GENERAL PATHOLOGY

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Human Genetics

The **cell** is the smallest functional unit of human body that can be divided and retain the characteristics necessary for life.

GENETIC CONTROL OF CELL FUNCTION

Genetic information is stored in the structure of deoxyribonucleic acid **(DNA).** DNA is an extremely stable macromolecule found in the nucleus of each cell. Because of the stable structure of DNA, the genetic information can survive the many processes of reduction division, in which the gametes ***(i.e.*, ovum and sperm)** are formed, and the fertilization process. This stability is also maintained throughout the many mitotic cell divisions involved in the formation of a new organism from the single-celled fertilized ovum called the ***zygote***.

the nucleus of the cell contains the important mechanisms of inheritance. They found that chromatin, the substance that gives the nucleus a granular appearance, is observable in the nuclei of non dividing cells. Just before a cell undergoes division, the chromatin condenses to form microscopically observable, thread like structures called chromosomes.

Genes, the basic unit of inheritance, are contained in chromosomes and consist of DNA. genes are composed of deoxyribonucleic acid (DNA) that provides the genetic blueprint for all proteins in the body.Thus, genes ultimately influence all aspects of body structur and function.Humans are estimated to have 20,000 to 25,000 genes(sequences of DNAthat code for ribonucleic acid[RNA]or proteins) .

DNA Structure

The structure that stores the genetic information in the nucleus is a long, double-stranded, helical molecule of DNA. DNA is composed of *nucleotides,* which consist of phosphoric acid, a five-carbon sugar called *deoxyribose,* and one of four nitrogenous bases. These nitrogenous bases carry the genetic information and are divided into two groups:

1- The *purine bases*, adenine and guanine, which have two nitrogen ring structures.
2- The *pyrimidine bases,* thymine and cytosine, which have one ring.

The backbone of DNA consists of alternating groups of sugar and phosphoric acid; the paired bases project inward from the sides of the sugar molecule. DNA resembles a spiral staircase, with the paired bases representing the steps.

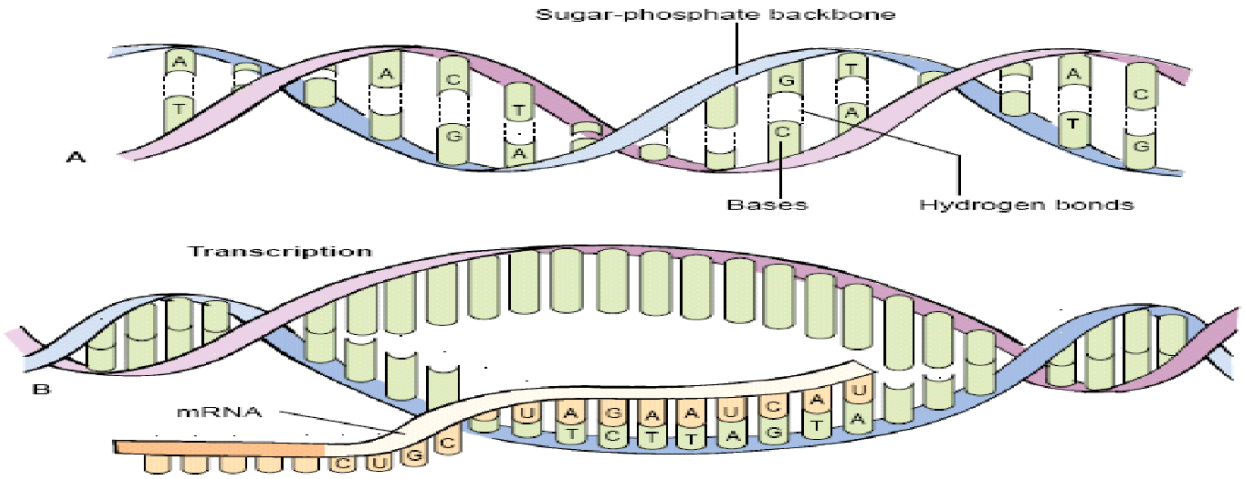
DNA is an almost universal genetic material, it contains all the instructions necessary to "tell" a living cell what it is supposed to do. there must exist a mechanism that copies DNA faithfully, to ensure that progeny cells contain the same genetic material as the maternal cell

