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Ministry of Higher Education  
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Biochemistry Department**



# **Inborn errors of metabolism**

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**Course Symbol:** BCH 545

**Course Title:** Inborn errors of metabolism

**Course Hours:** 3(3+0)

**Reference Book:** Genetics in Medicine

(Thompson & Thompson)

# Introduction

## GENETICS AND GENOMICS IN MEDICINE:

- Genetics in medicine start at the beginning of the 20th century.
- Medical genetics grew from a small subspecialty concerned with a few rare hereditary disorders to a recognized medical specialty whose concepts and approaches are important components of the diagnosis and management of many disorders, both common and rare.
- At the beginning of the 21st century, with the completion of the


## Human Genome Project

- Medical genetics has become part of the broader field of genomic medicine, which seeks to apply a large-scale analysis of the human genome, including the control of gene expression, human gene variation, and interactions between genes and the environment, to improve medical care.
- Medical genetics focuses not only on the patient but also on the entire family.
- A comprehensive family history is an important first step in the analysis of any disorder, whether or not the disorder is known to be genetic. **(to fail to take a good family history is bad medicine)**

- A family history is important because it can be critical in diagnosis, may show that a disorder is hereditary, can provide information about the natural history of a disease and variation in its expression, and can clarify the pattern of inheritance. Furthermore, recognizing a familial component to a medical disorder allows the risk in other family members to be estimated so that proper management, prevention, and counseling can be offered to the patient and the family.
- The Human Genome Project has made available the complete sequence of all human DNA;

- knowledge of the complete sequence allows the identification of all human genes, a determination of the extent of variation in these genes in different populations, and, ultimately, then explanation of how variation in these genes contributes to health and disease. Genetics is rapidly becoming a central organizing principle in medical practice.
- **Few examples of the vast array of applications of genetics and genomics to medicine.**

- 1- A child who has multiple congenital malformations and a normal routine chromosome analysis undergoes a high-resolution genomic test for submicroscopic chromosomal deletions or duplications.
- 2- A young woman with a family history of breast cancer receives education, test interpretation, and support from a counselor specializing in hereditary breast cancer.
- 3- An obstetrician sends a chorionic villus sample taken from a 38 year-old pregnant woman to a cytogenetics laboratory for examination for abnormalities in the number or structure of the fetal chromosomes.

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- 4- A hematologist combines family and medical history with gene testing of a young adult with deep venous thrombosis to assess the benefits and risks of initiating and maintaining anticoagulant therapy.
  - 5- Gene expression array analysis of a tumor sample is used to determine prognosis and to guide therapeutic decision-making.
  - 6- An oncologist tests her patients for genetic variations that can predict a good response or an adverse reaction to a chemotherapeutic agent.



7- Discovery of an oncogenic signaling pathway inappropriately reactivated by a somatic mutation in a form of cancer leads to the development of a specific and powerful inhibitor of that pathway that successfully treats the cancer.

We need to understand the underlying principles of human genetics like:

- The existence of alternative forms of a gene (**alleles**) in the population.
- The occurrence of similar **phenotypes** developing from mutation and variation at different loci.

- The recognition that familial disorders may arise from gene variants that cause susceptibility to diseases in the setting of gene-gene and gene-environmental interactions.

## Genome:

- Large amounts of the chemical deoxyribonucleic acid (**DNA**).
- DNA contains genetic information (embryogenesis, development, growth, metabolism, and reproduction).
- Every nucleated cell in the body carries its own copy of the human genome (25,000 genes).

## Genes:

- Units of genetic information, are encoded in the DNA of the genome.
- Organized into a number of rod-shaped organelles called chromosomes in the nucleus of each cell.
- Each species has a characteristic chromosome complement (karyotype) in terms of the number and the morphology of the chromosomes that make up its genome.
- The genes are in linear order along the chromosomes, each gene having a precise position or locus.

