COURSE: GENETIC FACTORS IN EFFECTIVE DRUG USE

SUBJECT: Mechanism of Genetic Differences Between Individuals in Drug Use

Professor Dr. H. Sinan SÜZEN

Pharmaceutical Toxicology Department

Absorption
Distribution
Metabolism
Excretion

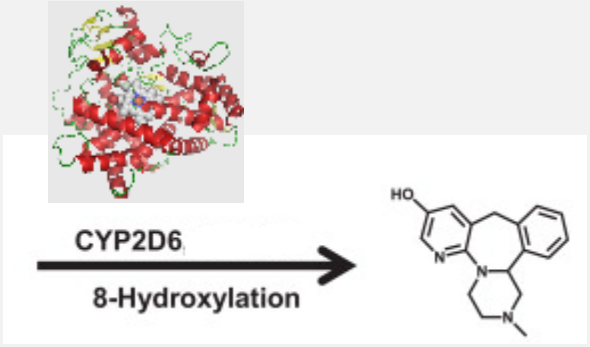
Drug targets
Disease related pathways

Pharmacokinetics + **Pharmacodynamics** → **Drug response / Toxicity**

Drug metabolising enzymes
Drug transporters

Enzymes
Receptors
Ion channels
Lipoproteins
Coagulation factors

DNA → RNA → Protein → Activity (Function: increase or decrease)



DNA → **RNA** → **Protein**

Person 1: CC CCA **G** GACG

Person 2: CC CCA **A** GACG

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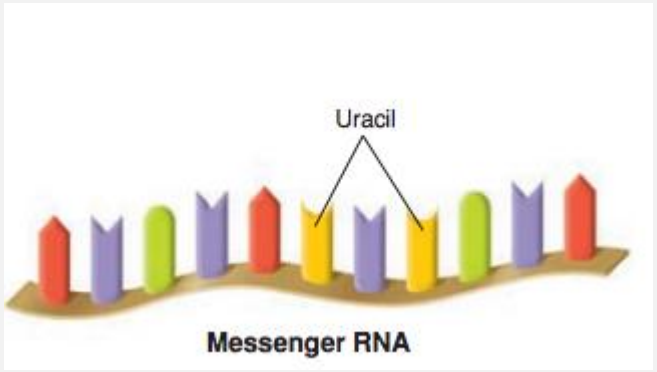
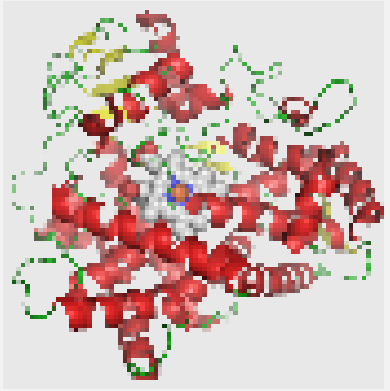
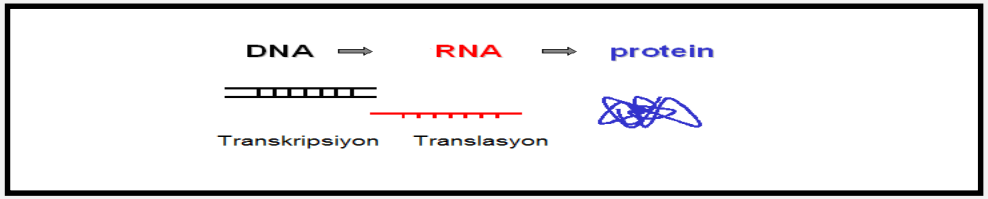


