GENETIC FACTORS IN EFFICIENT DRUG USE

Personalised Medicine

(Pharmaco- and Toxicogenetics)

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PROBLEM 1: WHY there is differences in EFFICACY between individuals in drug treatment?

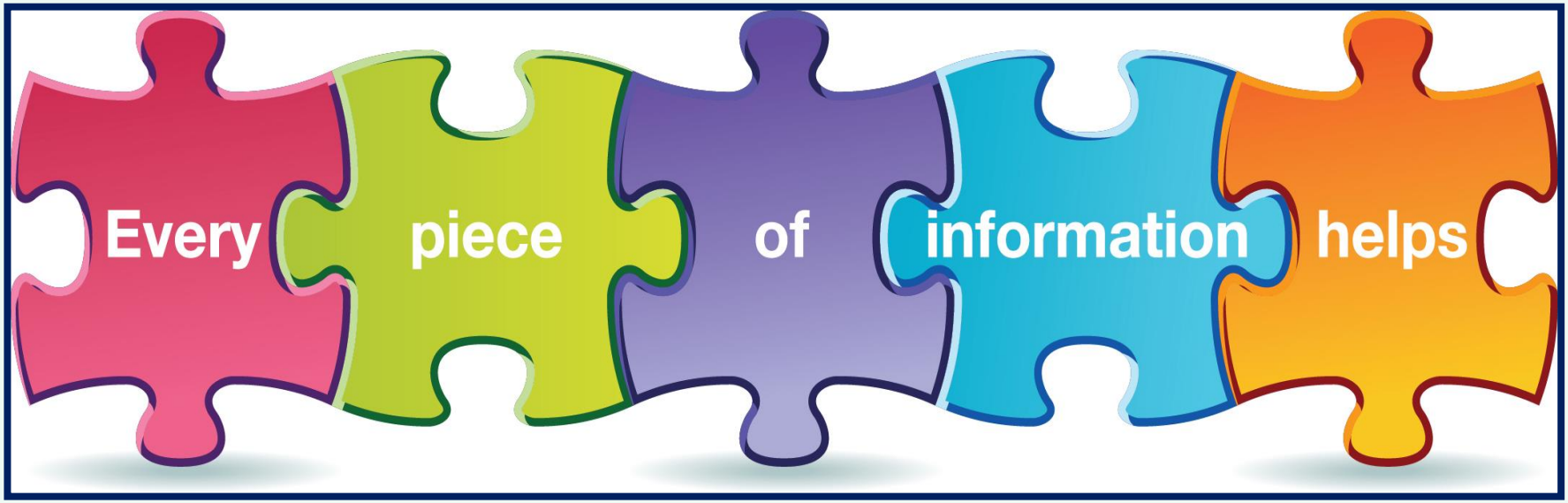
The effectiveness of drugs used in some diseases

Therapeutic area	Efficay rate (%)
Analgesics (COX-2 inhibitors)	80
Depression (SSRIs)	62
Cardiac arrhythmia	60
Schizophrenia	60
Alzheimer	30
Oncology	25

PROBLEM 2: WHY there is differences in SIDE EFFECTS between individuals who take same medicine?

HEALTH: In the USA, adverse drug reactions are 6.7% in hospital-treated patients, and about 100,000 of these have caused death (Lazarou et al .; JAMA, 1998).

ECONOMIC BURDEN: It is estimated that adverse drug reactions in the USA results in spending $ 100 billion.



Biological factors
Age, Gender, Race
Pregnancy, Body size,
Renal/hepatic function,
Existing diseases,
Medication compliance,
Gastric pH,
etc.

Drug-related factors
Drug structure and conformation,
Dosage scheme,
Half-life time,
Bioavailability,
Administration route,
Therp. ratio.

Environmental fac.
Diet / Nutrients,
Smoking/alcohol consumption/ coffee intake,
Co-delivered drugs and drug interactions.

