# Genetic Variation in Disease Susceptibility and Drug Response


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# Outline

- What is Disease Susceptibility
- Role of Variants in Disease Susceptibility.
- Mechanisms of Disease Susceptibility
- Role of Variants in Drug Response
- Mechanisms Linking Genetic Variation to Drug Response

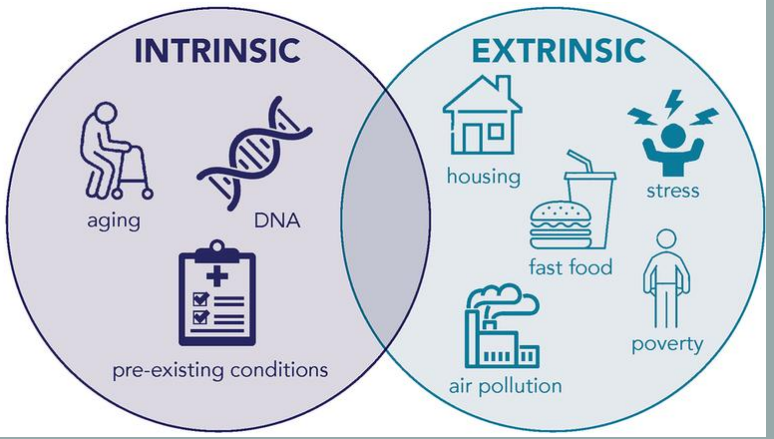
# Objectives

- To understand and explain the fundamental principles of Genetic Variation in Disease Susceptibility and Drug Response.

# ❑ What is Disease Susceptibility?

- It refers to the **likelihood or predisposition** of an individual to **develop a particular disease**.

- This predisposition can be influenced by a combination of **genetic variation**, **environmental**, and **lifestyle factors**.



## ❖ Role of Variants in Disease Susceptibility:

- Variations in DNA sequences, such as SNPs, and CNVs, can **increase or decrease** the **risk of developing certain diseases**.

i. **Monogenic Disorders**: Diseases caused by mutations in a single gene.

ii. **Polygenic Disorders**: Diseases influenced by multiple genetic variants.

iii. **Family History**: A family history of certain diseases can indicate a higher genetic risk.

## ❑ Method of Genetic Variation associated with diseases Susceptibility:

### ❖ Genome-Wide Association Studies (GWAS):

- A method used to identify genetic variants associated with diseases by scanning the genome of many individuals.

## ❑ Process:

❖ Collect DNA samples from a large cohort.

❖ Genotype individuals for millions of SNPs.

❖ Perform statistical analysis to identify associations between SNPs and diseases.

➢ Examples: **BRCA1/BRCA2 Mutations**, **APOE ε4 Allele**

# ❑ Mechanisms of Disease Susceptibility:

1. Genetic Mechanisms

2. Immune System Modulation

3. Metabolic Pathways

# ❑ Genetic Mechanisms:

## i. Loss-of-Function Mutations:

Mutations that reduce or eliminate the function of a protein, leading to disease (e.g., **BRCA1/BRCA2** mutations in breast cancer).

## ii. Gain-of-Function Mutations:

Mutations that **confer new** or **enhanced functions** to a protein, potentially leading to disease (e.g., **oncogenes in cancer**).

## iii. Regulatory Variants:

Variants in non-coding regions that affect **gene expression levels** (e.g., promoter or enhancer regions).

# ❑ Immune System Modulation:

**i. Autoimmune Diseases:**

Genetic variants can lead to an **overactive immune response** (e.g., rheumatoid arthritis, lupus).

**ii. Immunodeficiency:**

Genetic defects can impair the immune system, increasing susceptibility to infections.

# ❑ Metabolic Pathways:

**Enzyme Deficiencies:**

Genetic variants can lead to **deficiencies in enzymes**, disrupting metabolic pathways and causing diseases (e.g., **phenylketonuria**).

**Hormonal Imbalances:**

Genetic factors can affect hormone production and regulation, leading to diseases (e.g., diabetes, thyroid disorders).

# ❑ Examples of Disease Susceptibility

## 1. Cardiovascular Diseases:

- **Genetic Variants**: Variants in genes like **APOE, LDLR**, and **PCSK9** can influence **cholesterol levels** and **heart disease risk**.

- **Environmental Factors**: Diet, exercise, and smoking can significantly impact cardiovascular health.

## 2. Cancer:

- **Genetic Variants**: Mutations in tumor suppressor genes (e.g., **TP53**) and oncogenes (e.g., **KRAS**) can increase cancer risk.
- **Environmental Factors:** Exposure to carcinogens like **tobacco smoke** and **UV radiation** can contribute to cancer development.

## 3. Infectious Diseases:

- **Genetic Variants**: Variants in immune-related genes (e.g., **HLA**) can affect susceptibility to infections (e.g., **HIV, tuberculosis**).
- **Environmental Factors:** Living conditions, hygiene can influence infection risk.

# 4. **Neurodegenerative Diseases**:

- **Genetic Variants:** Variants in genes like **APOE, SNCA, and MAPT** can increase the risk of diseases like **Alzheimer's and Parkinson's**.

- **Environmental Factors**: Exposure to **toxins, diet, and physical** activity can influence neurodegenerative disease risk.

# ❖ Role of Variants in Drug Response:

- **Definition of Pharmacogenomics:** Is the study of how genetic variation affects an individual's response to drugs.

- It combines **pharmacology** and **genomics** to develop effective, safe **medications and doses** tailored to a person's genetic makeup.

- Understanding **genetic variation in drug response** can lead to **personalized medicine**, **improving drug efficacy** and **reducing adverse effects**.

# ❑ Mechanisms Linking **Genetic Variation** to Drug Response

## 1. Drug Metabolism:

✓ Variants in genes encoding drug-metabolizing enzymes (e.g., **CYP450 family**) can alter **drug efficacy** and **toxicity**.

## 2. Drug Targets:

✓ Variants in **drug target genes** can influence drug binding and activity.

## 3. Drug Transporters:

✓ Variants in **transporter proteins** can affect drug absorption, distribution, and excretion.

# ❑ Examples of Genetic Variants and Drug Response

## A. Warfarin:

✓ Variants in the **VKORC1** and **CYP2C9** genes affect dosing requirements and risk of bleeding.

## B. Abacavir:

✓ HLA-B gene is associated with hypersensitivity reaction to this HIV drug.

## C. Clopidogrel:

✓ Variants in the **CYP2C19** gene affect the drug's activation and efficacy in preventing blood clots.

# D. Tamoxifen:

- Variants in the **CYP2D6 gene** influence the drug's metabolism and effectiveness in treating breast cancer.

# References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# Thanks