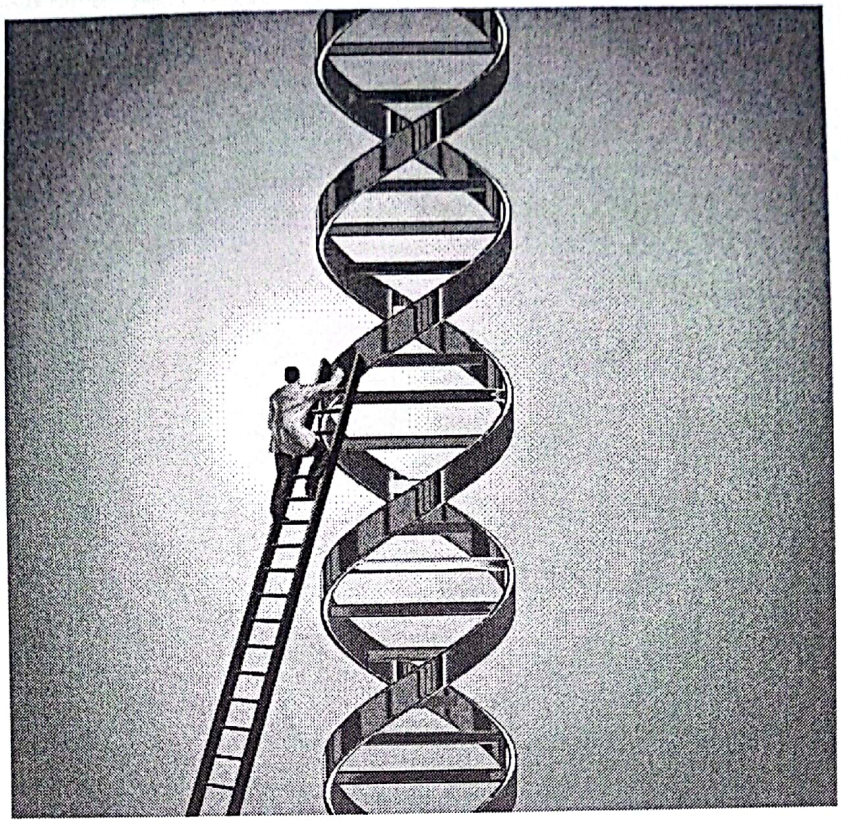
Pharmacogenetics



Pharmacogenetics and individual variation of drug response

Outline

- Introduction

Why does drug response vary?

- Potential causes of variability in drug effects
- Genetic variation

Pharmacogenetics

- What is Pharmacogenetics?
- Pharmacogenetics VS. Pharmacogenomics
- Genetic variation and drug response
- Determinants of Drug Efficacy and Toxicity
- Examples

Differential drug efficacy

two patient have:

Same symptoms,
Same findings,
Same disease? ⟷ **Different patients**

Same drug
Same dose

Different Effects

Differential drug efficacy

At a recommended prescribed dosage—

a drug is efficacious in most.

not efficacious in others. → **Lack of efficacy**

harmful in a few. → **Unexpected side-effects**

People react differently to drugs

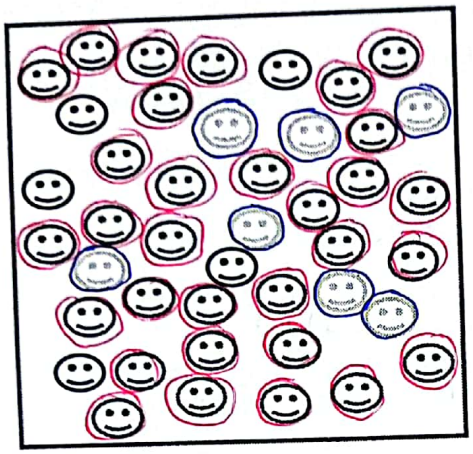
Toxic responders

Non-responders

Responders

"One size does not fit all …"

بسبب الاختلاف بالجينات



Patient population with same disease phenotype

Genotyping

Patients with drug toxicity

Patients with non-response to drug therapy

Patients with normal response to drug therapy

الغالبية ←

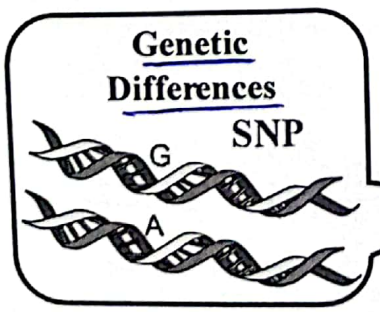
Same symptoms,
Same findings,
Same disease?

⟷ Different patients

Same drug
Same dose

Different Effects

Why does drug response vary?



Ethnicity
Age
Pregnancy
Genetic factors
Disease
Drug interactions
.....

Possible Reasons:
Individual variation
By chance…

Drug response بـ ينتج اختلاف Genetic factors نتيجة الاختلاف بال

Why does drug response vary?