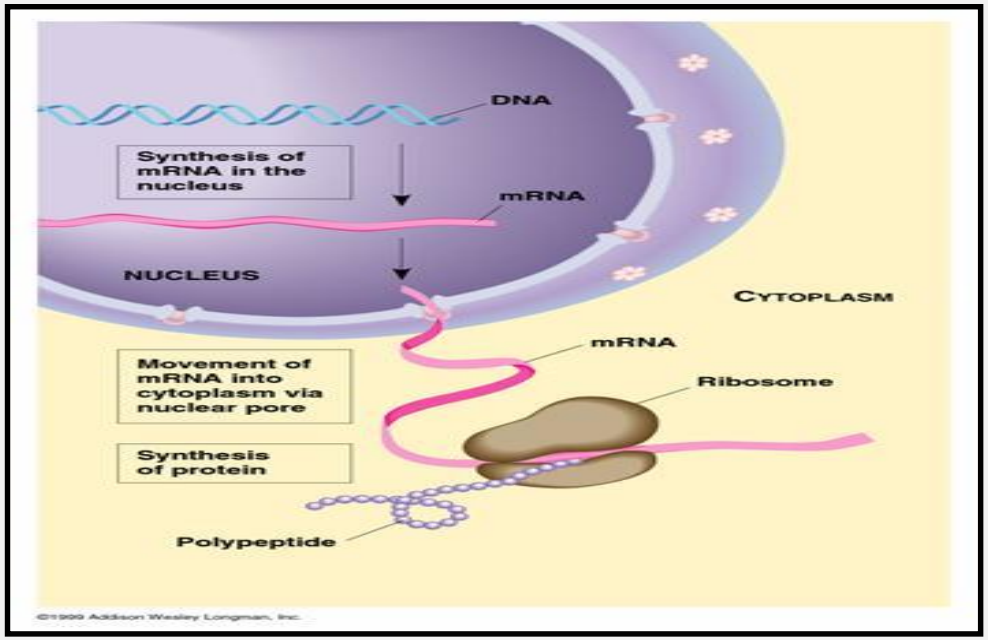


Protein

DNA controls many functions in the cell. It does this by determining which enzymes-proteins will be synthesized in the cell.

DNA → RNA → Protein





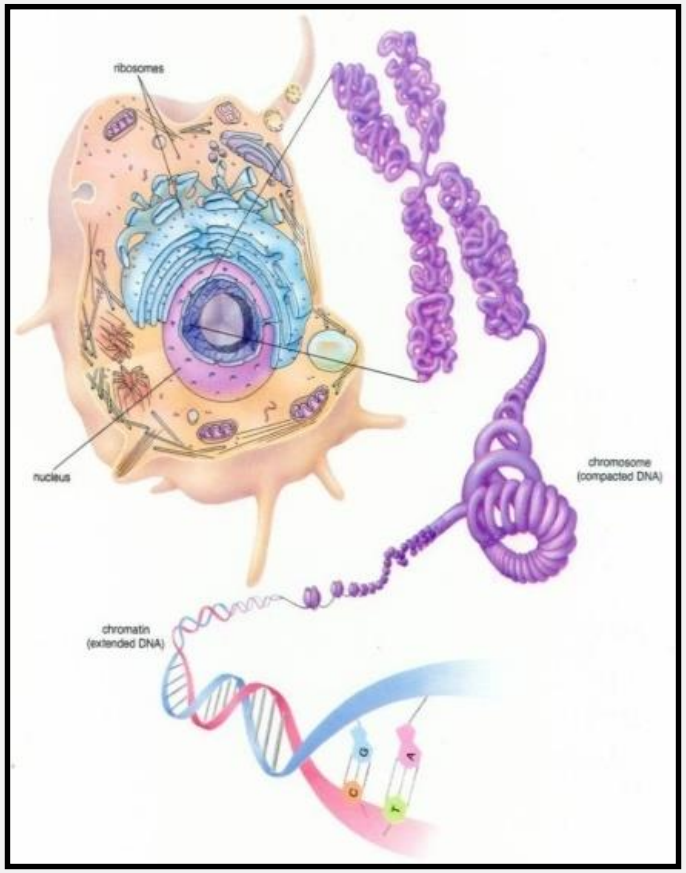
The genetic material is inside the nucleus in the cell.

There are 23 pairs of chromosomes in our cells.

Chromosomes are made up of DNA.

Our DNA consists of 3 billion base pairs.

DNA bases are A, C, G, T bases.



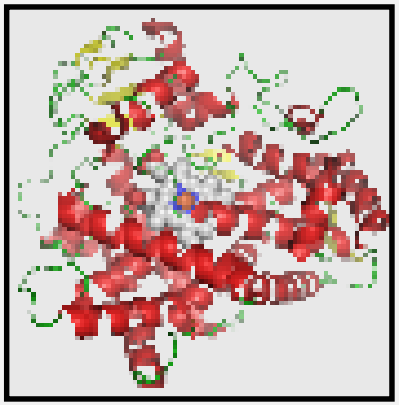
The number of genes in our genome is around 20-25 thousand.

