The History of Medical Genetics

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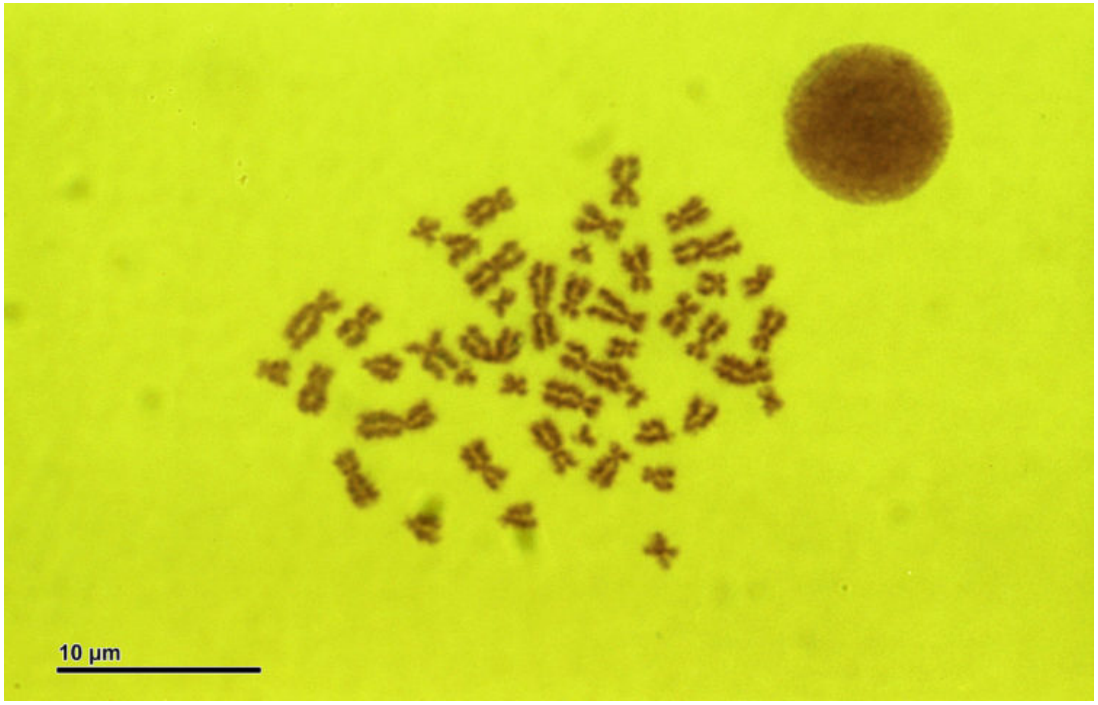
Medical genetics involves the application of genetics for the diagnosis and management of hereditary disorders. With the advancement of medical technology, the scope of medical genetics has widened to include the gene interactions, control of gene expressions, gene variations, and environmental interactions. Genetic diseases are now categorized as classical and non-classical. Classical diseases include chromosomal disorders, Mendelian disorders, and multifactorial disorders. In the non-classical genetic diseases, there is a single gene disorder with an atypical pattern of inheritance. They include the diseases caused by mutations in mitochondrial genes, triplet repeat mutations, genomic imprinting, gonadal mosaicism, and uniparental disomy. Medical genetics differs from human genetics in that human genetics is a field of scientific research that, or may not, apply to medicine, while medical genetics refers to the application of genetics to medical care.



History of Medical Genetics

Until the 21st century, medical genetics was considered as the **detection and treatment of a few phenotypic rare hereditary disorders** like:

- Pre- and perinatal diagnosis
- Analysis of congenital defects
- Treatment of developmental abnormalities

Genetic medicine is a new term for medical genetics and includes areas such as gene therapy, as well as the rapid emerging new medical specialties.

Present of Medical Genetics

Advancement in the fields of **genomics**, **proteomics** and **DNA sequencing** allowed for the development of genomic medicine. This includes:

- Personalized healthcare
- **Previvorship** – surveying a condition before it happens
- Predictive (precision) medicine
- Potential application of gene therapies

Applying the analysis of the human genome and its products to medicine, genetics and genomics go hand in hand. We now consider the following factors together:

- Gene interactions
- Control of gene expressions
- Gene variations
- Environmental interaction

Categories of Genetic Diseases

Classical genetic diseases

- Chromosomal disorders
- Single gene disorders (mendelian disorders/unifactorial disorders)
- Multifactorial disorders

Non-classical genetic diseases

These are single gene disorders with an atypical pattern of inheritance.

- Diseases caused by mutations in mitochondrial genes
- Triplet repeat mutations
- Genomic imprinting
- Gonadal mosaicism
- Uniparental disomy

There are a large group of disorders, congenital malformations, which manifest at birth. Genetic disorders cause many of these.