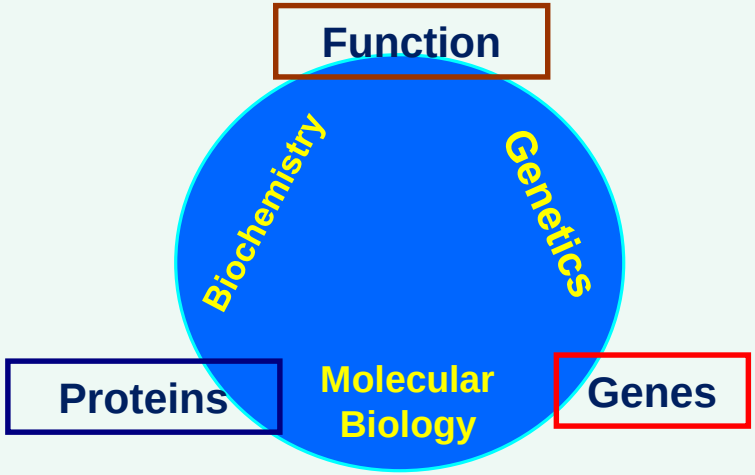
GENETIC FACTORS

Genetic variations in
DRUG
related pathways

GENETIC FACTORS

Advancements in Genetic Analyses Technologies

- Recombinant DNA Technology,
- Gene Cloning,
- Blotting of DNA and RNA,
- Polymerase chain reaction,
- FISH,
- DNA Chip Technology,
- Gene expression analysis.

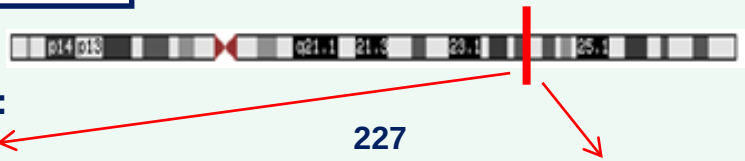


Human Genom Project

CYP2C19: EC 1.14.13.80

Omeprazole, diazepam, phenytoin, amitriptyline, citalopram, clopidogrel

10. Chrm:



CYP2C19: EC 1.14.13.80
DNA : 90.21 kb
mRNA: 1475 bp
AA : 490
Codon: 227 CCG → CCA
G → A
rs : 4244285

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).**

DNA → RNA → Protein → Activity / Function: increase or decrease

DRUG RELATED ENZYMES

Genetic variations in **DRUG** related pathways

Absorption
Distribution
Metabolism
Excretion

Drug targets
Disease related pathways

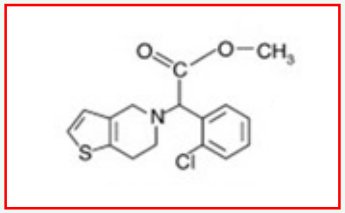
Pharmacokinetics + **Pharmacodynamics** → **Drug response / Toxicity**

Drug metabolising enzymes
Drug transporters

Enzymes
Receptors
Ion channels
Lipoproteins
Coagulation factors

PLAVİX® TABLET 75 mg

Clopidogrel



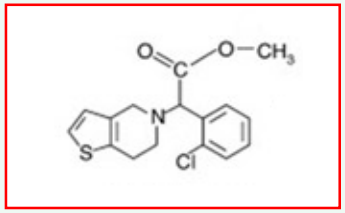
WHY there is differences in EFFICACY between individuals in drug treatment

Summary of Product Characteristic (SmPC)

4.1. Therapeutic indications

Prevention of atherothrombotic events:

- **Adult patients: Previous Myocardial Infarction, Previous Stroke or Peripheral Arterial Disease**
- **Adult patients: Acute Coronary Syndrome**
- **Prevention of atherothrombotic and thromboembolic events in atrial fibrillation**



CYP2C19 →

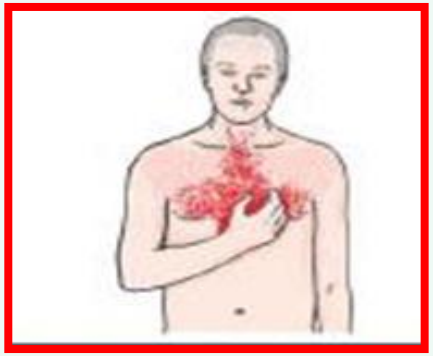
ACTIVE METABOLITE

2-oxo-clopidogrel →

inhibitor of platelet aggregation.