- *Genetic variation*
- Primarily two types of genetic mutation events create all forms of variations:

➢ Single base mutation which substitutes one nucleotide for another
--Single nucleotide polymorphisms (SNPs) → one nucleotide يصير على تغيير يعني

➢ Insertion or deletion of one or more nucleotide(s) ← ادخال
- حذف
--Tandem Repeat Polymorphisms
--Insertion/Deletion Polymorphisms coding protein يعمل sequence of genes

اذا كان في
اذا تغير واحد من النيوكليوتيدات لمنطقة مهمة تأثر على ال coding معناته, ح يتغير البروتين اللي يتصنع

- Polymorphism: *A genetic variation that is observed at a frequency of >1% in a population*

ال ← genetic variation غالبا ال

mutation يصير بنسبة اقل من 1% in a population

non coding gene يصير بـ ~~genetic~~ variation

mutation <1% و ال polymorphism >1% الفرق بين ال بالنسبة

Single nucleotide polymorphisms (SNPs)

يعني أليل واحد الي اختلف

- SNPs are single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist wherein the least frequent allele has an abundance of 1% or greater.

- For example a SNP might change the DNA sequence

AAGCTTAC
ATGCTTAC

AAGCTTAC
to ATGCTTAC

- SNPs are the most commonly occurring genetic differences.

Single nucleotide polymorphisms (SNPs)

- SNPs are very common in the human population.
- Between any two people, there is an average of one SNP every ~1250 bases.
- Most of these have no phenotypic effect
  - Venter et al. estimate that only <1% of all human SNPs impact protein function (lots of in "non-coding regions")
- Some are alleles of genes.

mutation or polymorphism

Tandem Repeat Polymorphisms

- Tandem repeats or variable number of tandem repeats (VNTR) are a very common class of polymorphism, consisting of variable length of sequence motifs that are repeated in tandem in a variable copy number.

- Based on the size of the tandem repeat units:
  - Microsatellites or Short Tandem Repeat (STR)
    - repeat unit: 1-6 (dinucleotide repeat: CACACACACACA)
  - Minisatellites
    - repeat unit: 14-100

Insertion/Deletion Polymorphisms

- Insertion/Deletion (INDEL) polymorphisms are quite common and widely distributed throughout the human genome.

Ex:

Insertion : A C G T A G C T → A C T T G T A G C T → T

Deletion : A T A G C T → C G

ح تغيير شكل البروتين (insertion / Deletion of nucleotide / gene ١ أو ١ غيرت على ال receptors + other trasporter و coding للبروتين

شرح تغيير ال

شرح تغيير التجاوب من الدوا

Due to individual variation...

- 20-40% of patients benefit from an approved drug
- 70-80% of drug candidates fail in clinical trials
- Many approved drugs removed from the market due to adverse drug effects

- The use of DNA sequence information to measure and predict the reaction of individuals to drugs.
- Personalized drugs
- Faster clinical trials
- Less drug side effects

→ **Pharmacogenetics**

Pharmacogenetics

metabolism/excretion

- *"Study of interindividual variation in DNA sequence related to drug absorption and disposition (Pharmacokinetics) and/or drug action (Pharmacodynamics) including polymorphic variation in genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins."*
- *"The study of how people respond differently to medicines due to their genetic inheritance is called pharmacogenetics."*
- الجينات الوراثية
- *"Correlating heritable genetic variation to drug response"*
- An ultimate goal of pharmacogenetics is to understand how someone's genetic make-up determines, how well a medicine works in his or her body, as well as what side effects are likely to occur.
- "Right medicine for the right patient"

to give

Pharmacogenetics VS. Pharmacogenomics

- *Pharmacogenetics:* Study of variability in drug response determined by single genes. specific gene
- *Pharmacogenomics:* Study of variability in drug response determined by multiple genes within the genome.

Pharmacogenetics ← The study of variations in genes that determine an individual's response to drug therapy.

↓

Genetic Polymorphism: SNPs; INDEL; VNTRs ← Common variation in DNA sequence (i.e. in >1% of population)

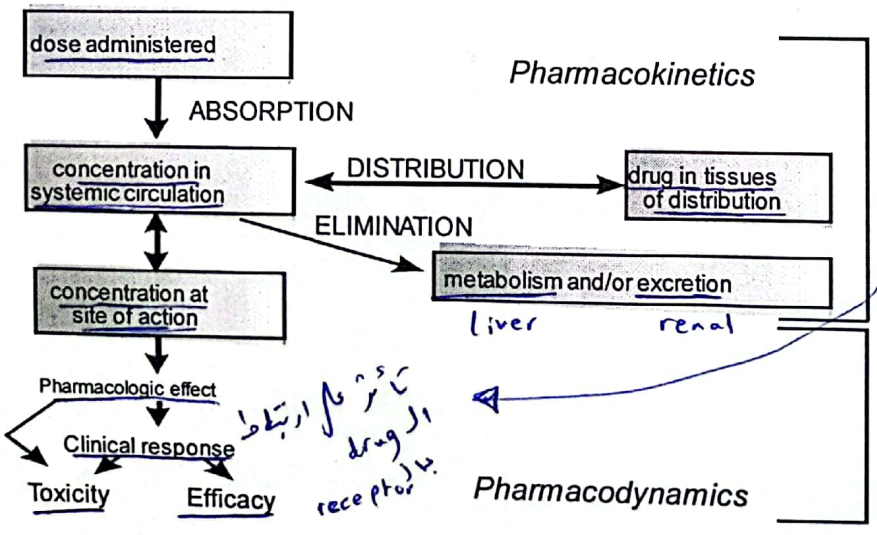
↓

Potential Target Genes are those that encode:

- Drug-metabolizing enzymes
- Transporters
- Drug targets

Determinants of Drug Efficacy and Toxicity

A patient's response to a drug may depend on factors that can vary according to the alleles that an individual carries, including :



➢ **Pharmacokinetic factors**

- Absorption — carrier
- Distribution — protein binding
- Metabolism — CYP450
- Elimination

➢ **Pharmacodynamic factors**

- Target proteins
- Downstream messengers

Examples:

- EM phenotype: Extensive metabolizer; IM phenotype: intermediate metabolizer; PM phenotype: poor metabolizer; UM phenotype: ultrarapid metabolizers

Protein	Drugs and Treatment/Action	Drug Responses	Polymorphism Rules and Year of Report
Cytochrome P450 1A2	Antipsychotic agents for schizophrenia patients	Tardive dyskinesia	Bsp120I (C→A) polymorphism in CYP1A2 gene, 2000 [Basile *et al.*, 2000]
Cytochrome P450 2C9	Anticoagulant agents for the initial phase of phenprocoumon treatment	Severe over-anticoagulation	CYP2C9*2 genotype, 2004 [Schalekamp *et al.*, 2004]
			CYP2C9*3 genotype, 2004 [Schalekamp *et al.*, 2004]
Cytochrome P450 2D6	Neuroleptic agents for chronic schizophrenic patients	Tardive dyskinesia	CYP2D6*4 genotype, 1998 [Kapitany *et al.*, 1998]
Cytochrome P450 2D6	Psychochopic drugs for psychiartric illness	Extrapyramidal drug side effects	CYP2D6 PM phenotypes, 1999 [Vandel *et al.*, 1999]
Cytochrome P450 2D6	CYP2D6-dependent antidepressants	Drug non-response	CYP2D6 EM phenotypes, 2004 [Rau *et al.*, 2004]
UDP-glucuronysltransferase	Capecitabine/irinotecan for the treatment of metastatic colorectal cancer	Greater antitumor response with low toxicity	UGT1A7*2/*2 genotype, 2005 [Carlini *et al.*, 2005]
			UGT1A7*3/*3 genotype, 2005 [Carlini *et al.*, 2005]
UDP-glucuronysltransferase I	Tranilast for the prevention of restenosis following coronary revascularization	Hyperbilirubinemia	Homozygosity for a (TA)7-repeat element within the promotor region of UGT1A1 gene, 2004 [Hosford *et al.*, 2004]
N-acetyltransferase 2	Trimethoprim-sulfamethoxazole for the treatment of infections in infants	Idiosyncratic reactions such as fever, skin rash and multiorgan toxicity	NAT2*5A allele, 1997 [Zielinska *et al.*, 1998]
			NAT2*5C allele, 1997 [Zielinska *et al.*, 1998]
			NAT2*7B, 1997 [Zielinska *et al.*, 1998]
N-acetyltransferase 2	Aromatic amine carcinogens in tobacco smoke	Hepatitis B related hepatocellular carcinoma	NAT2*4 allele, 2000 [Yu *et al.*, 2000]
N-acetyltransferase 2	Isonaiazid for the prophylaxis and treatment of tuberculosis	ADRs such as peripheral neuritis, fever and hepatic toxicity	SA type (NAT2*6/*6, NAT2*6/*7, and NAT2*7/*7), 2002 [Hiratsuka *et al.*, 2002]

Pharmacogenetics

- ***Pharmacogenetics*** is the study of how genes affect the way people respond to drug therapy.
- The goal of pharmacogenetics is to individualize drug therapy to a person's unique genetic makeup with greater efficacy and safety
- The environment, diet, age, lifestyle, and state of health can influence a person's response to medicine.
- Pharmacogenetics is an established discipline that studies the genetic basis of inter-individual variability in the response to drug therapy
- ***Pharmacogenomics*** involves study of the role of genes and their genetic variations (DNA, RNA level) in the molecular basis of disease, and therefore, the resulting pharmacologic impact of drugs on that disease.

- With some drugs, pharmacogenetics allows the recognition of subgroups with different genetic makeup that results in alterations in drug receptors and the pharmacodynamic response to drugs.
- Understanding the genetic and molecular differences in disease etiology and drug mechanism produce insight on how a patient will respond to a given drug.