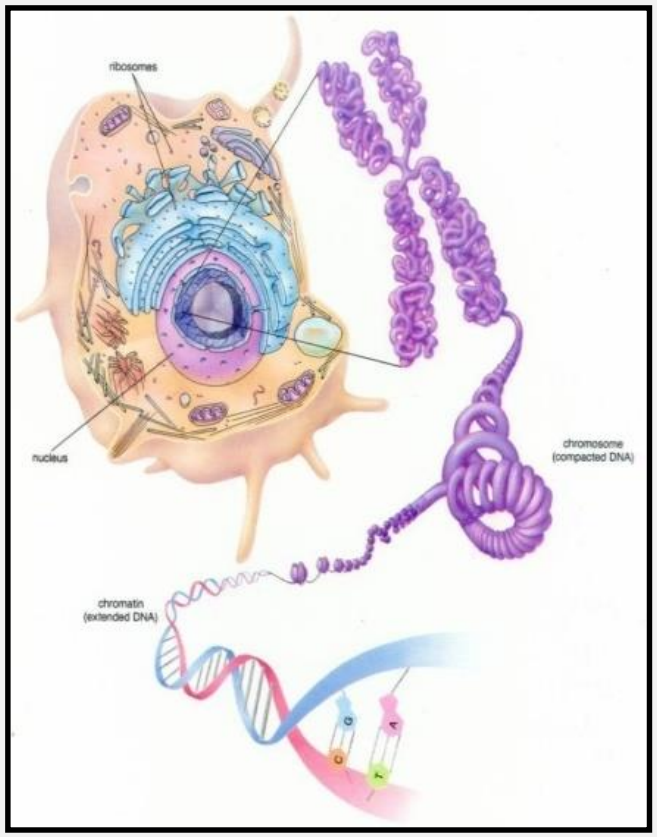
Each triple base in the protein-encoding DNA portion forms a codon.

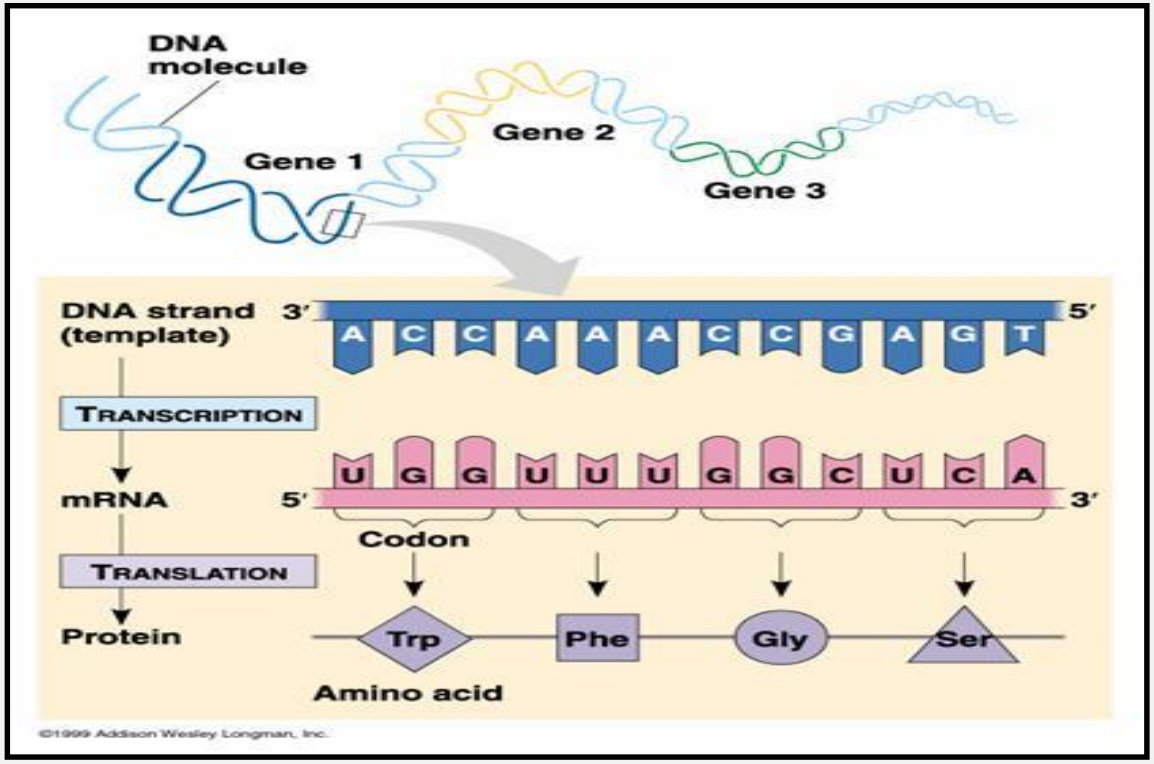
Each codon encodes an amino acid in the ribosome.