An increased risk of major adverse cardiovascular development (MI, stent thrombosis) in individuals with the *CYP2C19* * *2* allele.

→



Summary of Product Characteristic (SmPC)

4.1. Therapeutic indications

4.4 Special warnings and precautions for use

Cytochrome P450 2C19 (***CYP2C19***)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)

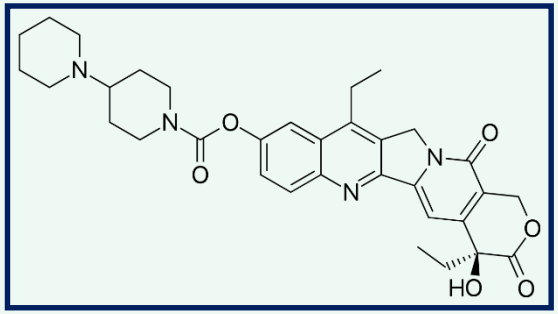
Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)

Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)

Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

WHY there is differences in **SIDE EFFECTS** between individuals who take the same medicine?

Irinotecan



Approximately 35% of patients receiving irinotecan experience ADRs such as severe diarrhea and neutropenia.

1. Name of the medicinal product

CAMPTO 20 mg/ml concentrate for solution for infusion

Irinotecan is indicated for the treatment of patients with advanced colorectal cancer

Patients with Reduced UGT1A1 Activity:

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan to inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. Patients known to be homozygous for UGT1A1*28 should be administered the normally indicated irinotecan starting dose. However, these patients should be monitored for haematologic toxicities.

Pharmacogenetic objectives:

To maximize drug effectiveness,

To minimize the toxicity that may occur,

Drug selection according to the genetic structure of the person,

Dose selection according to the genetic structure of the person.

Genetic biomarkers in Food and Drug Administration-approved drug product labeling

Biomarker	Drug	Label Context
Pharmacokinetic		
CYP2C19	Clopidogrel	Poor metabolizers have diminished response
	Voriconazole; omeprazole; pantoprazole; esomeprazole; diazepam; nelfinavir; rabeprazole	Variants lead to a change in drug exposure
CYP2C9	Celecoxib, Warfarin	Variants lead to a change in drug exposure Variant genotypes and drug dose
CYP2D6	Atomoxetine; venlafaxine; risperidone; tiotropium bromide; tamoxifen; timolol maleate	Variants lead to a change in drug exposure
	Fluoxetine HCl; fluoxetine ve olanzapine; cevimeline HCl; tolterodine; terbinafine; tramadol ve acetaminophen; clozapine; aripiprazole; metoprolol; propranolol; carvedilol; propafenone; thioridazine; protrytyline HCl; Tetrabenazine	Variants lead to a change in drug exposure and RISK
	Codeine sulfate; butalbital,	Ultrarapid metabolizers and overdose symptoms
N-acetyltransferaz 2	Rifampin, isoniazid, pyrazinamide; isosorbide dinitrate; hydralazine HCl	Slow and fast acetylators and toxicity
Tiyopurin metiltransferaz	Azathioprine; thioguanine; mercaptopurine	Mutation increases risk of myelotoxicity
UGT1A1	Irinotecan; nilotinib	Mutation changes drug exposure and susceptibility to toxicity
DPD	Capecitabine, 5-FU	Deficiency associated with systemic toxicity

Genetic biomarkers in Food and Drug Administration-approved drug product labeling

