Kingdom of Saudi Arabia
Ministry of Higher Education
King Saud University
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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.
- At the beginning of the 21st century, with the completion of the **Human Genome Project**

- 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.

- A family history is important in diagnosis (disorder may be hereditary)
- The Human Genome Project has made available the complete sequence of all human DNA.
- Knowledge of the complete DNA 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.

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.
- At any specific locus, they may have either identical or slightly different forms of the same gene, called alleles.

## Organization of Human Chromosomes

- The composition of genes in the human genome 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 (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 and encodes only 37 genes.

# Classification of Genetic Disorders

- Genetic variation and mutation have a role in modification of some diseases, or causing the disease itself.
- Disease is the result of the combined action of genes and environment.

**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). Chromosome disorders, affecting about 7 per 1000 live born infants.

## Single-gene Defects:

- Caused by individual mutant genes (sickle cell anemia).
- The mutation may be present on only one chromosome of a pair or on both chromosomes of the pair.
- Most such defects are rare, with a frequency that may be as high as 1 in 500 to 1000 individuals.
- Single-gene disorders affect 2% of the population sometime during an entire life span.

## Multifactorial Inheritance Disorders:

- Responsible for the majority of diseases, all of which have a genetic contribution.
- 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.

- 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.

**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.

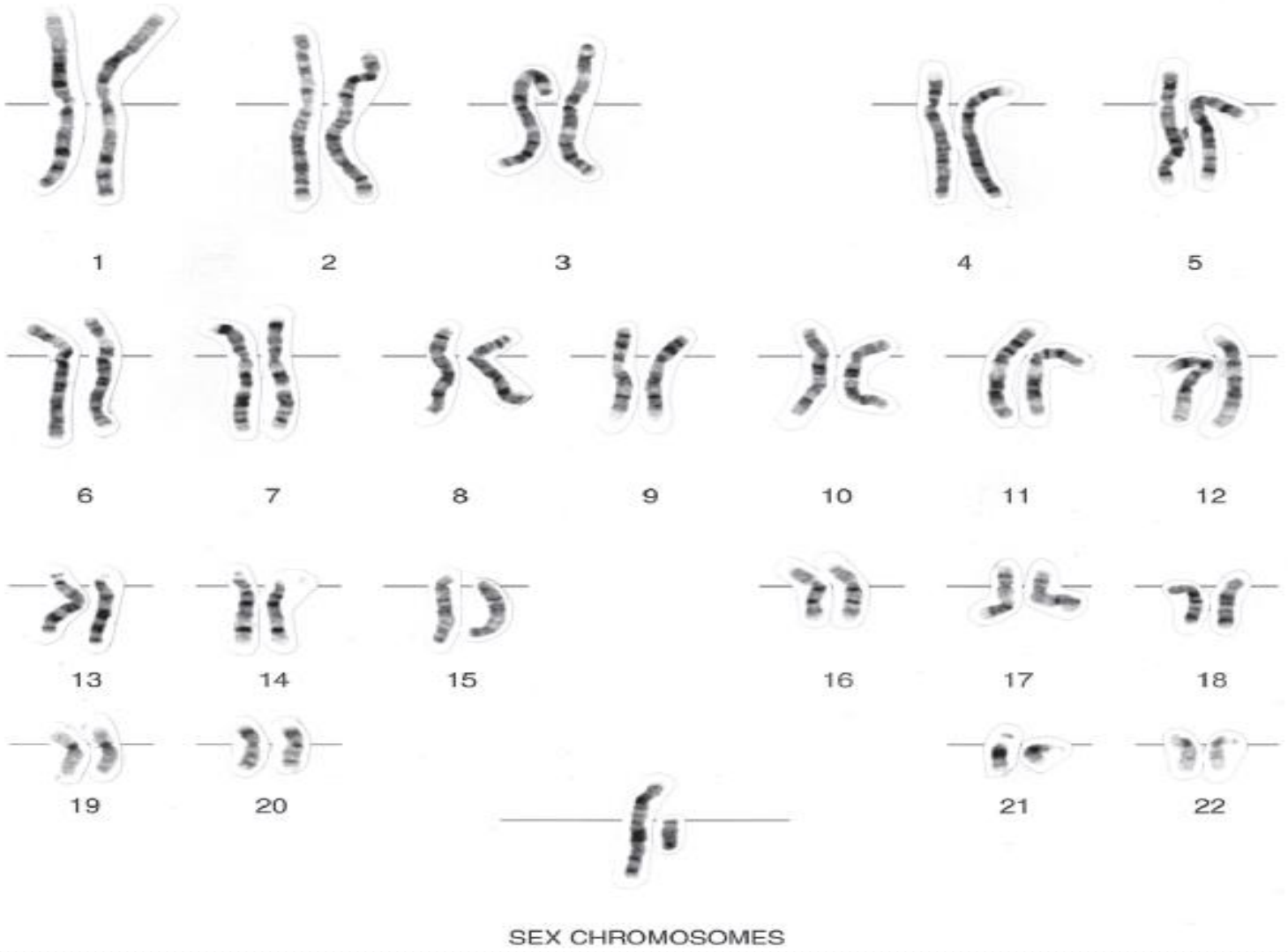


**Figure 4.** A human male karyotype with Giemsa banding (G-banding). The chromosomes are at the prometaphase stage of mitosis and are arranged in a standard classification, numbered 1 to 22 in order of length, with the X and Y chromosomes shown separately.