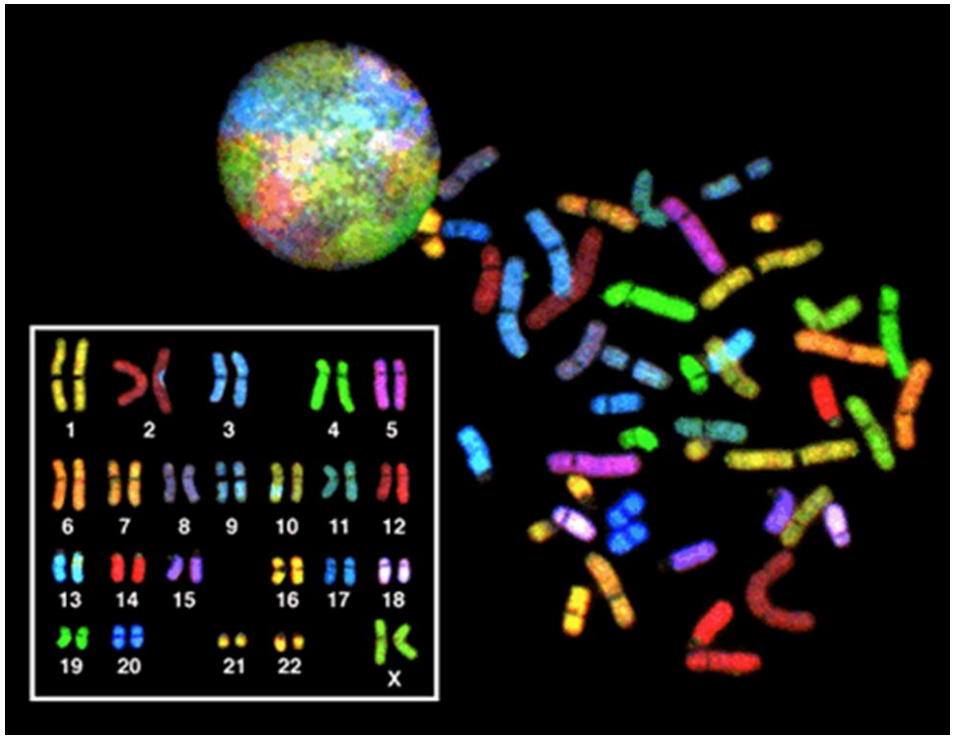
Genetic Disorders

Inheritance of Genetic Traits



Prof. Nilmini Silva Gunawardene
Molecular Medicine Unit
Faculty of Medicine

Learning Outcomes

Student by completion of the lectures should be able to :