DNA replication or **DNA synthesis** is the process of copying double stranded DNA strand, prior to cell division. Replication occurs in the nucleus during the interphase (S) Gives **daughter cells a complete set of genetic information identical to the parent cell.** The two resulting double strands are identical (if the replication went well), and each of them consists of one original and one newly synthesized strand. This is called semi conservative replication.

RNA: A second type of nucleic acid, ribonucleic acid is involved in the actual synthesis of cellular enzymes and proteins. Cells contain several types of RNA: messenger RNA, **transfer RNA**, and **ribosomal RNA**. **Messenger RNA (mRNA)** contains the transcribed instructions for protein synthesis obtained from the DNA molecule and carries them into the cytoplasm

Transcription :is the process by which an RNA sequence is formed from a DNA template. The type of RNA produced by the transcription

process is messenger RNA(mRNA).



The DNA double helix and transcription of messenger RNA (mRNA).
A) shows the sequence of four bases (adenine [A], cytosine [C], guanine [G], and thymine [T]), which determines the specificity of geneticinformation. The bases face inward from the sugar-phosphate backbone and form pairs (*dashed lines) with complementary* bases on the opposing strand. In the bottom panel (**B), transcription creates a** complementary mRNA copy from one ofthe DNA strands in the double helix.

Protein Synthesis

Transcription is followed by ***TRANSLATION*****,** the synthesis of proteins according to the instructions carried by mRNA. Ribosomal RNA (rRNA) provides the machinery needed for protein synthesis. Transfer RNA (tRNA) reads the instructions and delivers the appropriate amino acids to the ribosome, where they are incorporated into the protein being synthesized.

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Messenger RNA

Messenger RNA is the template for protein synthesis. It is a long molecule containing several hundred to several thousand nucleotides. Each group of three nucleotides forms a codon that is exactly complementary to the triplet of nucleotides of the DNA molecule. Messenger RNA is formed by a process called ***transcription,*** in which the weak hydrogen bonds of the DNA are broken so that free RNA nucleotides can pair with their exposed DNA counterparts on the meaningful strand of the DNA molecule.

As with the base pairing of the DNA strands, complementary RNA bases pair with the DNA bases. In RNA, **uracil** replaces thymine and pairs with **adenine**. During transcription, a specialized nuclear enzyme, called ***RNA polymerase,*** recognizes the beginning or start sequence of a gene. The RNA polymerase attaches to the double-stranded DNA and proceeds

to copy the meaningful strand into a single strand of RNA as it travels along the length of the gene.

Transfer RNA

The tRNA molecule contains only 80 nucleotides, making it the smallest RNA molecule. Its function carrying an amino acid to the protein synthetic machinery of a cell (ribosome) as directed by a three-nucleotide sequence (codon) in a messenger RNA (mRNA). At least 20 different types of tRNA are known, each of which recognizes and binds to only one type of amino acid. Each tRNA molecule has two recognition sites: the first is complementary for the mRNA codon and the second is for the amino acid itself. Each type of tRNA carries its own specific amino acid to the ribosomes, where protein synthesis is taking place; there it recognizes the appropriate codon on the mRNA and delivers the amino acid to the newly forming protein molecule.