With the combination of amino acids, proteins are formed.

Proteins are the building blocks of us and are molecules that carry out all our vital functions.






DNA molecule
Gene 1
Gene 2
Gene 3
DNA strand (template)
3′
5′
A C C A A A C C G A G T
TRANSCRIPTION
mRNA
5′
3′
U G G U U U G G C U C A
Codon
TRANSLATION
Protein
Trp
Phe
Gly
Ser
Amino acid
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Genetic differences

between individuals

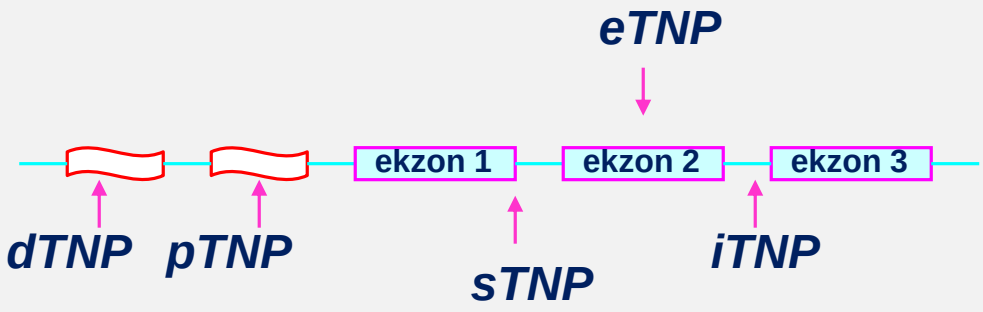
All human beings are 99.9 percent identical in their genetic makeup. Differences in the remaining 0.1 percent hold important clues about the causes of diseases and adverse drug reactions. These differences:

- **Single nucleotide polymorphisms (SNPs),**
- **Single base additions (insertions),**
- **Single base deletions (deletions),**
- **Big deletions,**
- **Variable number Tandem repeats,**
- **Gene copy number variations (CNVs).**

SNPs constitute the most common DNA difference in the human genome. If the difference in DNA in a population is greater than 1%, this change is called genetic polymorphism. SNPs can take place:

1. **In exon: synonymous and non-synonymous (one in amino acid results in a change),**
2. **In Intron,**
3. **Among the genes,**
4. **In the regulatory region**

SNPs in our genome



NUMBERS

There are approximately 3 billion base pairs (bp) in the human genome; there is a change every 100-300 bp. So we have about 10 million SNPs in our genome.