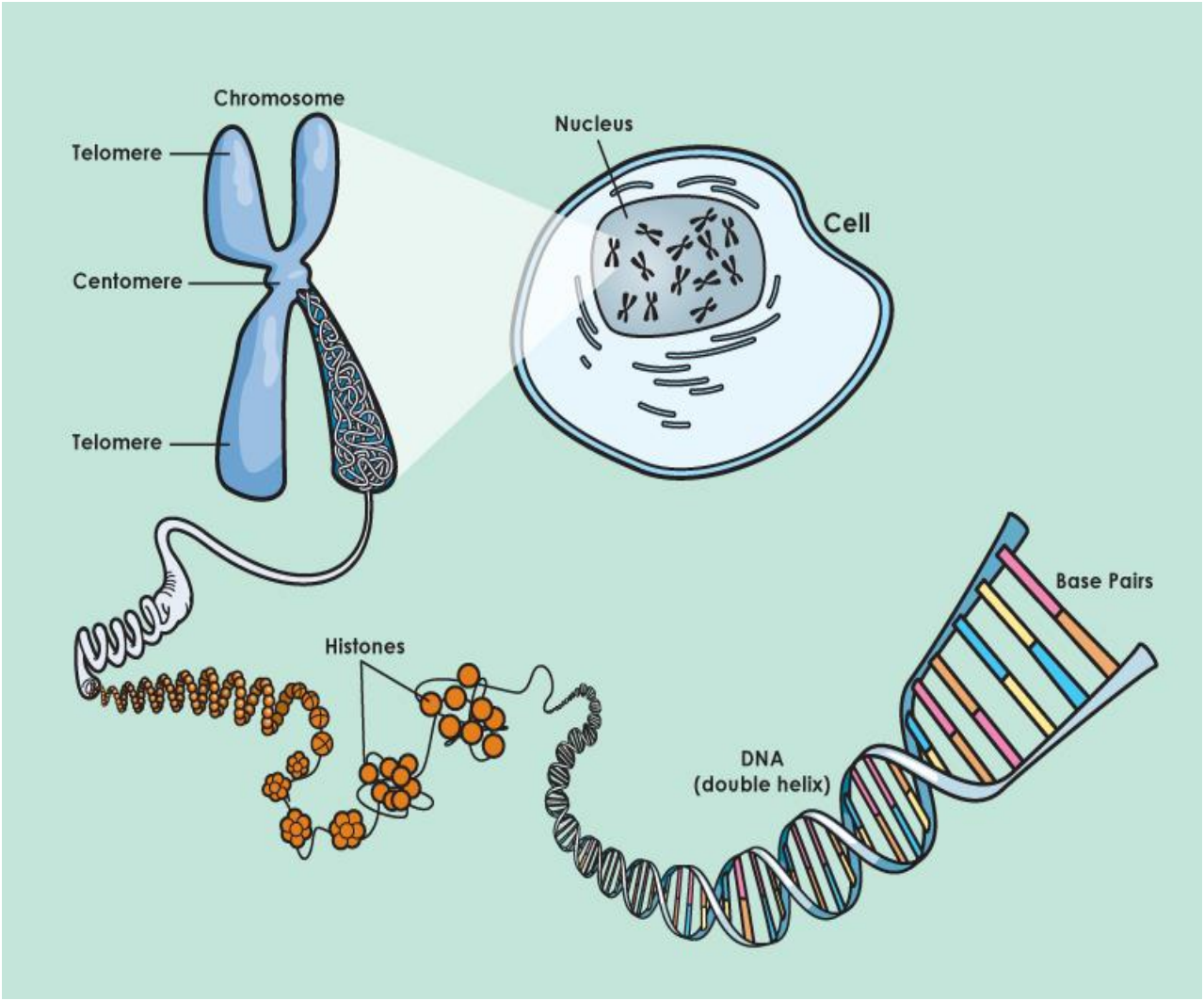
- List the types of genetic disorders that could affect the humans.
- Briefly describe each of the above disorders; namely chromosomal, single gene, polygenic, mitochondrial and somatic disorders giving examples.
- Understand the basis of the numerical and structural chromosomal abnormalities leading to human disorders and give examples of each of the above.
- Outline the mechanism of non disjunction and translocation in the causation of chromosomal trisomies.
- Briefly explain the maternal age effect and its relevance to chromosomal trisomies.

Overview

- DNA, Chromosomes & Genes
- Genetic disease
- Types of genetic diseases
  - Single gene disorders
  - Polygenic disorders
  - Chromosomal disorders
  - Mitochondrial & somatic disorders