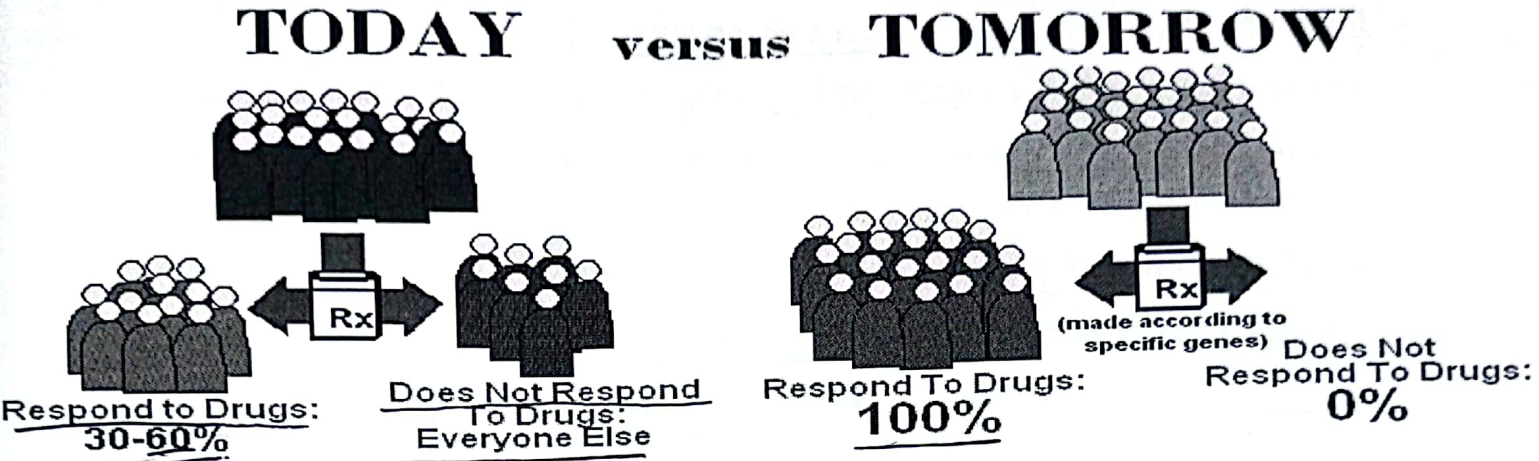
- For example, the monoclonal antibody Herceptin was designed to treat a subset of breast cancer patients who overexpress the HER-2 (human epidermal growth factor receptor-2) gene. Patients who lack HER-2 overexpression are considered to be nonresponders to Herceptin therapy.

- In the past, such differences would be apparent only after a trial-and-error period.

- **This genetic knowledge improves our ability to select or design the proper drug for individuals suffering from a disease with a varying range of molecular defects.**

Rationale for Pharmacogenetics

To provide real-time decision support thereby facilitating individualized drug therapy to maximize efficacy, minimize adverse drug reactions, and reduce health care costs



يعني خسرت الـ drug من 40% من الـ patients

الهدف من التجربة المتكررة انو نعمل drug الـ according to specific gene

بعد التجربة الاولى رح تكون عارف انو هاذ الدوا لما تعطيه لهذول الـ patients رح يتجاوبو معه 100% بالتالي تكون قللت الـ Nonresponders وزدت الـ drug Efficacy وقللت احتمال الدوا يضل بدون تأثير (without effect)

Genetic Influences

- **Pharmacokinetics**
  - Drug metabolism polymorphism in many cytochrome P-450 family enzymes (CYPs) and others
  - P-glycoprotein or other drug transporter (difference in genetic expression)

- **Drug receptor (PD)**
  - Variation in receptor number, affinity, or response to drug
- **Indirect drug response**
  - Inherited differences in coagulation may predispose women to deep vein thrombosis when taking oral contraceptives

[redacted] تسبب

Non-genetic influences

- Environmental (PK, PD, or disease prognosis)
  - Cigarette smoking, enzyme induction
  - Exposure to mutagenic agents and occupational or environmental hazards
  - Geographic differences
  - Climate (ultraviolet light on skin tumor)
  - Diet (effect of diet, including grapefruit, and influence on GI enzymes and drug absorption)
  - Drinking water (dissolved minerals and effect on health)
  - Nutrients or supplements

Mixed Covariates

- Gender, age, body weight/surface (PK/PD)
  - Male, female
  - Infant, young adult, or geriatric patient
- Pathophysiology (PK/PD)
  - Renal, hepatic, cardiovascular, or other disease
- Drug-drug interactions (PK/PD)
  - Metabolic, binding, or PD interactions

Terms to know

الاليليز
اذا اختلفوا بجين واحد

Monogenic: due to allelic variation at a single gene

Polygenic: due to variations at two or more genes

اذا اختلفوا باكثر من جين
الاليليز

What is the Difference Between Allele and Gene?

صفة

- A gene is a portion of DNA that determines a trait. A trait is a characteristic, or a feature, passed from one generation to another, like height or eye color.

- Genes come in multiple forms, or versions. Each of these forms is called an allele. For example, the gene responsible for the hair color trait has many alleles: an allele for brown hair, an allele for blonde hair, an allele for red hair, and so on.

What is the Difference Between Allele and Gene?