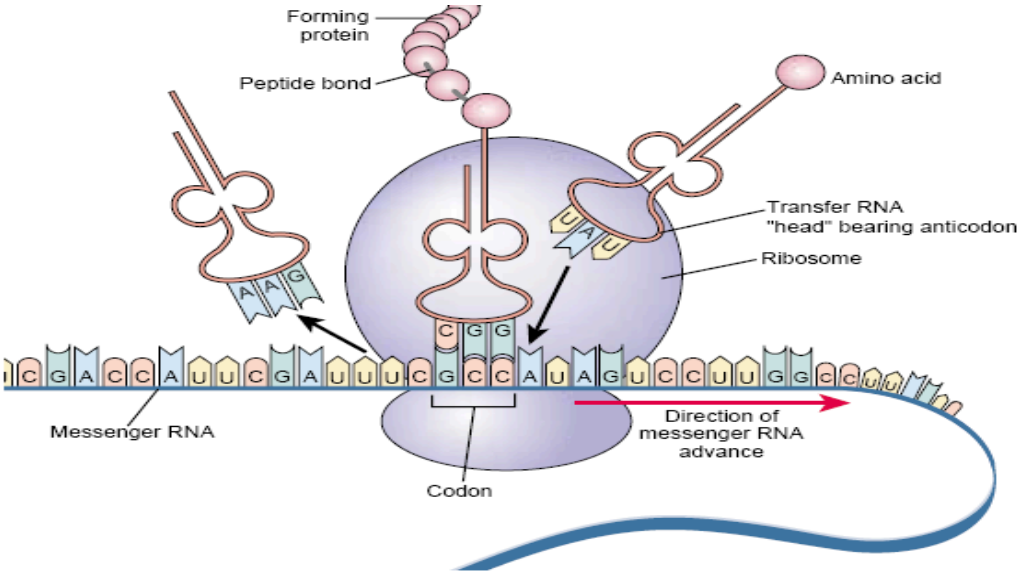
Ribosomal RNA

The ribosome is the physical structure in the cytoplasm where protein synthesis takes place. Ribosomal RNA forms 60% of the ribosome, with the remainder of the ribosome composed of the structural proteins and enzymes needed for protein synthesis. As with the other types of RNA, rRNA is synthesized in the nucleus. Unlike other RNAs, ribosomal RNA is produced in a specialized nuclear structure called the *nucleolus.* The formed rRNA combines with ribosomal proteins in the nucleus to produce the ribosome, which is then transported into the cytoplasm. On reaching the cytoplasm, most ribosomes become attached to the endoplasmic reticulum and begin the task of protein synthesis.

Proteins are made from a standard set of amino acids, which are joined end to end to form the long polypeptide chains of protein molecules. Each polypeptide chain may have as many as 100 to more than 300 amino acids in it. The process of protein synthesis is called ***translation*** because the genetic code is translated into the production language needed for protein assembly.

Messenger RNA provides the information needed for placing the amino acids in their proper order for each specific type of protein. During protein synthesis, mRNA contacts and passes through the ribosome which “reads” the directions for protein synthesis in much the same way that a tape is read as it passes through a tape player.

As mRNA passes through the ribosome, tRNA delivers the appropriate amino acids for attachment to the growing polypeptide chain.



-**Genes** are the **fundamental unit of information storage** in the cell. They determine the types of proteins and enzymes made by the cell and therefore control inheritance and day-to-day cell function.

- Genes store information in a stable macromolecule called ***DNA.***

-Genes transmits information contained in the DNA molecule as a triplet code. The arrangement of the nitrogenous bases of the four nucleotides (*i.e.,* adenine, guanine, thymine [or uracil in RNA], and cytosine) forms the code.

- The transfer of stored information into production of cell products is accomplished through a second type of macromolecule called *RNA.* Messenger RNA transcribes the instructions for product synthesis from the DNA molecule and carries it into the cell's cytoplasm, where ribosomal RNA uses the information to direct product synthesis. Transfer RNA acts as a carrier system for delivering the appropriate amino acids to the ribosomes, where the synthesis of cell products occurs.

-Although all cells contain the same genes, only a small, select group of genes is active in a given cell type. In all cells, some genetic information is repressed, whereas other information is expressed.
- Gene mutations represent accidental errors in duplication, rearrangement, or deletion of parts of the genetic code. Fortunately, most mutations are corrected by DNA repair mechanisms in the cell.

