Exposure disrupts developmental fields to which rostral neural crest cells contribute and produces CNS maldevelopment, especially of the posterior fossa; ear anomalies (often absence of pinnae); congenital heart disease (great vessel anomalies); and tracheoesophageal fistula. These findings constitute a partial phenocopy of DiGeorge syndrome and demonstrate the continuum of contributing genetic and epigenetic factors in morphogenesis. It is now recognized that vitamin A itself, when taken during pregnancy in the active form of retinoic acid in doses exceeding 10,000 IU/d, can produce partially affected phenotypes. Maternal ingestion of even large amounts of vitamin A taken as retinol during pregnancy, however, does not increase risks, because conversion of this precursor to active retinoic acid is regulated by the body.

Maternal Substance Abuse

Maternal substance abuse is generally associated with increased risks for adverse perinatal outcomes, including

miscarriage, preterm delivery, growth retardation, and increased risk for injury to the developing CNS. For most abused substances, the link between exposures and adverse outcomes is less well demonstrated than with alcohol. Multiple factors are probably involved, and it should be recognized that substance abuse often involves more than one drug. Maternal inhalant abuse appears to be associated with findings similar to those of fetal alcohol syndrome. Reports of abnormal outcomes following cocaine abuse (and the crack baby syndrome) have been contradicted by some studies that found no effects. In these cases the form of the drug used and its route of administration may be important determinants of risk.

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PRENATAL DIAGNOSIS

Prenatal screening for birth defects in the form of analyte analyses in maternal blood, fetal and placental tissues or ultrasound evaluation, is now routinely offered to pregnant women. Prenatal diagnosis for specific genetic disorders is indicated in 7–8% of pregnancies. As technology improves, the indications for and the accuracy of prenatal diagnosis are expected to increase. Prenatal diagnosis introduces options for management including interruption of abnormal pregnancies, prenatal surgical and medical interventions, and preparation for specialized perinatal care.

Methods

Prenatal diagnosis techniques analyze maternal blood, image the conceptus, and sample fetal and placental tissues (Table 33-4).



Maternal blood screening such as α -fetoprotein, estriol, hCG ("triple screen")
Trisomies 21 and 18
Neural tube defects
Smith-Lemli-Opitz syndrome
Fetal cells in maternal blood (research only)
Fetal ultrasound
Structural defects
Fetal hydrops
Poly- or oligohydramnios
Fetal x-ray
Skeletal defects
Fetal MRI
Amniocentesis
Karyotyping
Fetal cells for molecular or metabolic studies
Amniotic fluid α -fetoprotein level for neural tube defects
Biochemical studies on fluid
Chorionic villus sampling
Karyotyping
Fetal cells for molecular or metabolic studies
Fetal tissues
Blood by percutaneous umbilical blood sampling
Biopsy of other fetal tissues
Direct fetal visualization via fetoscopy (rarely used today) because of the advances in fetal visualization by ultrasound and MRI

¹MRI = magnetic resonance imaging.

Table 33-4. Prenatal diagnostic techniques.¹

MATERNAL BLOOD

The use of maternal serum alpha-fetoprotein as a screening test was introduced because higher than normal values were found in association with open neural tube defects. It was later noted that 25% women who carried a fetus with Down syndrome had a 45% lower alpha-fetoprotein value than those in whom the fetus was normal. Additional measurements of human chorionic gonadotropin and unconjugated estradiol (the "triple screen") can increase rates of detection for trisomy 21 to approximately 60%, and predict many cases of trisomy 18 as well. Low estradiol can also predict cases of Smith-Lemli-Opitz, a devastating autosomal recessive disorder.

Fetal cells, including lymphocytes, trophoblasts, and nucleated red blood cells, are present in the maternal circulation. Research is being directed toward isolating these cells for prenatal diagnosis using culture, hybridization, and PCR-based techniques.

TESTING OF FETAL TISSUE

1. Amniocentesis

This technique has been available for many years. Its accuracy and safety are well established. Fluid surrounding the fetus is sampled, and cells are cultured for

cytogenetic, molecular, or metabolic analysis. Alpha-fetoprotein (AFP) and other chemical markers can also be measured. This is a safe procedure with a complication rate (primarily for miscarriage) of less than 1% in experienced hands.