	Gene	Allele
Definition	A gene is a portion of DNA that determines a certain trait.	An allele is a specific form of a gene.
Function	Genes are responsible for the expression of traits.	Alleles are responsible for the variations in which a given trait can be expressed.
Pairing	Genes do not occur in pairs.	Alleles occur in pairs.
Examples	Eye color, hair color, hairline shape	Blue eyes, blonde hair, V-shaped hairline

Polymorphism

- ***Polymorphisms*** or genetic variations with a frequency of greater than 1% of the population, or *mutations,* in less than 1% of the population, in genetic sequences can affect patient therapeutic response or metabolism of a given drug
- Many alleles encoding different drug receptors are being discovered and studied with increasing frequency.
- Pharmacokinetic parameters now known to be influenced by genetic differences include drug bioavailability, distribution, metabolism and tissue binding.
- Polymorphism in cytochrome isozymes is well known in drug metabolism, and the corresponding allele genes involved have been widely studied and are fairly well understood clinically at this time.

Polymorphism

- Genetic polymorphism within a specific genotype may occur with different frequencies depending on racial or population factors, which evolved from selective geographic, regional, and ethnic factors.
- Genetic polymorphisms with higher frequencies are more important because they are likely to affect more people. However, some rare mutations are important because they cause extreme medical consequences or may be fatal for the individual.
- Using genetic polymorphism considerations, drugs may be developed that have less inter-subject variation in pharmacodynamic response and less risk of an adverse event.
- In addition, doses for patients can be based on their metabolic capacity by using the frequency of genotypes of "poor metabolizers" or "ultrarapid metabolizers."
- Molecular studies in pharmacogenetics began with cloning of **CYP2D6** and now have been extended to more than two dozen drug-metabolizing enzymes and several drug transport systems

Example of Polymorphisms

- Inter-individual differences in response to drug therapy due to differences in **acetylation of drugs** is a well studied example of genetic polymorphism.
- Patients' ability to metabolize certain drugs such as hydralazine, procainamide, and isoniazid can be categorized as either "**fast acetylators**," "**normal acetylators**," or "**slow acetylators**"
- **Acetylation status** is dependent on the patient's **genetic composition**, which determines the **activity** of the acetylation enzyme N-acetyltransferase.
- Acetylation status determines whether a patient is dosed with a correspondingly **higher** or **lower** dose compared to "normal acetylators."
- Genetic variations are well known in **bacteria** and other microorganisms because the rapid changes in these organisms are easily observed.
- In humans, mutations and related changes occur to different degrees in thousands of proteins and other macromolecules.

- A change or mutation in gene sequence **may or may not** result in chronically reduced or increased level or activity of a protein or an essential enzyme. In **some cases**, such changes result in an exaggerated or reduced therapeutic response to a drug.
- The cell is **homozygous** if the **genetic sequences** occupying the locus are **the same** on the **maternal** and **paternal** chromosome; if they are **different**, the cell is **heterozygous**.
- When more than one alternative forms of a gene exists, they are referred to as **alleles** of the gene. The **identity of the alleles** carried by an individual at a given **gene locus** is referred to as the **genotype**.
- **Alleles** that vary by a single nucleotide change can now be characterized rapidly at the DNA level by single-nucleotide polymorphism (SNP). The physical effect observed as a result of genotype difference is referred to as phenotype.

Adverse Drug Reactions Attributed to Genetic Differences

- Prolonged muscle relaxation in some subjects after receiving **a cholinergic drug** was explained by an inherited deficiency of a plasma cholinesterase.
- Hemolysis caused by **antimalarial drugs** is recognized as being caused by inherited variants of glucose 6-phosphate dehydrogenase.
- Slow metabolism of isoniazid in some patients (acetylation of isoniazid) has been found to be the cause of peripheral neuropathy caused by this drug.
- Adverse drug reactions of **debrisoquin** have led to the discovery of the genetic polymorphism of the drug-metabolizing enzyme, debrisoquin hydroxylase CYP2D6.
- The same isozyme deficiency causes more nausea, diplopia, and blurred vision after dosing of the **antiarrhythmic drug sparteine** in deficient patients.
- A method used to distinguish **hereditary and environmental** components of variability is the comparison of monozygotic and dizygotic twins, or pharmacokinetically by repeated drug administration and comparison of the variability of the responses within and between individuals.

ETHNIC DIFFERENCES IN THE DISTRIBUTION OF ACETYLATOR PHENOTYPE

Population	% Slow	% Hetero Fast	% Homo Fast
South Indians	59	35.6	5.4
Caucasians	58.6	35.9	5.5
Blacks	54.6	38.6	6.8
Eskimos	10.5	43.8	45.7
Japanese	12	45.3	42.7
Chinese	22	49.8	28.2

From: Kalo W. *Clin Pharmacokinet* 7:373-4000, 1982.