Besides nuclear DNA, part of the DNA of a cell resides in the mitochondria. Mitochondrial DNA is inherited from the mother by her offspring **(*i.e.,* matrilineal inheritance).** Several genetic disorders are attributed to defects in mitochondrial DNA

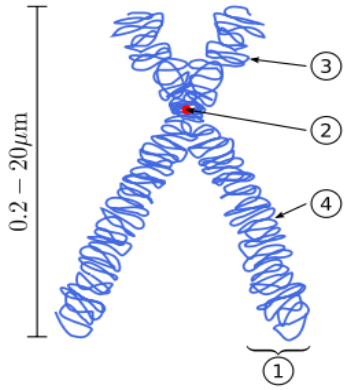
CHROMOSOMES .

Chromosomes: A single piece of coiled DNA and protein that is found in cell nucleus. Chromosomes are packaged by proteins into a condensed structure called **chromatin.** This allows the very long DNA molecules to fit into the cell nucleus.

Chromosome forms the classic four arm structure, a pair of sister chromatids attached to each other at the centromere. Centromere is a narrow region that divides the chromosome into short arm and long arm. The short arms are called *p arms* (from the French *petit*, small) and the long arms are called *q arms* (*q* follows *p* in the Latin alphabet).

1. Chromatid –one of the two identical parts of the chromosome.

2. Centromere – the point where the two chromatids touch.



3. Short arm.

4. Long arm.

Diagram of a duplicated and condensed metaphase chromosome.

Most genetic information of a cell is organized, stored, and retrieved in small intracellular structures called **chromosomes.** Although the chromosomes are visible only in dividing cells, they retain their integrity between cell divisions. The chromosomes are arranged in pairs; one member of the pair is inherited from the father, the other from the mother.

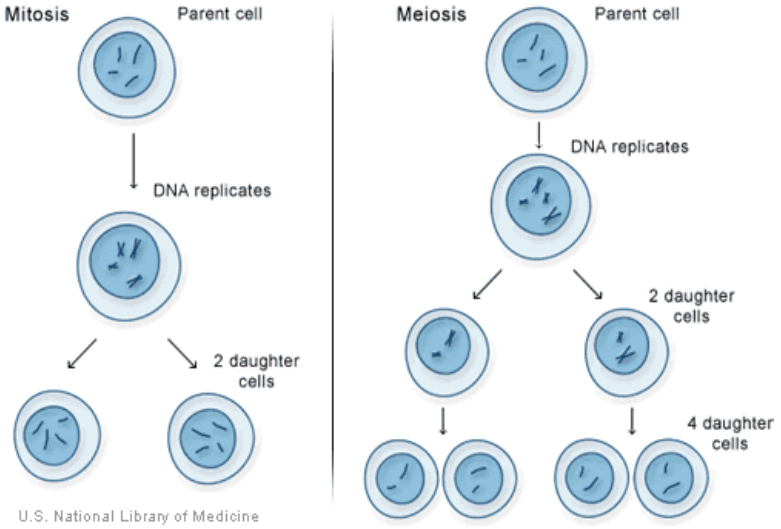
Each species has a characteristic number of chromosomes. In the human, 46 single or 23 pairs of chromosomes are present. Of the 23 pairs of human chromosomes, there are 22 pairs called ***autosomes*** that are alike in males and females. Each of the 22 pairs of autosomes has the same appearance in all individuals, and each has been given a numeric designation for classification purposes.

The sex chromosomes make up the 23rd pair of chromosomes. Two sex chromosomes determine the sex of a person. All males have an X and Y chromosome (*i.e.,* an X chromosome from the mother and a Y chromosome from the father); all females have two X chromosomes (*i.e.,* one from each parent). Only one X chromosome in the female is active in controlling the expression of genetic traits; however, both X chromosomes are activated during gametogenesis (*i.e.,* formation of the germ cell or ovum).