Chromosomal Disorders

Each nucleated cell in the human body has **46 chromosomes** in the form of **22 homologous pairs and 1 pair of sex chromosomes** that can either be **XX or XY**. The arrangement of these pairs on the length of upper and lower arms of the chromosomes, based on the position of the **centromere**, is known as a **karyotype**.

- Chromosomal disorders are large scale mutations of chromosomes.
- There is no mutation in individual genes.
- There is a duplication or deletion of smaller segments.
- An estimate of 1 in every 200 newborns has some form of chromosomal

abnormality.

Chromosomal disorders can effect autosomes or sex chromosomes, and they can be a result of an alteration in the number or structure; hence,

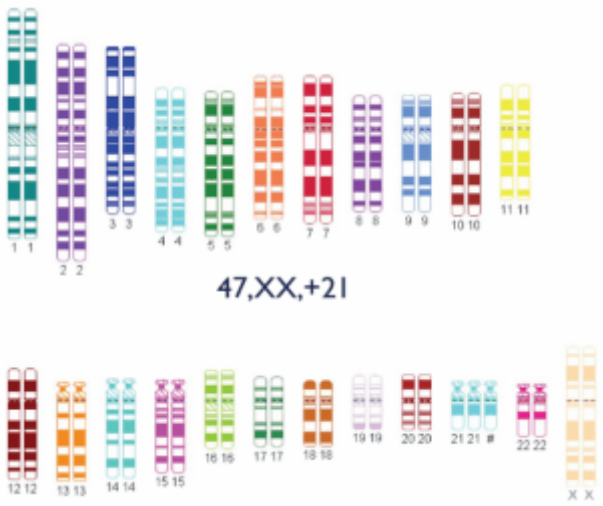
- Numerical abnormalities
- Structural abnormalities

Chromosome mutation was formerly used in a strict sense to mean a change in a chromosomal segment, involving more than one gene. Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis.

Numerical abnormalities

This is called aneuploidy (an abnormal number of chromosomes) and occurs when an individual is either missing a chromosome from a pair (monosomy) or has more than two chromosomes of a pair (trisomy, tetrasomy, etc.) There is a **gain or loss of one or more chromosomes**, autosomal or recessive. A whole set of chromosomes can also be affected.

As the chromosomes are arranged in two sets (2n), the normal chromosomal count is 46.



- Image: "Trisomy 21" by UPO649 1112 mreycor1. License: CC BY-SA 3.0

Euploid: An exact multiple of haploid number n.

- **Aneuploid**: Any number other than the exact multiple of haploid number n. (It is the most common change seen in malignant tissues.)
- **Polyploidy**: A gain of one or more sets of chromosomes. Polyploidy is not long-lived; it results in abortions. It can be of two types:
    - Triploidy is when cells have 3n.
    - Tetraploidy is when cells have 4n.
- **Trisomy**: It is the gain of one chromosome. Examples of autosomal trisomies are:
    - Trisomy of chromosome 21 is called Down's syndrome
    - Trisomy of chromosome 18 is called Edward's syndrome
    - Trisomy of chromosome 13 is called Patau's syndrome
    - **Autosomal trisomies** are not very common. Examples of **trisomy**

of the sex chromosome are:
        - **Klinefelter's syndrome** (XXY) in males
        - **Triple X** (XXX) syndrome in females
- **Monosomy**: It is a loss of one chromosome. **Turner's syndrome** (45 XO) is the monosomy of sex chromosome in a female.

All trisomies and monosomies by definition are aneuploidies.

Gain or loss of X and Y chromosomes is more common. It is compatible with life. However, any loss of autosomal chromosomes leads to abortions in the early stages of pregnancy.

The causes of trisomy and monosomy:

- Nondisjunction of a homologous pair of chromosomes at the 1st meiotic division.
- A failure of sister chromatids to separate during the 2nd meiotic division.
- A failure of sister chromatids to separate during somatic cell division, leading to the production of two aneuploidy cells.

Structural abnormalities

In the case of structural abnormalities, the chromosome number is normal, but there are morphological and structural abnormalities. The usual cause of such abnormalities is **chromosomal breakage** resulting in **loss or re-arrangement** of material.

Types of structural abnormalities are as follows:

- **Deletion** is the loss of a terminal or interstitial piece of chromosome.
    - **Terminal**: There is only one break in the chromosome, and the portion distal to the break is lost. Loss of this piece produces signs and symptoms based on the genes that were lost.
    - **Interstitial**: There are two breaks, and the piece between these two breaks is lost, resulting in a shorter chromosome. The consequences are the same as that of terminal Example: Cri du chat which is the loss of short arm of the chromosome.