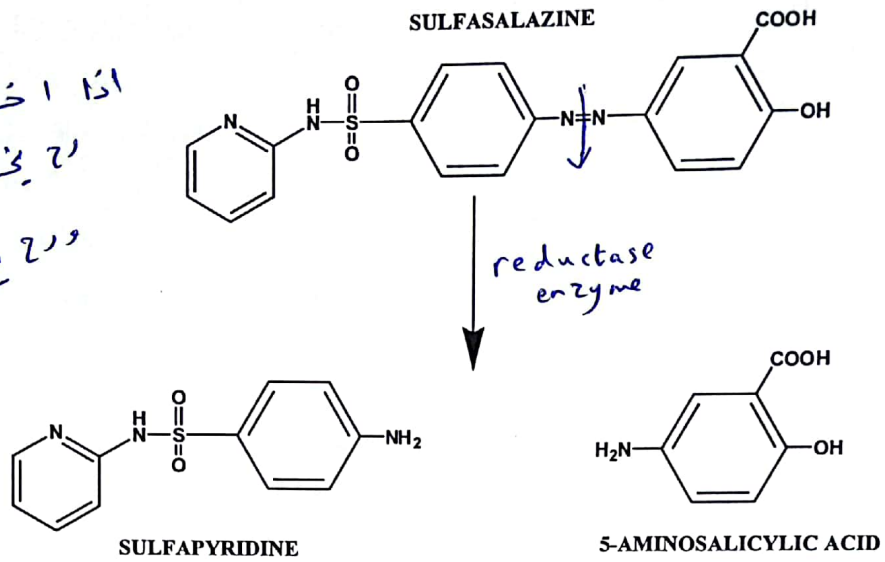
Xenobiotics Subject to Polymorphic Acetylation in Man

Hydrazines	*Arylamines*	*Carcinogenic Arylamines*
isoniazid	dapsone	benzidine
hydralazine	procainamide	β-naphthylamine
phenylzine	sulfamethazine	4-aminobiphenyl
acetylhydrazine	sulfapyridine	
hydrazine	aminoglutethimide	

Drugs metabolized to amines

sulfasalazine	nitrazepam
clonazepam	caffeine

Adverse Effects to Sulfasalazine in Patients with Inflammatory Bowel Disease



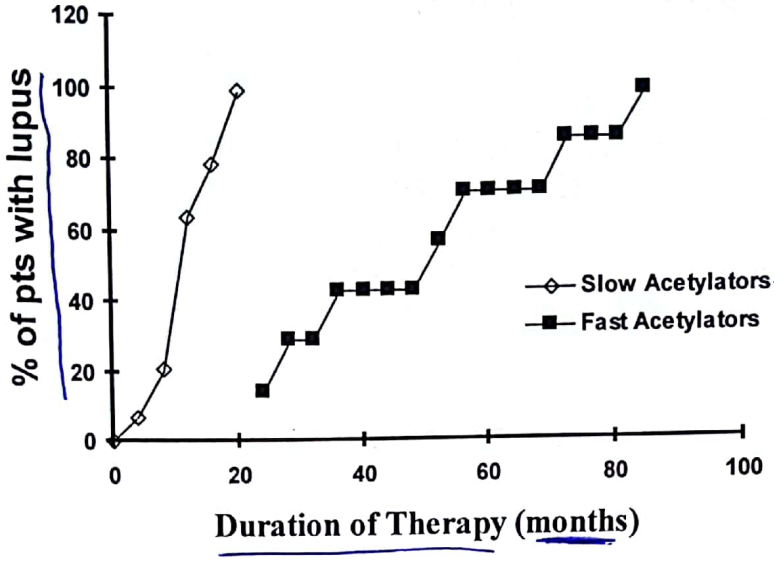
Adverse effects to sulfasalazine in patients with inflammatory bowel disease

Side Effect	Frequency of side effect: Slow Acetylators	Fast Acetylators
cyanosis	9	1
hemolysis	5	0
transient reticulocytosis	6	0

Data from: Das et al. *N Engl J Med* 289:491-495, 1973.

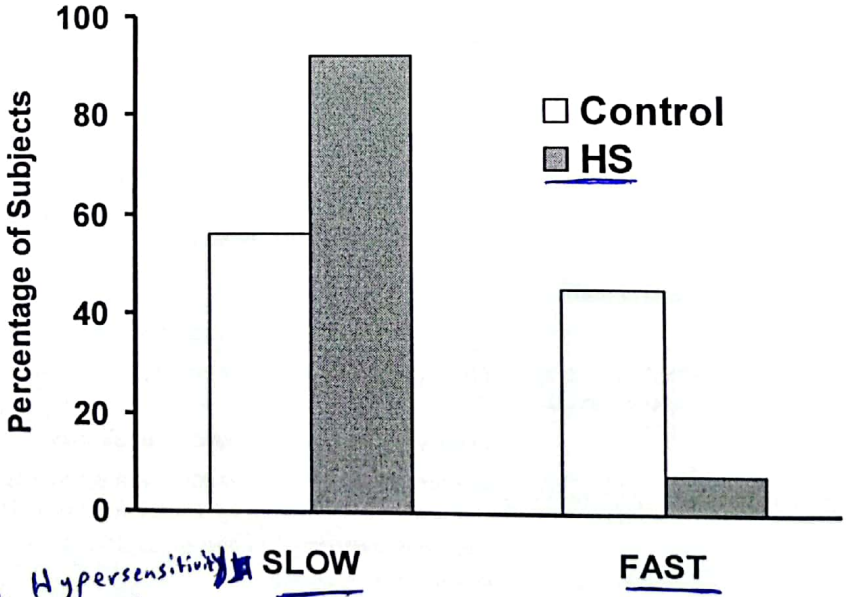
Relationship Between Onset of Lupus Syndrome in Fast and Slow Acetylators Receiving Procainamide.