## Gene map:

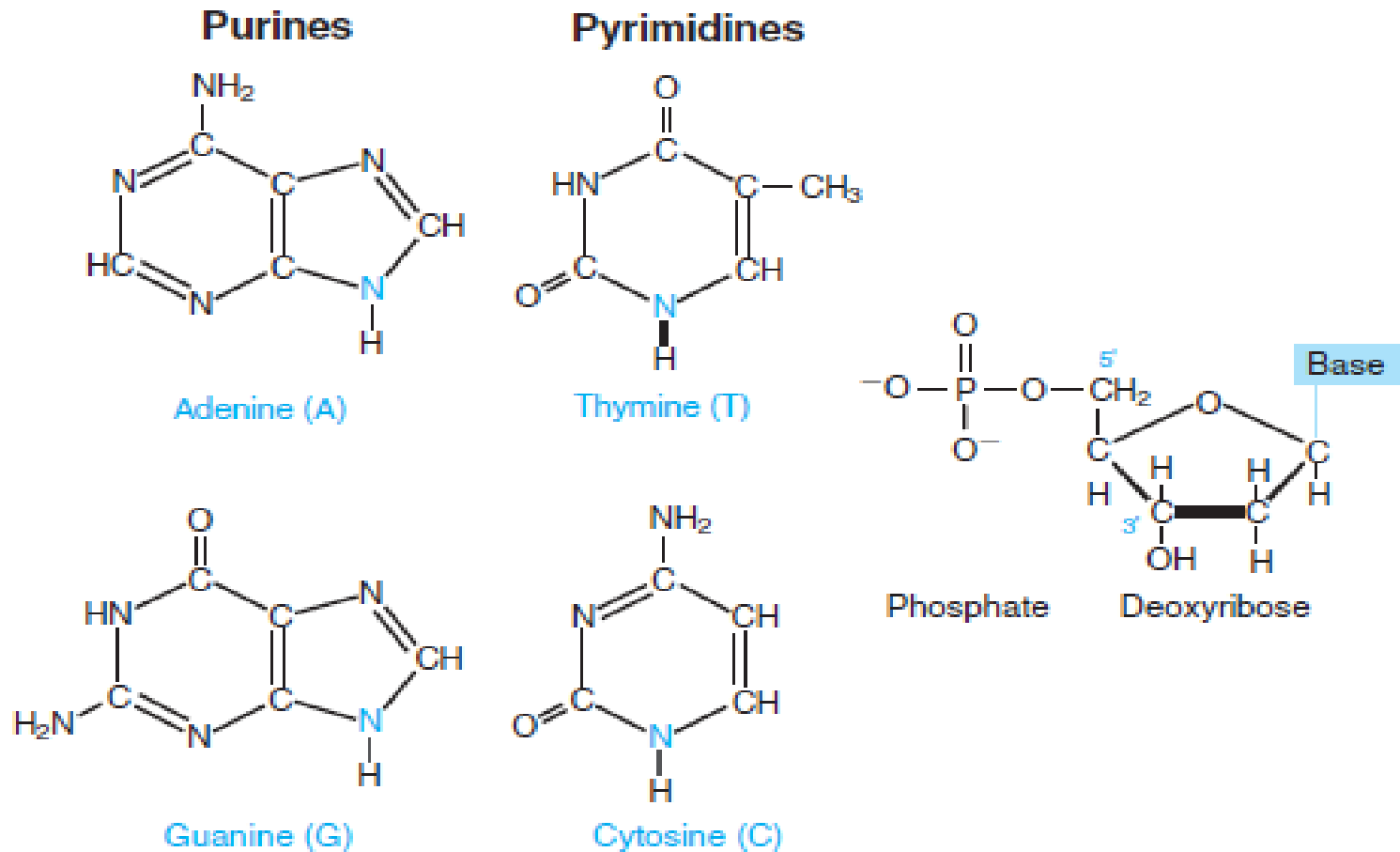
The map of the chromosomal location of the genes and characteristic of each species and the individuals within a species. The study of chromosomes, their structure, and their inheritance is called **cytogenetics**.

## The human genome and its chromosomes

- The cells that develop into **gametes** (the germline).
- all cells that contribute to one's body are called **somatic cells** (soma, body).
- The genome contained in the nucleus of human somatic cells consists of 46 chromosomes, arranged in 23 pairs of those 23 pairs, 22 are alike in males and females and are called **autosomes**, numbered from the largest to the smallest.