Known disorders in humans include Wolf-Hirschhorn syndrome, which is caused by partial deletion of the short arm of chromosome 4; and Jacobsen syndrome, also called the terminal 11q deletion disorder.

- **Inversion**: There are two breaks in the chromosome. The piece between these two breaks rotates 180 degrees and is fixed back in the same rotated position. The breaks can involve either the short arm or the long arm. This type of inversion is called **paracentric**. The break can also involve both arms and is called **pericentric**. This type is more severe.
- **Translocation** is the exchange of chromosome segments between the non-homologous chromosomes. There are two main types of translocations: 1) Robertsonian translocation: An entire chromosome has attached to another at the centromere – in humans, these only occur with chromosomes 13, 14, 15, 21, and 22. 2) Reciprocal translocation: Segments from two different chromosomes have been exchanged.

- **Isochromosomes**: This type of abnormality results from the aberrant division of the centromere. The resulting chromosomes are such that once is formed of

two short arms and the other has two long arms. Each of these is called isochromosome. They are seen in some cases of Down's syndrome and Turner's syndrome.
- **Ring chromosomes**: There is a deletion of both ends of chromosomes and these ends, due to the sticky nature of DNA, stick together to form a ring or a circle shaped chromosome.

Single Gene Disorders (Mendelian Disorders/Unifactorial Disorders)

There are more than 5,000 known Mendelian disorders. They account for a total 1% of adult hospital admissions and 6-8% of all hospital pediatric admissions. These disorders represent the most common genetic abnormality. They are caused by **mutation in a single gene**.

Part of the DNA that codes for a polypeptide chain is called a gene. DNA that codes directly for information is only 2%. Non-coding sequence within the genes (**intronic sequence**) is 24%. The remaining 74% is the non-coding sequence that is outside the genes. There are almost 30,000 genes in the human body.

Exon is the coding sequence of the genes. Some genes have many exons, and some have only a few. Some genes are large in size, while others are small. This is the reason why chromosomal deletion or duplication of some genes have minimal or no clinical presentation.

Genes behave as:

- **Dominant**, i.e. when only one of the alleles becomes mutated, it results in a genetic disease.
- **Recessive**, i.e. the diseases result only when both alleles (of both the maternal and paternal origin) are affected by the same mutation.
- The 3rd category of genes is the ones that are situated on the sex chromosomes, but they determine the autosomal character. They are called **sex-linked genes**.

So, we have:

- Autosomal dominant (AD) disorders
- Autosomal recessive (AR) disorders
- Sex-linked disorders

Why do some genes act in a dominant manner, while others behave in a recessive one?

Previously, it was thought that one gene is responsible for the formation of only one type of protein; however, today, the fact is that a single gene is responsible for the formation of a single type of polypeptide. The structure and function of our body is determined by proteins. There are different kinds, such as:

- Structural proteins (fibrous tissue, elastic tissue)
- Immunoglobulins
- Signal transducing proteins
- Receptors
- Enzymes

- Hormones

Whether the action of a gene is dominant or recessive depends upon the type and function of the protein being produced by that gene, e.g. HLA and ABO blood group antigens.

Usually, the dominant genes produce the following types of proteins:

- **Major structural/non-enzymatic proteins**, which form or are present in many parts of the body such as:
    - Collagen
    - Spectrin
    - Fibrillin
    - Elastin

Mutation in genes producing these proteins will lead to **achondroplasia**, **Ehlers-Danlos syndrome**, etc.

- A **key enzyme** in a complex metabolic pathway usually under feedback control e.g. AD porphyria.
- A **membrane receptor** regulating a metabolic pathway, e.g. when the receptors for LDL are mutated, leads to AD familial hypercholesterolemia disease.
- **Membrane transport proteins.**

Therefore, one single defected copy of a dominant gene can produce signs and symptoms related to the deficient protein.

Relevant terms

- **Pleiotropy**: Multiple phenotypic effects are seen as a result of single gene mutation; for example, there is skeletal, cardiovascular and eye defect in Marfan's syndrome.
- **Genetic heterogeneity**: When the same trait is produced as a result of mutations at several genetic loci; for example, retinitis pigmentosa.
- **Recessive genes** usually produce those enzymes which share in catabolic pathways and are generally non-key enzymes. Loss of one copy of the gene is compensated by the other copy of the active and normal gene, and therefore, 50% of the protein is still present. Examples:
    - Some types of thalassemia
    - Mucopolysaccharidosis
    - Lipidosis
    - Phenylketonuria (PKU)