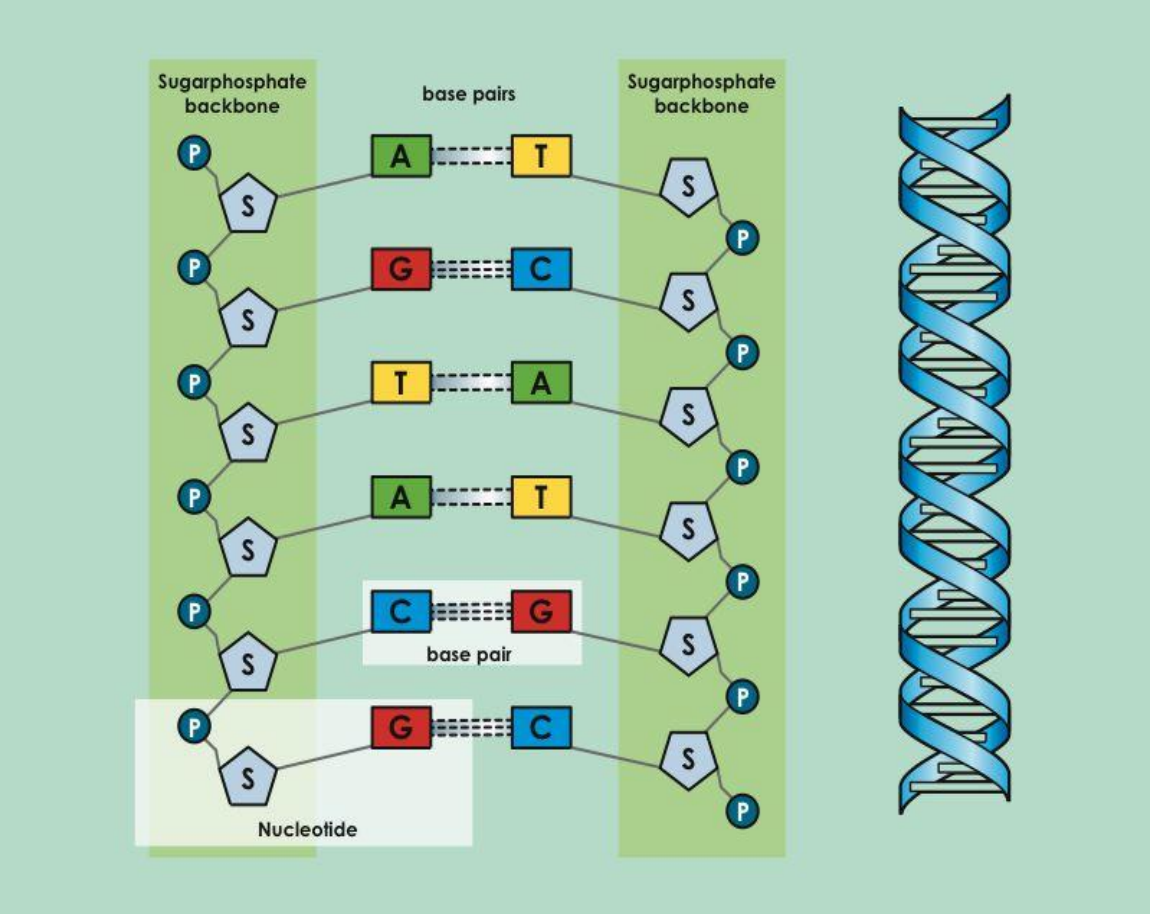
DNA – genetic blueprint

- **Deoxyribonucleic acid (DNA)**
- **Located in the nucleus**
- **rapped up in structures called chromosomes.**
- **46 Chromosomes - 23 Pairs in every cell**



DNA is made of segments called Nucleotides

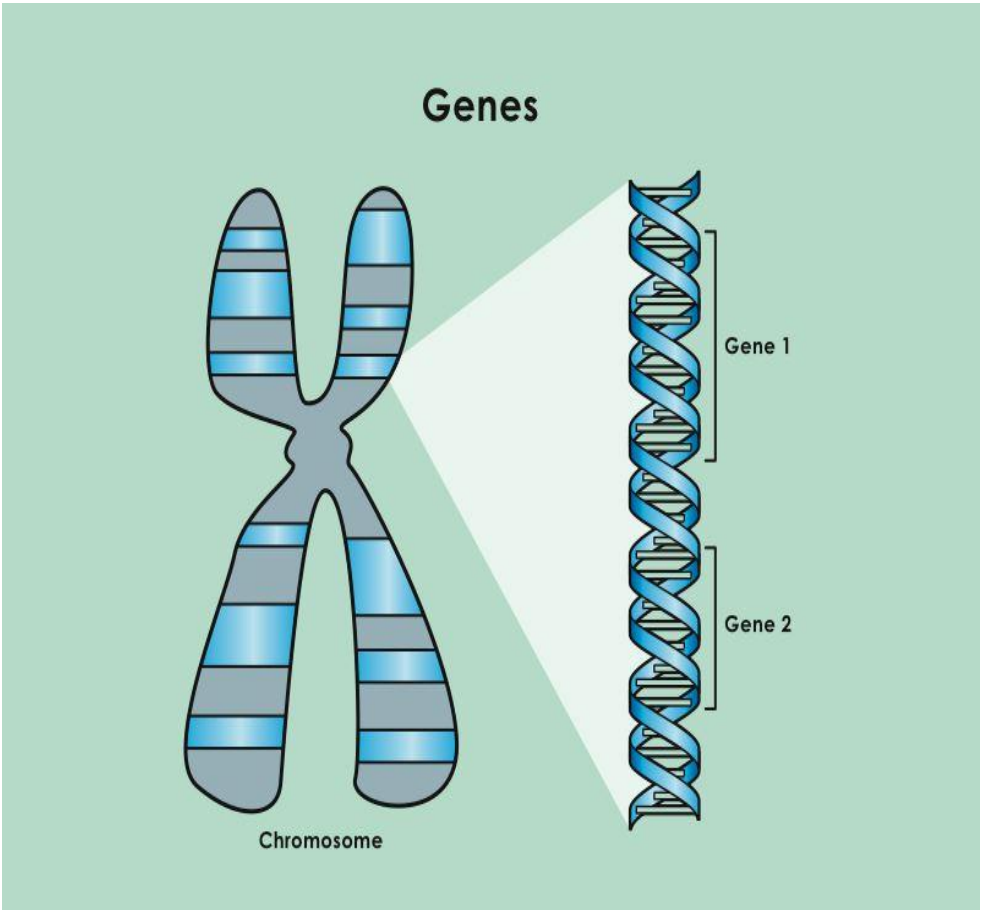
- The building blocks of DNA are nucleotides.
- Each nucleotide has a sugar (S), a phosphate (P) and a nitrogen base (A, G, T or C)
- There are 4 different nitrogen bases in DNA and they can vary from one nucleotide to the next
- The alternating bases provide the CODE