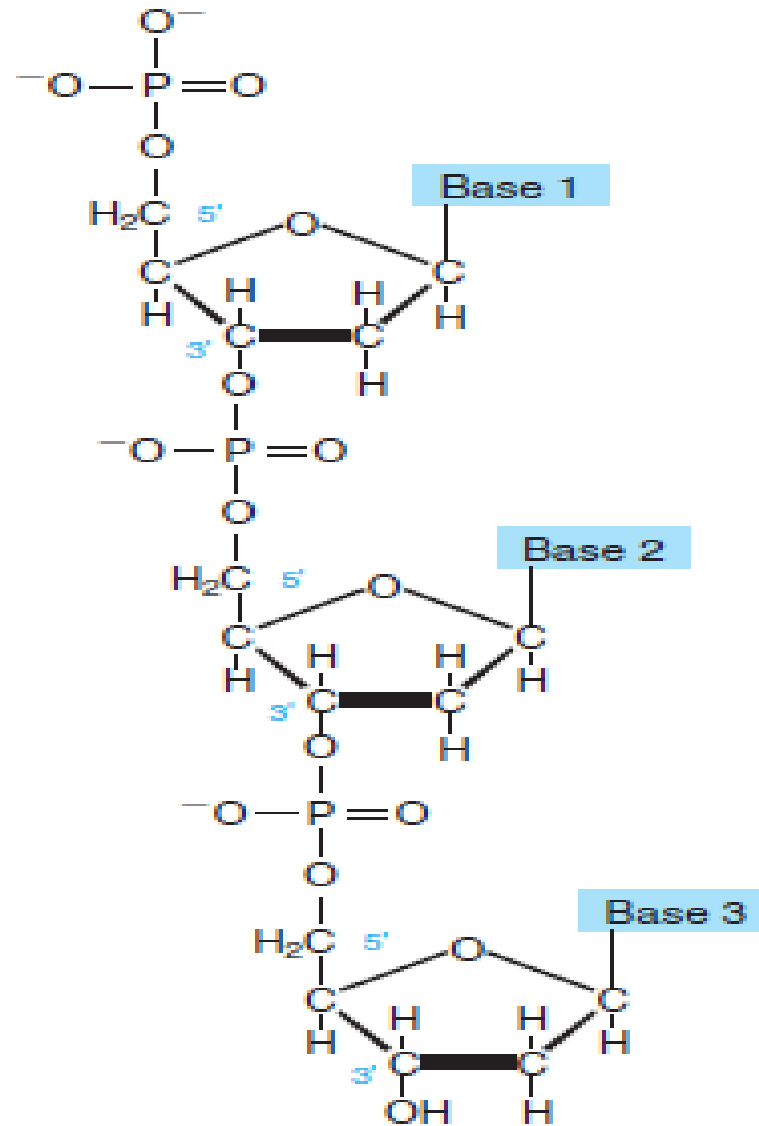
- The remaining pair comprises the **sex chromosomes**: two X chromosomes in females and an X and a Y chromosome in males.
- Members of a pair of chromosomes (referred to as homologous chromosomes or homologues) carry matching genetic information; that is, they have the same genes in the same sequence.
- At any specific locus, they may have either identical or slightly different forms of the same gene, called alleles.

# DNA Structure



**Figure 1.** The four bases of DNA and the general structure of a nucleotide in DNA. Each of the four bases bonds with deoxyribose and a phosphate group to form the corresponding nucleotides.