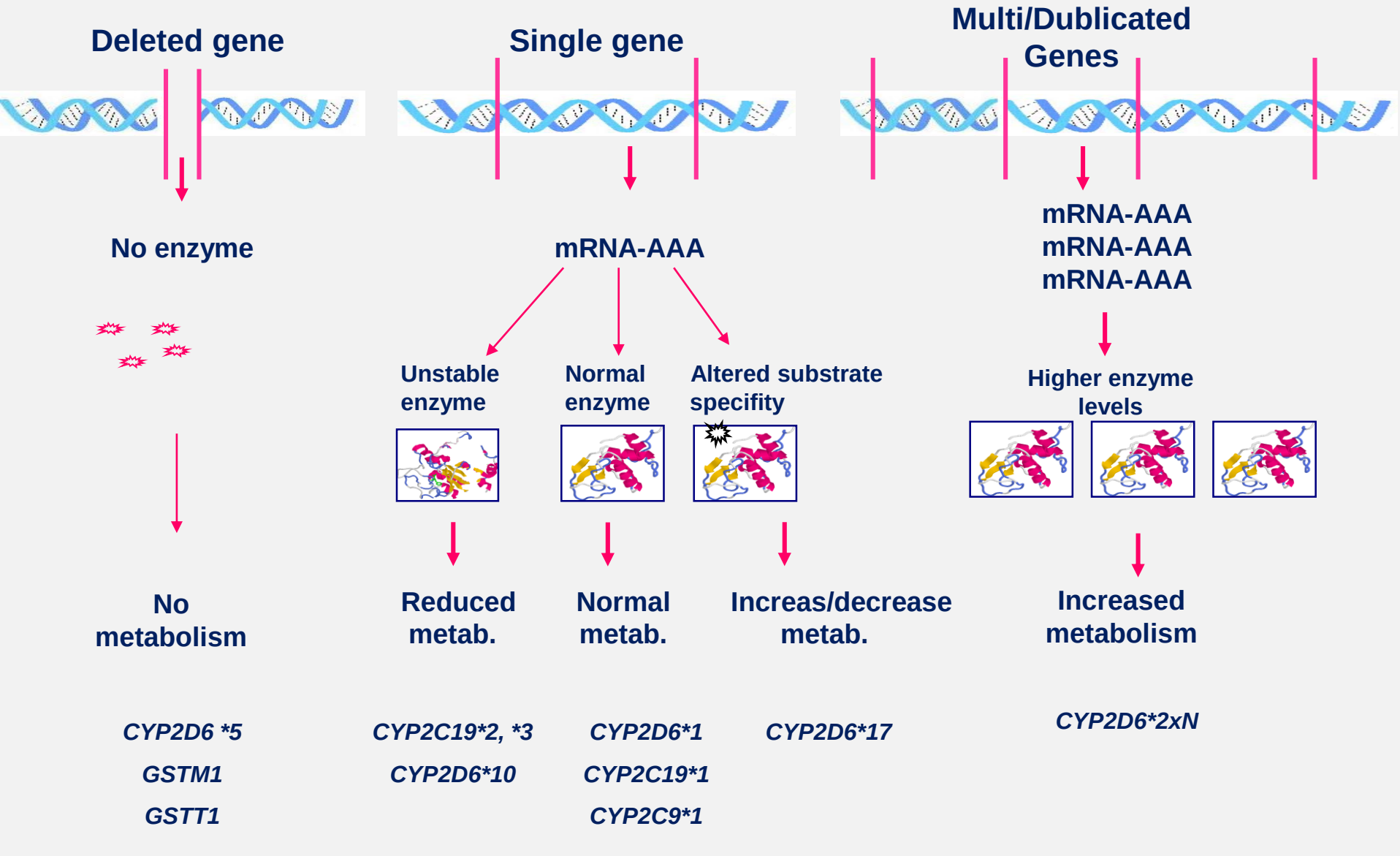
FUNCTIONAL

- Alterations in gene expression,
- Decrease or increase enzyme activity,
- Stopping protein synthesis,
- Changes in protein activity, stability and interaction,
- Alteration in mRNA stability, splysing, and translation.

DNA → RNA → Protein ⇒ Function (Activity : increase or decrease)

The steps of SNPs in the field of pharmacogenetics:

1. **SNP discovery,**
2. **SNP function,**
3. **SNP's relationship with drug response and toxicity.**



Some of the major molecular mechanisms that can result in altered human drug metabolism.

Functional genetic differences considered in drug development and treatment

Gene / Protein	Abbrevi.	Associated molecules / substrates
Glucose-6-phosphate dehydrogenase	*G6PDH*	Drugs that forming electrophilic reactive metabolite
Butyrylcholinesterase	*BCHE*	Mivakurium, Procaine, succinylcholine
N-acetyltransferase-2	*NAT2*	Isoniazid, Aromatic amines
Cytochrome P-450 2D6	*CYP2D6*	Amitriptyline, Clomipramine, Paraoxetine, Tamoxifen
Cytochrome P-450 2C19	*CYP2C19*	Omeprazole, Diazepam, Citalopram, Clopidogrel
Cytochrome P-450 2C9	*CYP2C9*	Warfarin, Tolbutamid, Diclofenac, Lozartan
thiopurine S-methyltransferase	*TPMT*	6-mercaptopurine, 6-thioguanine, Azathiopurine
Dihydropyrimidine dehydrogenase	*DPD*	5-Fluorouracil, Capecitabine
Uridine diphospho-glucuronosyl transferase	*UGT1A1*	Bilirubin, Irinotecan