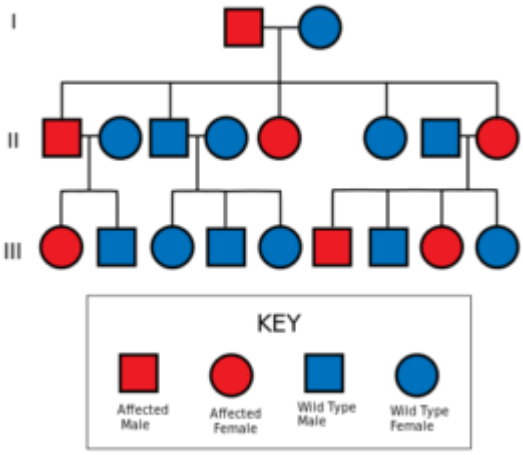


Image: “Autosomal dominant pedigree chart. In autosomal dominance, the chance of receiving and expressing a particular gene is 50% regardless of the sex of parent or child.” by Jerome Walker – Own work. License: CC BY 2.5

Sex-linked diseases

Sex linkage is the phenotypic expression of an allele related to the all some (sex chromosome) of the individual. The pattern of sex-link disease transfer is shown in the following figures. Gene mutations can be of the following types:

1. **Point mutations**: Single base substitution, which is the most common type.
    - Silent
    - Neutral
    - Missense
    - Non-sense
    - Longer protein
2. **Unequal crossing over**

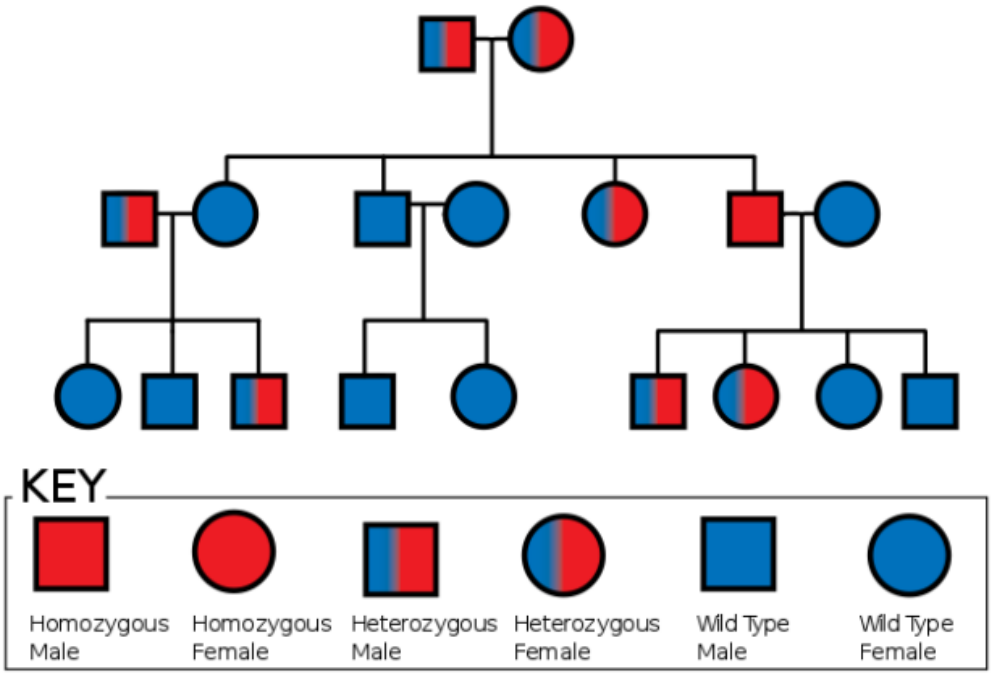


Image: "An example of a family pedigree displaying an autosomal recessive trait." by Jerome Walker – Own work. License: CC BY 2.5

3. **Addition or deletion mutation**
    - Single base addition/deletion leads to a frameshift
    - Two bases lead to a frameshift mutation
    - 3 or a multiple of 3
    - A piece of DNA

Multifactorial Disorders

Multifactorial disorders affect many of the physiologic characteristics, such as:

- Weight
- Height
- Blood pressure
- Hair color

These disorders have abnormalities in two or more genes of small effect, but environmental non-genetic factors are also involved. Even monozygotic twins can have different weights and heights because of environmental influences. Examples of multifactorial disorders are:

- Diabetes mellitus
- Hypertension
- Gout
- Certain forms of congenital heart disease
- Skeletal abnormalities
- Schizophrenia
- Bipolar disorders

Future of Medical Genetics

Ever-expanding database of human genetic variations and our understanding of genomics will inevitably lead to extensive discovery and development in public health and availability of tools in practice medicine.

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