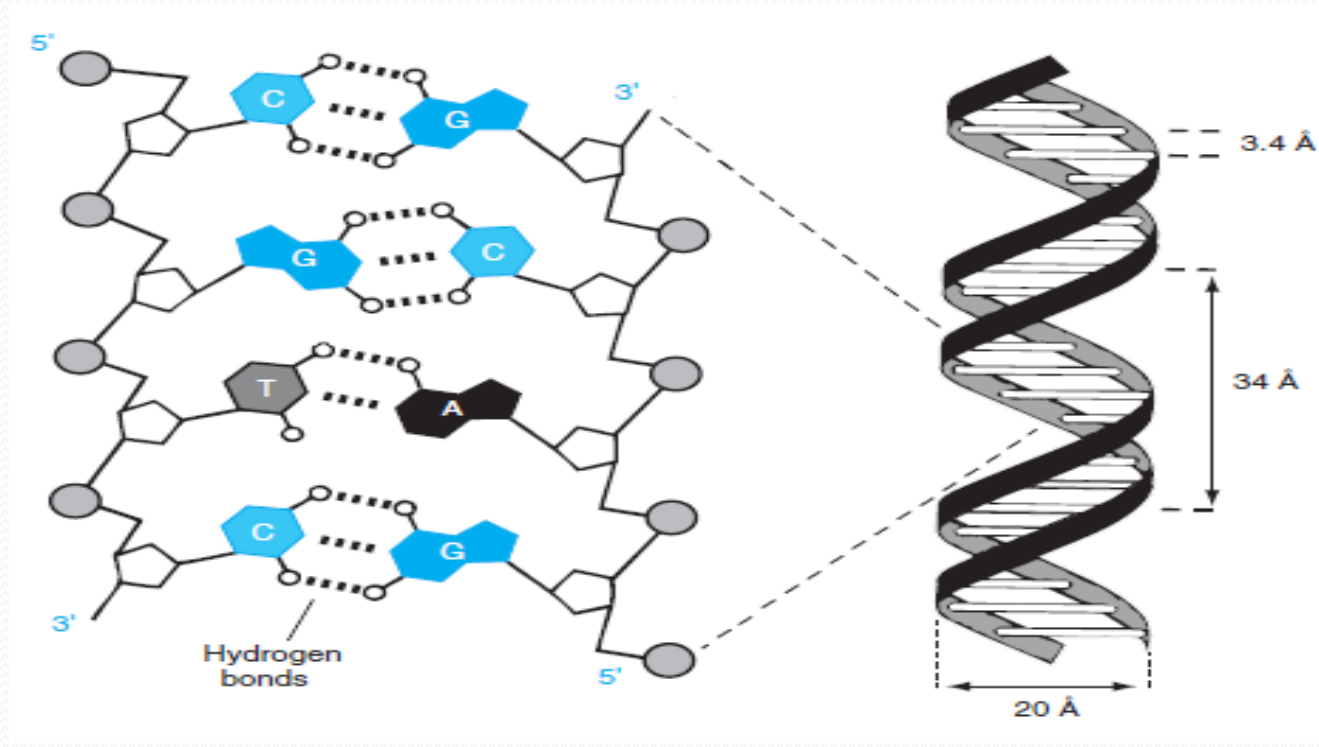
5' end



3' end

**Figure 2.** A portion of a DNA polynucleotide chain, showing the 3'-5' phosphodiester bonds that link adjacent nucleotides.

**Figure 3.** The structure of DNA. **Left,** A two-dimensional representation of the two complementary strands of DNA, showing the AT and GC base pairs. Note that the orientation of the two strands is antiparallel. **Right,** The double-helix model of DNA, as proposed by Watson and Crick. The horizontal “rungs” represent the paired bases. The helix is said to be right-handed because the strand going from lower left to upper right crosses over the opposite strand.





- The anatomical structure of DNA carries the chemical information that allows the exact transmission of genetic information from one cell to its daughter cells and from one generation to the next. At the same time, the primary structure of DNA specifies the amino acid sequences of the polypeptide chains of proteins,

## Organization of Human Chromosomes

- The composition of genes in the human genome, as well as the determinants of their expression, is specified in the DNA of the 46 human chromosomes in the nucleus plus the mitochondrial chromosome. Each human chromosome consists of a single, continuous DNA double helix; that is, each chromosome in the nucleus is a long, linear double-stranded DNA molecule, and the nuclear genome consists, therefore, of 46 DNA molecules, totaling more than 6 billion nucleotides.