Data from: Woosley RL, et al. *N Engl J Med* 298:1157-1159, 1978.



Distribution of Acetylator Phenotype in Control Subjects and Those Experiencing a Sulfonamide Hypersensitivity Reaction.

Rieder et al. *Clin Pharmacol Ther* 49:13-17, 1991.



Polymorphism

- To determine whether a patient is a rapid or slow metabolizer, the patient is given a known substrate for that enzyme and the patient's intrinsic clearance is measured.
- Traditionally, inter-subject variation in metabolism has been investigated by this method followed by in-vitro verification of enzyme level. Alternatively, it is possible to determine metabolic-status genotype directly from subjects' DNA. The latter approach is more definitive and offers much insight during drug development into how genes affect the metabolism of drugs.
- Many drugs have been elucidated with both approaches. In practice, fragments of DNA samples are compared based on SNPs. If the SNP and its functional activity are known, the probable individual drug response can be predicted.

Table 12.2 Clinically Important Genetic Polymorphisms of Drug Metabolism that Influence Drug Response

Enzyme/Receptor	Frequency of Polymorphism	Drug	Drug Effect/Side Effect
CYP2C9	14â€"28% (heterozygotes)	Warfarin	Hemorrhage
	0.2â€"1% (homozygotes)	Tolbutamide	Hypoglycemia
		Phenytoin	Phenytoin toxicity
		Glipizide	Hypoglycemia
		Losartan	Decreased antihypertensive effect
CYP2D6	5â€"10% (poor metabolizers)	Antiarrhythmics	Proarrhythmic and other toxic effects
	Polymorphism		
			Toxicity in poor metabolizers
	1â€"10% (ultrarapid metabolizers)	Antidepressants	Inefficacy in ultrarapid metabolizers
		Antipsychotics	Tardive dyskinesia
		Opioids	Inefficacy of codeine as analgesic, narcotic side effects, dependence
		Beta-adrenoceptor antagonists	Increasedâ€"blockade

metabolism ال يؤثر على
warfarin ك

CYP2C9 ACTIVITY

Prescribed Daily Warfarin Dose and CYP2C9 Genotype

Warfarin Dose*	Genotype
5.63 (2.56)	*1/*1
4.88 (2.57)	*1/*2
3.32 (0.94)	*1/*3
4.07 (1.48)	*2/*2
2.34 (0.35)	*2/*3
1.60 (0.81)	*3/*3

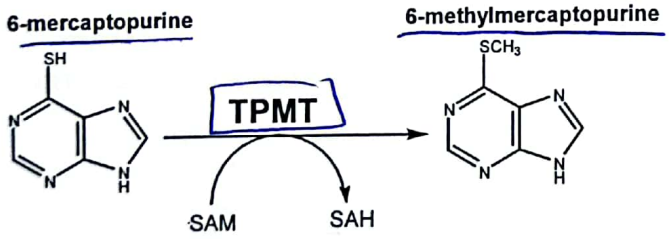
dose ال تختلف ج
drug ك
gene باختلاف ال

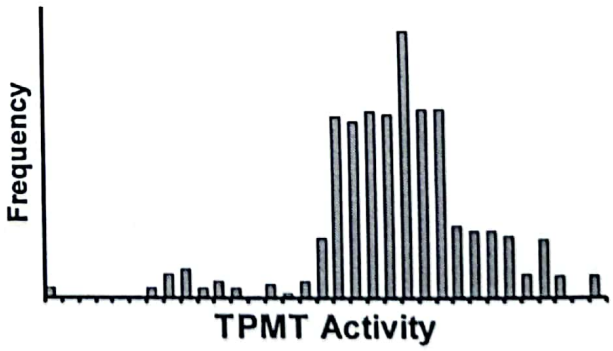
*Data presented as mean (SD) daily dose in mg

From: Higashi MK, et al. *JAMA* 287:1690-1698, 2002.

mercapto purine ال metabolism بال يستخدم

Thiopurine Methyltransferase (TPMT)





Distribution of Thiopurine Methyl-transferase Activity.