Biomarker	Drug	Label Context
Pharmacodynamic		
Low-density lipoprotein receptor	Atorvastatin	Dosage adjustment for homozygous and heterozygous familial hypercholesteremia
G6PD	Rasburicase*a; dapsone*	Deficiency and risk of severe hemolysis
	Primaquine; chloroquine	Deficiency and tolerance
Human leukocyte antigen-B*1502	Carbamazepine	Serious dermatologic reactions
Human leukocyte antigen-B*5701	Abacavir	Hypersensitivity reactions
Urea cycle disorder deficiency	Valproic acid	Reports of hyperammonemic encephalopathy
Viatmin Kepoxide reductase	Warfarin	Variant genotypes and drug dose
Chemokine (C-C motif) receptor 5	Maraviroc	Indicated for chemokine (C-C motif) receptor 5-tropic human

Pharmaco-Toxicogenetic marker	DRUG	Test Purpose
Test-MANDATORY		
EGFR Express.	Cetuximab	Efficacy
HER2/NEU over express.	Trastuzumab	Efficacy
CCR-5-tropic HIV-1	Maraviroc	Efficacy
Philadelphia Chr.-positive	Dasatinib	Efficacy
Test-RECOMMEND		
*HLA-B*1502*	Carbamazepine	Safety
*HLA-B*5701*	Abacavir	Safety
CYP2C9	Warfarin	Safety
VKORC1	Warfarin	Safety
Protein C defciency	Warfarin	Safety
TPMT polymorp.	Azathioprine, mercaptopurine, thioguanine	Safety Safety Safety
UGT1A1 polymorrp.	Irinotecan	Safety
G6PD deficiency	Rasburicase	Safety
Üre cycle disorder	Valproic acid	Safety

Pharmaco-Toxicogenetic marker	DRUG	Test purpose
Only-INFORMATIVE		
c-KIT expression	Imatinib	Efficacy
CYP2C19 polymorp.	Voriconazole	Safety
CYP2C9 poliymorp.	Celecoxib	Safety
CYP2D6 polymorp.	Atomoxetine,	Eff & Safety
	tamoxifen,	Eff & Safety
	voriconazole	Eff & Safety
DPD deficiency	Capecitabine,	Safety
	fluorouracil	Safety
EGFR ekspresyon	Erlotinib	Efficacy
G6PD deficiency	Rasburicase, primaquine	
NAT polymorp	Isoniazid,	Safety
	rifampin	Safety
Philadelphia chromosome negative	Busulfan	Efficacy
PML/RAR gene expression	Tretinoin	Safety

Drugs that have contraindication as a pharmacogenetic (FG) biomarker in their use

Drug	Group	Gene	FG Inform.
Abacavir	Infection	*HLA-B*	*HLA-B*5701* carriers
Capecitebine	Oncology	*DPYD*	*DPD* deficiency
Fluorouracil	Dermatology	*DPYD*	*DPD* deficiency
Pegloticase	Rheumotogy	*G6PD*	*G6PD* deficiency
Pimozide	Psychiatry	*CYP2D6*	*CYP2D6* slow metabolisors
Quinine sulfate	Infection	*G6PD*	*G6PD* deficiency
Rasbucirase	Oncology	*G6PD*	*G6PD* deficiency
Thioridazine	Psychiatry	*CYP2D6*	*CYP2D6* slow metabolisors

CONCLUSION

Drug safety and personalized medicine are clearly the future of pharmacy practice.

In pharmacotherapy, differences in drug response and in ADRs between individuals are still serious health problems. Individual genetic differences are a strong tool to overcome these problems.

Pharmacogenetic tests have a great potential in determining safety and effectiveness of drugs.

In clinical practice of pharmacogenetic tests, pharmacists have an important task in the interpretation and evaluation of the test results.

Application, research and education opportunities in the field of pharmacogenetics for pharmacists will increase by the use of these tests in the clinic now and in the future.