2. Chorionic villus sampling (placental)

This means of analysis is now available in most centers and is generally performed at 11 to 12 weeks. Tissue obtained

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by chorionic villus sampling provides more DNA for molecular analysis and contains dividing cells (cytotrophoblasts) that can be rapidly karyotyped. However, direct cytogenetic preparations may be of poor quality. In addition, chromosomal abnormalities detected by this technique may be confined to the placenta (*confined placental mosaicism*). Cultured preparations may be more relevant. Certainly, if an unusual cytogenetic picture is found on chorionic villus sampling, further studies should be considered before management decisions are made. Numerous studies have been done comparing the safety of first-trimester chorionic villus sampling with amniocentesis. Of some concern is the possible association of chorionic villus sampling prior to 11 weeks with terminal transverse limb defects, perhaps secondary to vascular disruption.

Fetal blood can be sampled directly in late gestation through ultrasound-guided percutaneous umbilical blood sampling (PUBS).

It is occasionally necessary to biopsy fetal tissues such as liver or muscle for accurate prenatal diagnosis. These procedures are available in only a few perinatal centers.

Amniocentesis or chorionic villus sampling is indicated in the following circumstances:

1. Maternal age over 35 years.
2. Previous child with a chromosome abnormality.
3. Either parent a translocation carrier. In this case, the risk for a fetus with an unbalanced chromosome abnormality depends on the type of translocation.
4. A history of any genetic disorder diagnosable by biochemical techniques or by DNA analysis. The list of such conditions changes daily, and a genetic center should be contacted for the most recent information.
5. A request by the parents for fetal sex determination because of a history of an X-linked disorder that is not otherwise diagnosable.
6. Maternal blood testing (eg, triple screen) indicating increased risks for chromosomal abnormalities.
7. As part of the workup of fetal anomalies found by ultrasonography.

3. Fetal ultrasonography

Ultrasonography is indicated whenever an abnormality characterized by a structural defect is suspected. The defect may be suspected because of the family history, potential exposure to teratogens during pregnancy, or questionable abnormalities noted

on a routine ultrasound examination done in the obstetrician's office. In any case, the patient should be referred for further evaluation to a medical center staffed by personnel experienced in fetal ultrasonography.

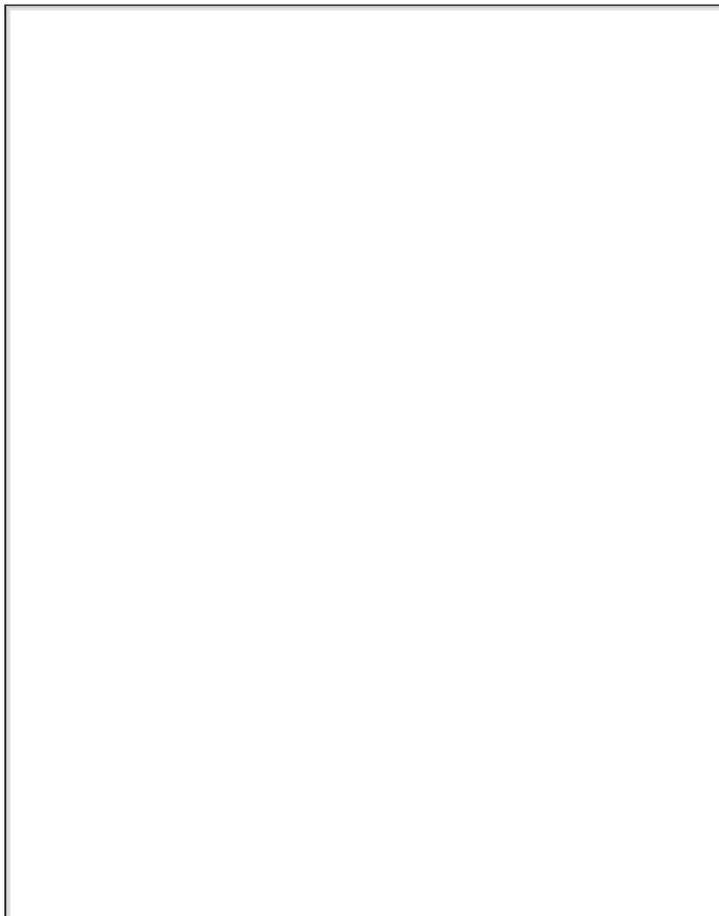
By 16 to 18 weeks' gestation, transabdominal real-time ultrasonography can visualize all major fetal organs, including the kidneys, heart, brain, spinal cord, bladder, and limbs. Beginning at 12 weeks' gestation, transvaginal ultrasonography can provide even earlier imaging. It is therefore possible to look for almost any genetic syndrome that includes a specific defect. Routine ultrasound screening has demonstrated many unexpected abnormalities. Most of these are major defects, however, and minor anomalies are easily missed, especially if unexpected.