- **In humans, the DNA molecule in a cell, if fully extended, would have a total length of 1.7 metres. If you unwrap all the DNA you have in all your cells, you could reach the moon ...6000 times!**

What is a gene?

- **A part of the DNA that codes for a protein.**
- **Not all the DNA codes for proteins.**
- **30,000 genes in the human genome.**



What is the genome ?

- **Genome of an organism is its total hereditary information and is encoded in the DNA (or, for some viruses, RNA). This includes both the genes and the non-coding sequences of the DNA.**

What is the human genome ?

- **The human genome is stored on 23 chromosome pairs.**

- **Twenty-two of these are autosomal chromosome pairs, while the remaining pair is sex-determining.**

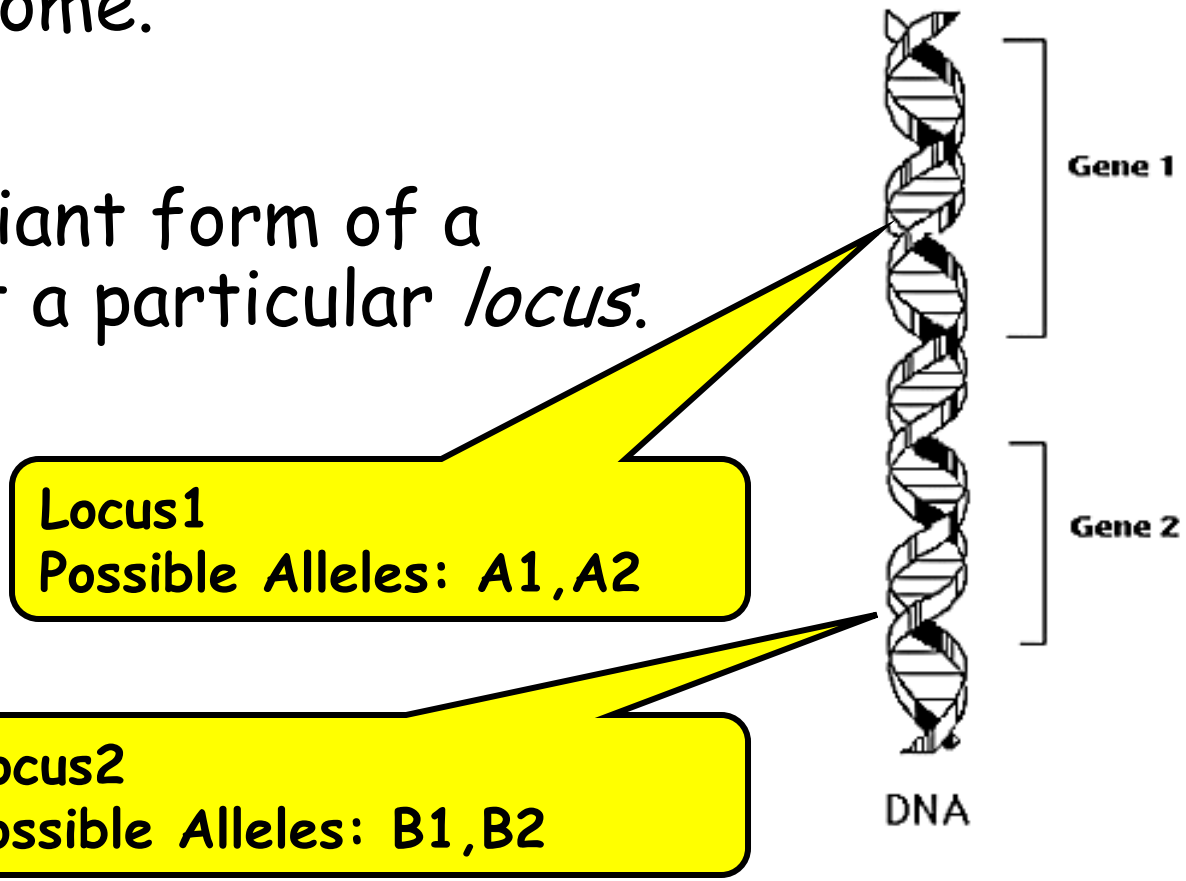
- **The haploid human genome occupies a total of just over 3 billion DNA base pairs and contains an estimated 20,000–30,000 protein-coding genes.**