CYP2C19

- The polymorphic enzyme has a poor metabolizer (PM) frequency of about 3% in Caucasians, 15-25% among Asians, and 4-7% among Black Africans.
- The major defective allele responsible for the PM phenotype is CYP2C19*2, which is found among 13% and 32% of Caucasians and Asians, respectively.
- A second allele, CYP2C19*3, is found mostly among Asians and rarely in Caucasians.

place 2

place 3

metabolism لازم يصير
activation ممكن يصير

Clopidogrel - PLAVIX

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.**

activation drug

Patients with reduced function alleles have:

- **significantly lower levels of the active metabolite**
- **diminished platelet inhibition and higher rate of platelet aggregation**
- **higher rate of major adverse cardiovascular events and higher risk of stent thrombosis**

تناقص

Genetic Polymorphism in Drug Transport: p-Glycoprotein and Multidrug Resistance

- ***Transporter pharmacogenetics*** is a rapidly developing field that is concerned with drug **uptake** and **efflux** into or through tissues. Significant problems in the clinical application of drugs result from poor or variable oral drug bioavailability, and high intra- and inter-individual variation in pharmacokinetics.
- Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into nonintestinal tissues, or into specific target sites of action.
- ***Drug efflux*** **is an important cause of drug resistance in certain types of cells.**
- In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally very effective, but in the case of *intrinsic* or *acquired multidrug resistance*, usually highly effective antineoplastic compounds, eg, vincristine, vinblastine, daunorubicin, or doxorubicin, fail to produce cures.
- One of the major causes of such multidrug resistance is the appearance of special integral membrane proteins, the *P-glycoprotein multidrug transporter*, or MDR1, which is one of the major causes of low drug level in targeted cells.

Genetic Polymorphism in Drug Transport: p-Glycoprotein and Multidrug Resistance

- The multidrug resistance-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) superfamily with six members currently, of which MRP1, MRP2, and MRP3 are commonly known to affect drug disposition. MRP1 is ubiquitous in the body.
- Substrates for MRP1 include glutathione, glucuronide, and sulfate. MRP1 is expressed basolaterally in the intestine, although its role in extruding drugs out of the enterocytes is still uncertain.

GENETIC POLYMORPHISM IN DRUG TARGETS

- In the future, proteins involved in disease will become identified as important biomarkers for pharmacodynamic studies. Genomics has led to the development of proteonomics, which involves the study of biologically interesting proteins and their variants.
- Proteins can be used as probes for drug discovery or as biomarkers for drug safety, such as cell surface proteins (eg, COX-2, D-2R), intracellular proteins (eg, troponin I), and secreted proteins (eg, Monocyte Chemoattractant Protein-1 (MCP-I)).
- The physiologic response of the body to a drug is generally the result of interaction of the drug at a specific target site in the body. It is estimated that **about 50% of drugs act on membrane receptors, about 30% act on enzymes, and about 5% act on ion channels**.
- Many of the genes encoding these target proteins exhibit polymorphisms that may alter drug response. Clinically relevant examples of polymorphism leading to variable responses are listed. For example, the **beta-2-adrenergic receptor**, and its common mutation of Arg /Gly at amino acid 16, greatly reduces the bronchodilator response of albuterol.

Arginine glycine

Ex:

- In addition, mutations in the **angiotensin-converting enzyme** (ACE) gene have been proposed to account for variations in the response to ACE inhibitors.
- Another study has shown that a combination of two mutations in the gene encoding a high **affinity sulphonylurea receptor** leads to a 40% reduction in the insulin response to tolbutamide.
- The response to clozapine in patients with schizophrenia appears to involve genetic polymorphisms in the **5-hydroxytryptamine (serotonin) receptor**, HTR2A.
- Finally, mutations in five genes involved in the **cardiac ion channels** affect the risk of drug-induced long-QT syndrome, a potential cause of **sudden cardiac death** in young individuals without structural heart disease. The prevalence of long-QT syndrome is about 1 in 10,000.
- All five genes code for membrane ion channels affecting sodium or potassium transport and are influenced by antiarrhythmics and other drugs

GENETIC POLYMORPHISM IN DRUG TARGETS

مو للحفظ

Table 12.3 Clinically Important Genetic Polymorphisms of Drug Targets and Drug Transporters

Gene	Frequency	Drug	Drug Effect
Multidrug resistance gene (*MDR1*)	24%	Digoxin	Increased concentrations of digoxin in plasma
Beta-2 adrenergic receptor gene (*2AR*)	37%	Albuterol	Decreased response to Beta-2 adrenergic agonists
Sulphonylurea receptor gene (*SUR1*)	2â€"3%	Tolbutamide	Decreased insulin response
Five genes coding for cardiac ion channels	1â€"2%	Antiarrhythmics, terfenadine, many other drugs	Sudden cardiac death due to long-QT syndrome

- Not all therapeutic variations and side effects result from genetic differences in the receptor or drug metabolism.
- Drug response (including therapeutic and unintended side effects) is influenced by many direct and indirect factors, including modifying effects from environmental factors on the disease process and drug disposition.
- As a result, some researchers are unsure whether prescribing drugs based on a pharmacogenetic profile will significantly reduce side effects for most drugs, since many side effects and therapeutic failures may be the result of **incorrect diagnosis** or **failure to account for other influencing variables such as the nature and severity of the disease, the individual's age and race, organ function, concomitant therapy, drug interactions, and concomitant illnesses**

تشخيص خاطئ

متزامن