Fetal motion has been a major deterrent to the use of MRI as a tool for prenatal diagnosis. However, new techniques are being developed to overcome this problem, making MRI a potentially valuable noninvasive means of fetal assessment.

X-ray studies of the fetus are rarely necessary because ultrasonography has improved so greatly. If a skeletal abnormality or bone dysplasia is suspected, however, x-ray films may be helpful.

EVALUATION OF THE DEVELOPMENTALLY DELAYED CHILD

Mental retardation or developmental delays affect 8% of the population. Disorders associated with symptoms of delayed development are heterogeneous but frequently include heritable components. Evaluation should be multidisciplinary; Table 33-5 lists its main features, emphasizing the major clinical and genetic considerations.



History

- Pregnancy history
- Growth parameters at birth
- Neonatal complications
- Feeding history
- History of somatic growth
- Motor, language, and psychosocial milestones
- Seizures
- Loss of skills
- Abnormal movements
- Results of previous tests and examinations

Family history

- Developmental and educational histories
- Psychiatric disorders
- Pregnancy outcomes
- Medical history
- Consanguinity

Physical examination

- General pediatric examination
- Focused dysmorphic evaluation including measurement of facial features and assessment of dermatoglyphics
- Complete neurologic examination
- Parental growth parameters (especially head circumferences) and dysmorphic features should also be assessed

Imaging studies

- See text

Laboratory assessment¹

- Chromosomes (high-resolution analyses)
- Fragile X testing (analysis of *FMR1* gene for triplet repeats)
- FISH analyses guided by dysmorphic features
- Other blood analyses: completed blood count, electrolytes, liver function tests, creatinine kinase (CK), lactate, pyruvate
- Serum amino acid analysis
- Urine amino and organic acid analyses
- Urine analysis for mucopolysaccharides

¹In many cases, negative results may be important.

Table 33-5. Evaluation of the child with developmental delay.

Patterns and timing of growth and development are particularly important to discern. For example, prenatal-onset growth retardation is less likely to have a metabolic origin than is postnatal growth delay. Loss of skills raises suspicion about possible metabolic or neurodegenerative disorders. Behavioral abnormalities are commonly associated with developmental delays, but behavioral diagnoses such as attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, autism, or autistic-like behaviors are better viewed as descriptive than as etiologically informative diagnoses.

Physical examination provides helpful clues. Close scrutiny for presence of dysmorphic disorders is a clinical skill that requires practice. Referral to a clinical geneticist is indicated whenever unusual features are encountered. Neurologic, ophthalmologic, and audiologic consultation should be sought when indicated. Brain

imaging should be requested in most cases involving otherwise unexplained deviations from normal head growth. Neuro-imaging and skeletal studies may also be

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indicated when dysmorphic features are present. Neurologic consultation can often help sort through indications for imaging.

As molecular explanations for genetic disorders accumulate, opportunities for molecular genetic testing increase. Unlike the majority of the studies listed in Table 33-4, these are not screening tests—they may confirm but often do not entirely rule out specific diagnoses. In general, it will not be cost-effective to proceed with molecular genetic testing without clinical genetic consultation.

Metabolic and genetic testing procedures other than those listed in the table may also be indicated. Appropriate consultations should be sought to coordinate these investigations.

Interpretation & Follow-Up

Clinical experience indicates that specific diagnoses can be made in approximately half of patients evaluated according to the protocol presented here. With specific diagnosis comes prognosis, ideas for management, and insight into recurrence risks. Prenatal diagnosis may also become possible.

Follow-up is important both for patients in whom diagnoses have been made and for those patients initially lacking a diagnosis. Genetic information is accumulating rapidly and can be translated into new diagnoses and better understanding with periodic review of clinical cases.