Human body have somatic cells (body cells), which are diploid [2n] having two sets of chromosomes, one from the mother and one from the father. Gametes, reproductive or germ cells, are haploid [one n], they have one set of chromosomes.

During cell division **(mitosis)** in non germ cells (somatic cell), the chromosomes replicate so that each cell receives a full diploid number [2n]. In germ cells, a different form of division **(meiosis)** takes place in which the double sets of 22 autosomes and the 2 sex chromosomes (normal diploid number) are reduced to single sets (haploid number) in each gamete. At the time of conception, the haploid number in the ovum and that in the sperm join and restore the diploid number of

chromosomes. So chromosomes are the essential unit for cellular division and must be replicated, divided, and passed successfully to their daughter cells so as to ensure the genetic diversity and survival of daughter cells.



CHROMOSOME STRUCTURE: Key points:

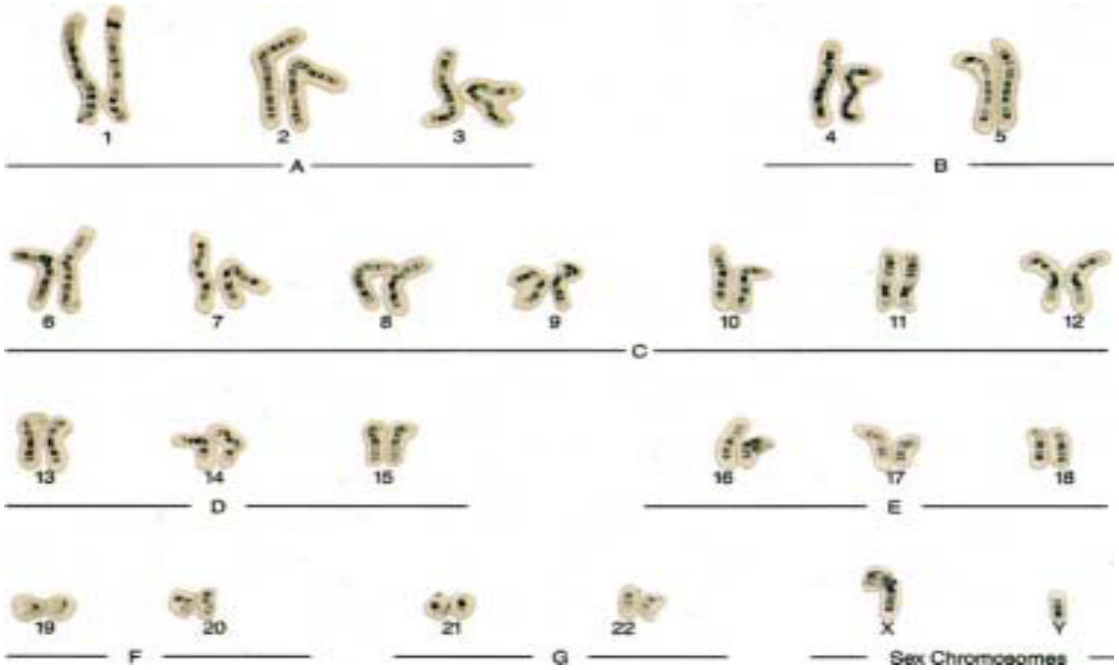
- The DNA that stores genetic material is organized into 23 pairs of chromosomes. There are 22 pairs of autosomes, which are alike for males and females, and one pair of sex chromosomes, with XX pairing in females and XY pairing in males.
- **Mitosis** refers to the duplication of chromosomes in somatic cell lines, in which each daughter cell receives a pair of 23 chromosomes.
- **Meiosis** is limited to replicating germ cells and results in the formation of a single set of 23 chromosomes.

Human karyotype:

Cytogenetic is the study of the structure and numeric characteristics of the cell's chromosomes. Chromosome studies can be done on any tissue or cell that grows and divides in culture. **Lymphocytes** from venous blood are frequently used for this purpose..