- Within each cell, the genome is packaged as chromatin, in which genomic DNA is complexed with several classes of chromosomal proteins.
- The DNA molecule of a chromosome exists in chromatin as a complex with a family of basic chromosomal proteins called histones and with a heterogeneous group of non histone proteins that are much less well characterized but that appear to be critical for establishing a proper environment to ensure normal chromosome behavior and appropriate gene expression.

## The Mitochondrial Chromosome

- A small but important subset of genes encoded in the human genome resides in the mitochondria.
- Human cells can have hundreds to thousands of mitochondria, each containing a number of copies of a small circular molecule, the mitochondrial chromosome. The mitochondrial DNA molecule is only 16 kb in length (less than 0.03% of the length of the smallest nuclear chromosome) and encodes only 37 genes.

- The products of these genes function in mitochondria, although the majority of proteins within the mitochondria are, in fact, the products of nuclear genes. Mutations in mitochondrial genes have been demonstrated in several maternally inherited as well as sporadic disorders.

# Classification of Genetic Disorders

- The role of genetic variation and mutation in predisposing to disease, modifying the course of disease, or causing the disease itself.
- Disease is the result of the combined action of genes and environment, but the relative role of the genetic component may be large or small..

**Three main types are recognized:** Chromosome disorders, single-gene disorders, and multifactorial disorders.

## Chromosome Disorders:

- The defect is due to an excess or a deficiency of the genes contained in whole chromosomes or chromosome segments. **For example**, the presence of an extra copy of one chromosome, chromosome 21, produces a specific disorder, Down syndrome, even though no individual gene on the chromosome is abnormal.
- Chromosome disorders, affecting about 7 per 1000 live born infants.

## Single-gene Defects:

- Caused by individual mutant genes.
- The mutation may be present on only one chromosome of a pair (matched with a normal allele on the homologous chromosome) or on both chromosomes of the pair. In a few cases, the mutation is in the mitochondrial rather than in the nuclear genome.
- Single-gene disorders such as cystic fibrosis and sickle cell anemia.
- Most such defects are rare, with a frequency that may be as high as 1 in 500 to 1000 individuals but is usually much less.



- Single-gene disorders as a group are responsible for a significant proportion of disease and death.
- Single-gene disorders affect 2% of the population sometime during an entire life span.
- In a population study of more than 1 million live births, the incidence of serious single-gene disorders in the pediatric population was estimated to be 0.36%; among hospitalized children, 6% to 8% probably have single-gene disorders.

## Multifactorial Inheritance Disorders:

- Responsible for the majority of diseases, all of which have a genetic contribution, as evidenced by increased risk for recurrence in relatives of affected individuals or by increased frequency in identical twins.
- Multifactorial diseases include prenatal developmental disorders, resulting in congenital malformations such as cleft lip and palate, or congenital heart defects, as well as many common disorders of adult life, such as Alzheimer disease, diabetes, and hypertension.

- There appears to be no single error in the genetic information in many of these conditions. Rather, the disease is the result of one, two, or more different genes that together can produce or predispose to a serious defect, often in concert with environmental factors.
- Estimates of the impact of multifactorial disease range from 5% in the pediatric population to more than 60% in the entire population.