- **Only about 1.5% of the genome codes for proteins, while the rest is comprised of RNA genes, regulatory sequences, introns and (controversially) "junk" DNA.**

Alleles and Locus

- **Locus** – location of a *gene/marker* on the chromosome.

- **Allele** – one variant form of a gene/marker at a particular *locus*.



Mutations

- **PERMANENT change in DNA.**
- **Gene mutations can be either inherited from a parent or acquired.**
- **A hereditary mutation is a mistake that is present in the DNA of virtually all body cells.**
- **Also called *germ line* mutations because the gene change exists in the reproductive cells and can be passed from generation to generation.**
- **The mutation is copied every time body cells divide.**

Genetic disease

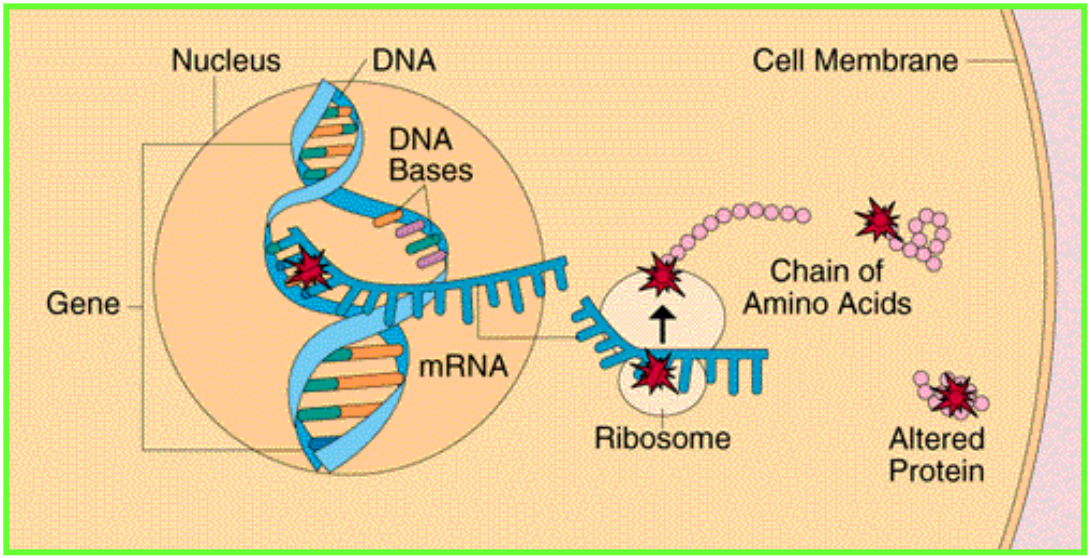
What is a genetic disease?

A genetic disease or disorder is any disease that is caused by an abnormality in an individual's genome.

The abnormality can range from a discrete mutation in a single base in the DNA of a single gene to a gross chromosome abnormality involving the addition or subtraction of an entire chromosome or set of chromosomes.