A karyotype is a photographic representation of a stained metaphase spread in which the chromosomes are arranged in order of decreasing length.

Karyotypes describe the number of chromosomes, and what they look like under a light microscope. Attention is paid to their length, the position of the centromeres, banding pattern, any differences between the sex chromosomes, and any other physical characteristics.



Karyotype of normal human boy

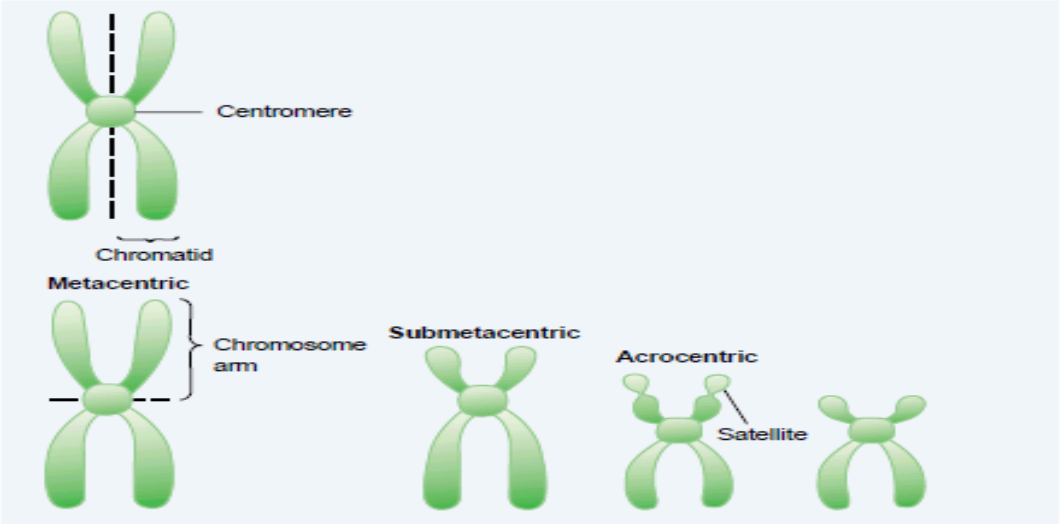
Staining:

A variety of techniques for staining chromosomes have been developed. With the widely used **Giemsa stain (G banding) technique**, each chromosome set can be seen to possess a distinctive pattern of alternating light(C&G) and dark bands(more A&T) of variable widths. The use of banding techniques allows certain identification of each chromosome, as well as precise localization of structural changes in the chromosomes.

Chromosomal number and structure:

The basic number of chromosomes in the somatic cells of an individual or a species is called the *somatic number* and is designated *2n*. In humans 2n = 46. In the germ-line (the sex cells) the chromosome number is *n* (humans: n = 23).

So, in normal **diploid** organisms, autosomal chromosomes are present in two copies. **Polyploid** cells have multiple copies of chromosomes and **haploid** cells have single copies.



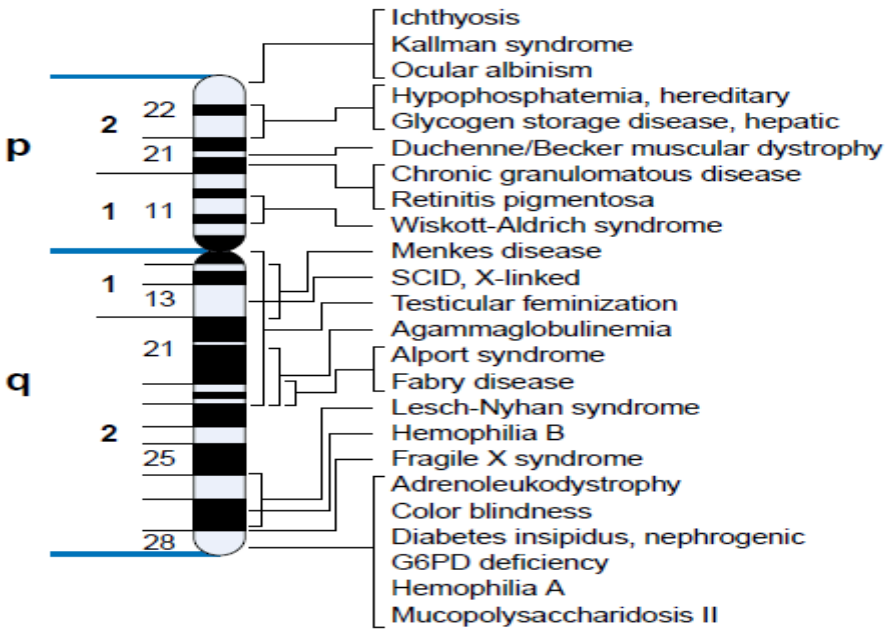
■ **FIGURE 3-10** ■ Three basic shapes and the component parts of human metaphase chromosomes. The relative size of the satellite on the acrocentric is exaggerated for visibility. (Adapted from Cormack D.H. [1993]. *Essential histology*. Philadelphia: J.B.