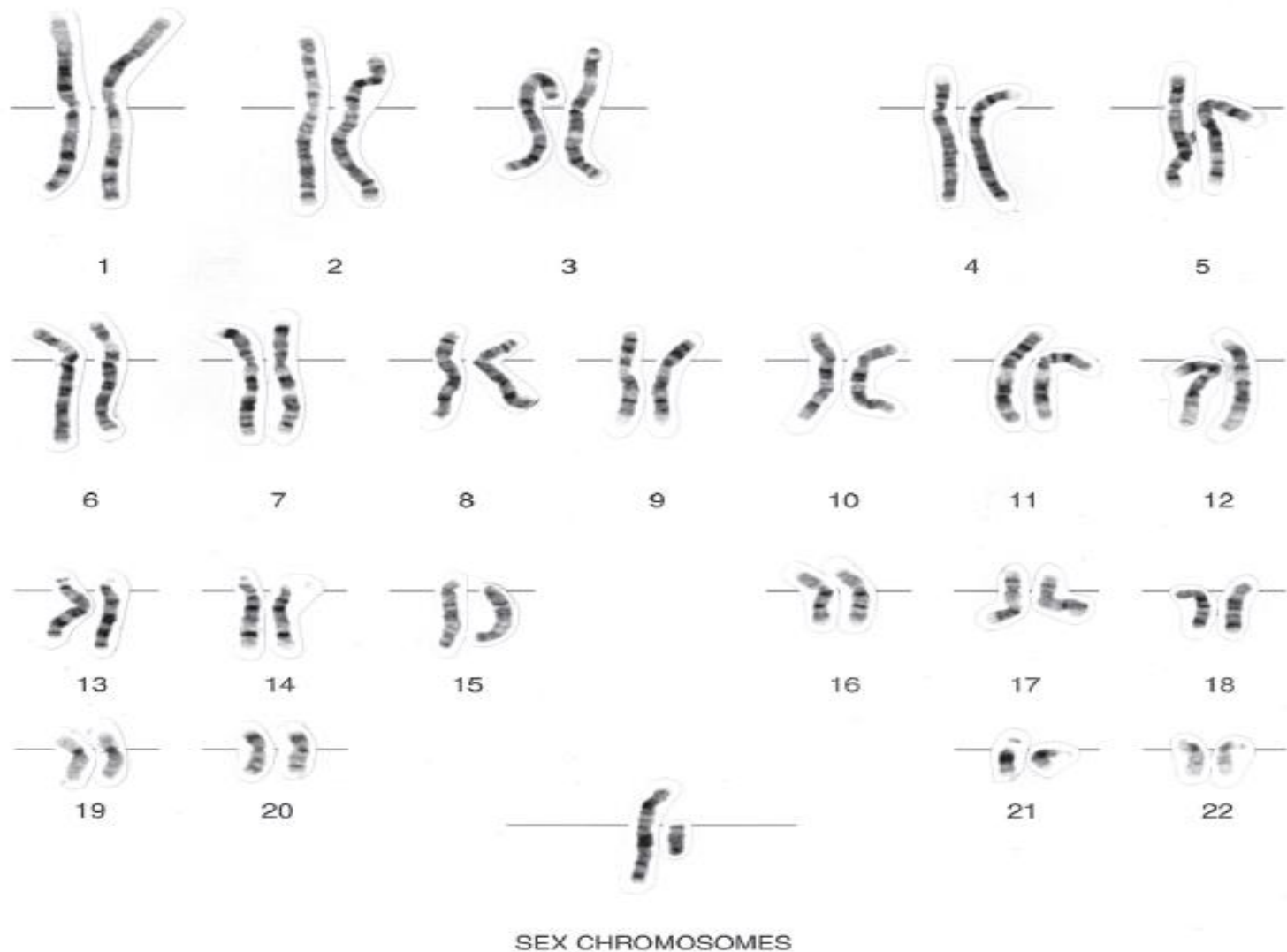
## CELL DIVISION

**Mitosis:** Ordinary somatic cell division, by which the body grows, differentiates, and effects tissue regeneration. Mitotic division normally results in two daughter cells, each with chromosomes and genes identical to those of the parent cell. There may be dozens or even hundreds of successive mitoses in a lineage of somatic cells.

**Meiosis** occurs only in cells of the germline. Meiosis results in the formation of reproductive cells (**gametes**), each of which has only 23 chromosomes

one of each kind of autosome and either an X or a Y. Thus, whereas somatic cells have the **diploid** (*diploos*, double) or the  $2n$  chromosome complement (i.e., 46 chromosomes), gametes have the **haploid** (*haploos*, single) or the  $n$  complement (i.e., 23 chromosomes).

Abnormalities of chromosome number or structure, which are usually clinically significant, can arise either in somatic cells or in cells of the germline by errors in cell division.



**Figure 4.** A human male karyotype with Giemsa banding (G-banding). The chromosomes are at the prometaphase stage of mitosis and are arranged in a standard classification, numbered 1 to 22 in order of length, with the X and Y chromosomes shown separately.