How are genes linked to disease

More than 6,000 diseases are thought to stem from mutated genes inherited from one's mother and/or father. Common disorders such as heart disease and most cancers arise from a complex interplay among multiple genes and between genes and factors in the environment and also some diseases associate with alteration of gene expression.



sickle-cell disease

	Thr	Pro	Glu	Glu	beta^A chain
...A C T	C C T	G A G	G A G...	beta^A gene	
Codon #	4	5	6	7	
...A C T	C C T	G T G	G A G...	beta^S gene	
	Thr	Pro	Val	Glu	beta^S chain

beta chain of hemoglobin

cystic fibrosis

Patient	Mutation	Result
A	482 C G C → C A C	Arg-117 → His-117
B	1609 C A G → T A G	Gln-493 → STOP
C	**Insertion** of 2 nucleotides (AT) at 2566	**Frameshift**
D	**Deletion** of one C at 3659	**Frameshift**
E	**Deletion** of 3 nucleotides at 1654-1656	Deletion of **Phe-508**

cystic fibrosis transmembrane conductance regulator (CFTR)

What are the different types of Genetic diseases?

- **Number of different types of genetic disorders.**
  - **Single gene disorders**
  - **Polygenic disorders**
  - **Chromosomal disorders**
  - **Mitochondrial & somatic disorders**

Frequency of Different Types of Genetic Disease

Type	*Incidence at Birth (per 1,000)*	*Prevalence at Age 25 Years (per 1,000)*	*Population Prevalence (per 1,000)*
Diseases due to genome/chromosome mutations	6	1.8	3.8
Disease due to single gene mutations	10	3.6	20
Disease with multifactorial inheritance	~50	~50	~600

Single gene disorders

(Mendelian or monogenic)

- **Caused by changes or mutations that occur in the DNA sequence of a single gene.**

- **Over 4,000 known single-gene disorders, which occur in about 1 out of every 200 births. The global prevalence of all single gene diseases at birth is approximately 10/1000 (WHO, 2018).**

Single gene disorders continued

(Mendelian or monogenic)

- **Examples of single gene disorders are cystic fibrosis, sickle cell anemia, Marfan syndrome, Huntington's disease, and hemochromatosis.**

- **Single-gene disorders are inherited in recognizable patterns: autosomal dominant, autosomal recessive, and X-linked.**

Cystic Fibrosis (CF)

- **Mutations in the *Cystic Fibrosis Transmembrane Conductance Regulator* (*CFTR*) gene**
- **Cause: deletion of only 3 bases on chromosome 7**
- **Body produces abnormally thick mucus in the lungs and intestines**
- **The thick mucus fills the lungs; potential respiratory failure**
- **Common among Caucasians; Disease occurs in 1 in 2,500 to 3,500 white newborns and 1 in 20 Caucasians are carriers**

Sickle cell disease (sickle cell anemia)

- **Mutations in the *HBB* gene cause sickle cell disease.**

- **The haemoglobin molecule is defective. After haemoglobin molecules give up their oxygen, some may cluster together and form long, rod-like structures which become stiff and assume sickle shape.**

Sickle-cell disease cont

- **sickled red blood cells cannot squeeze through small blood vessels. Instead, they stack up and cause blockages that deprive organs and tissues of oxygen-carrying blood. This process produces periodic episodes of pain and ultimately can damage tissues and vital organs.**

Sickle-cell disease cont'd

- **One mutated allele - person will produce both normal and sickle shaped cells. These people will not usually have symptoms of the disease.**

- **Possible cure: bone-marrow transplants.**

- **Treatment:**
  - **Avoid being overly active**
  - **Watch your diet**

Single gene disorders continued

Marfan syndrome

- **Genetic disorder of the connective tissue. The degree to which people are affected varies. People with Marfan tend to be tall and thin, with long arms, legs, fingers and toes.**
- **Reduced, absent or structurally abnormal fibrillin seen in skin fibroblasts cultures.**
- **Variety of mutations in fibrillin 1.**

Huntington's disease

✓ **Degenerative brain disorder which results in an eventual loss of both mental and physical control.**