Metacentric: The centromere is in the center and the arms are of approximately the same length.
Submetacentric: if it is off center and the arms are of clearly different lengths.
Acrocentric: it is near one end.

The short arm of the chromosome is designated as "p" for "petite," and the long arm is designated as "q" for no other reason than it is the next letter of the alphabet.

Arms of the chromosome are indicated by the chromosome number followed by the p or q designation. Chromosomes 13, 14, 15, 21, and 22 have small masses of chromatin called *satellites* attached to their short arms by narrow stalks. At the ends of each chromosome are special DNA sequences called *telomeres*. Telomeres allow the end of the DNA molecule to be replicated completely.

The banding patterns of a chromosome are used in describing the position of a gene. Regions on the chromosomes are numbered from the centromere outward. The regions are further divided into bands and subbands, which are also numbered .These numbers are used in designating the position of a gene on a chromosome. For example, Xp23.4 refers to subband 4, band 3, region 2 of the short arm (p) of the X chromosome.



■ **FIGURE 3-11** ■ The localization of representative inherited diseases on the X chromosome. Notice the nomenclature of arms (P,Q), regions (1,2), bands (*e.g.,* 11,22). (Rubin E., Farber J.L.

PATTERNS OF INHERITANCE

The characteristics inherited from a person's parents are inscribed in gene pairs located along the length of the chromosomes. Alternate forms of the same gene are possible (*i.e.,* one inherited from the mother and

the other from the father), and each may produce a different aspect of a trait.

Definitions

The ***genotype*** of a person The genetic composition of a person is the genetic information stored in the base sequence triplet code.

The ***phenotype*** The observable expression of a genotype in terms of morphologic, biochemical, or molecular traits. More than one genotype may have the same phenotype. Some brown-eyed persons are carriers of the code for blue eyes, and other brown-eyed persons are not. Phenotypically, these two types of brown-eyed persons are the same, but genotypically they are different.

When it comes to a genetic disorder, not all persons with a mutant gene are affected to the same extent. ***Expressivity*** refers to the manner in which the gene is expressed in the phenotype, which can range from mild to severe.

The position of a gene on a chromosome is called its ***locus,*** and alternate forms of a gene at the same locus are called ***alleles.*** These alleles can be the same (homozygous) or different (heterozygous),

When only one pair of genes is involved in the transmission of information, the term ***single-gene trait*** is used. Single-gene traits follow the **Mendelian laws** of inheritance.

Polygenic inheritance involves multiple genes at different loci, with each gene exerting a small additive effect in determining a trait. Most human traits are determined by multiple pairs of genes, many with alternate codes, accounting for some of the dissimilar forms that occur with certain genetic disorders. Polygenic traits are predictable but less so than single-gene traits.

Multifactorial **inheritance** is similar to polygenic inheritance in that multiple alleles at different loci affect the outcome; the difference is that .multifactorial inheritance includes environmental effects on the genes