✓**causes the progressive breakdown of nerve cells in the brain.**

✓**Mutation in HTT gene;** codes for a protein - **huntingtin.**

Hereditary Hemochromatosis

- **A disorder that causes the body to absorb too much iron from the diet. The excess iron is stored in the body's tissues and organs, particularly the skin, heart, liver, pancreas, and joints.**
- **Because humans cannot increase the excretion of iron, excess iron can overload and eventually damage tissues and organs. For this reason, hereditary hemochromatosisis also called an iron overload disorder.**
- **A gene called HFE is most often the cause of hereditary hemochromatosis. The HFE gene has two common mutations, C282Y and H63D.**
- **Homozygotes – increased serum iron, transferrin saturation.**
- **Heterozygotes normal – 3 to 10-fold increase in serum ferritin.**

Polygenic disorders
(Multifactorial)

- **Polygenic traits are traits that are controlled by multiple genes instead of just one. The genes that control them may be located near each other or even on separate chromosomes. Because multiple genes are involved, polygenic traits do not follow Mendel's pattern of inheritance.**

Polygenic disorders

(Multifactorial)

- **Traits are discontinuous (with distinct phenotypes e.g. diabetes mellitus) or continuous (with a lack of distinct phenotypes e.g. Height)**
- **Determined by an interaction of a number of genes at different loci together with environmental factors.**
- **For example, different genes that influence breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22.**

Polygenic disorders

(Multifactorial)

- **Some common chronic diseases are multifactorial disorders. Examples include heart disease, high blood pressure, Alzheimer's disease, arthritis, diabetes, cancer, and obesity.**

- **Associated with heritable traits such as fingerprint patterns, height, eye color, and skin colour.**

Diabetes mellitus

- **Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period.**
- **Disease in which the body does**

  not produce or properly use insulin.
  - **Insulin is a hormone that is needed to convert sugar, starches, and other food into energy needed for daily life.**
  - **Diabetes is the leading cause of kidney failure, blindness, and amputation in adults, and can also lead to heart disease.**

Diabetes

- **Type 1 diabetes: It is due to the body's malfunction to produce insulin in the body, and requires the person to inject insulin. "Insulin-Dependent Diabetes Mellitus" (IDDM) or "Juvenile Diabetes".**
- **Type 2 diabetes: It is due to insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. Non insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".**
- **Genetic mutation can lead to Type 1 diabetes, but no one sure if relative to a specific gene.**

Albinism

- **Rare group of genetic disorders that cause the skin, hair, or eyes to have little or no colour. Albinism is also associated with vision problems.**
- **Patients are unable to produce skin or eye pigments, and thus are light-sensitive**
- **A defect in one of several genes that produce**

or distribute melanin causes albinism.

Mitochondrial disorders

- **Caused by mutations in the nonchromosomal DNA of mitochondria.**

- **Mitochondria are;**
  1. **Small round or rod-like organelles**
  2. **Involved in cellular respiration**
  3. **Found in the cytoplasm of plant and animal cells.**
  4. **Each mitochondrion may contain 5 to 10 circular pieces of DNA.**
  5. **Growth and division dependent on genes from both mitochondrial and nuclear chromosomes.**

❖ **Mitochondrial DNA is maternally inherited as sperm does not contribute mitochondria to zygote.**

❖ **Diseases are maternally inherited and affected males cannot transmit the disease.**

Mitochondrial disorders continued

Examples of mitochondrial diseases

Disease	Phenotype
Leber's hereditary optic atrophy	Rapid optic nerve death, leading to blindness in young adult life.
Pearson syndrome	Pancreatic insufficiency, pancytopenia, Lactic acidosis.

Somatic disorders

- Results from a culmination of genetic mutations.
- Mutations only occur after conception and confined to certain somatic cells.
- Not inherited.
- Examples are Cancers; Retinoblastoma (point mutation)

Mitochondrial disorders continued

Examples of mitochondrial diseases

Disease	Phenotype
Leber's hereditary optic atrophy	Rapid optic nerve death, leading to blindness in young adult life.
NARP, Leigh disease	Neuropathy, ataxia, retinitis pigmentosa, Developmental delay, mental retardation, Lactic acidemia
MELAS	Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes
MERRF	Myoclonic Epilepsy with Ragged Red Fibers in muscle Ataxia, sensorineural deafness
Pearson syndrome	Pancreatic insufficiency, pancytopenia, Lactic acidosis.