



Pharmacogenetics

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Overall Objective

- **What is pharmacogenetics – L1**
- **The complexity of Pharmacogenetics – L2**
- **The application of Pharmacogenetics – L3**

Lecture 1 Objectives

- * What is the genetic test?
Saliva test send it to the company
to get your report within a week
 - * Some advance hospital has this tests
 - Understanding the basics of pharmacogenetics
 - Research examples of gene-drug interactions
- * what make us study pharmacogenetics?
to understand gene - drug interaction

Adverse Drug Reaction (ADR)

You may get hospitalized + buy medications to come over these SE , that's why we understand the pharmacogenetic to predict the outcomes

“Any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use”

Pirmohammed et al., 1998



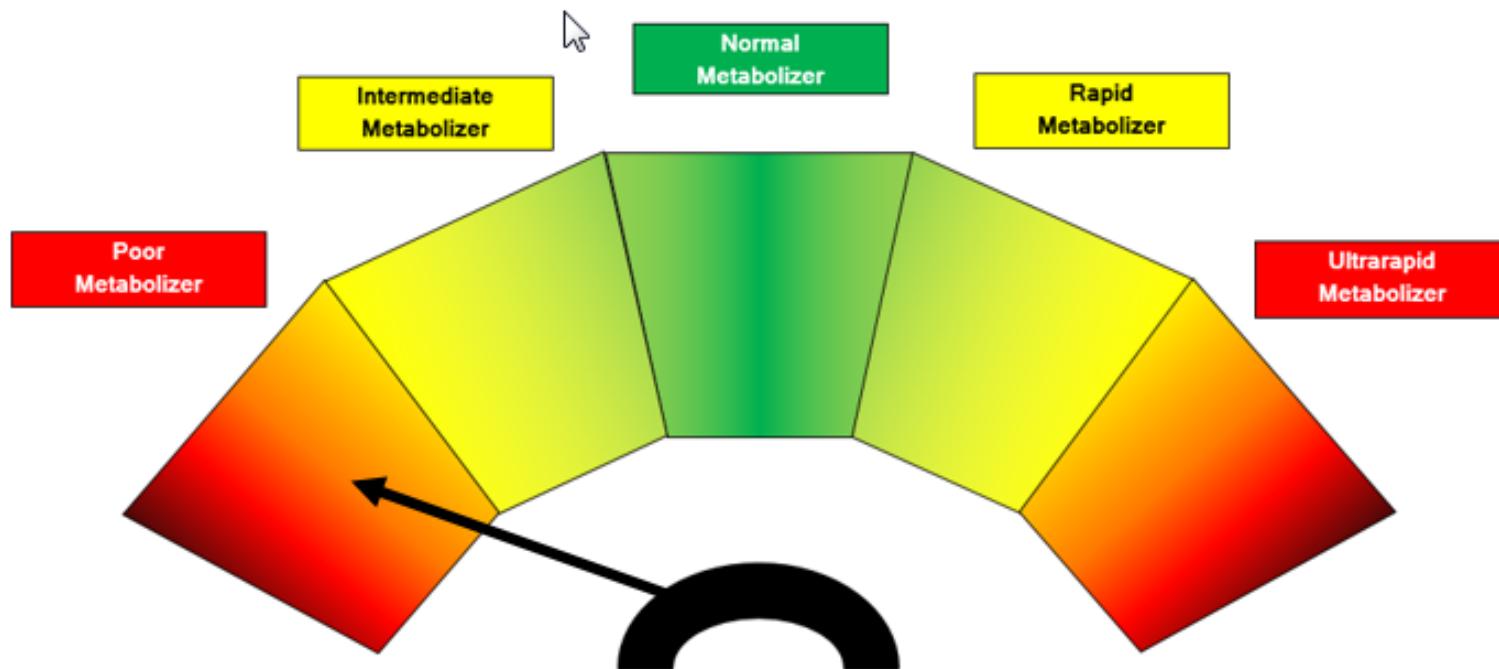
ADR

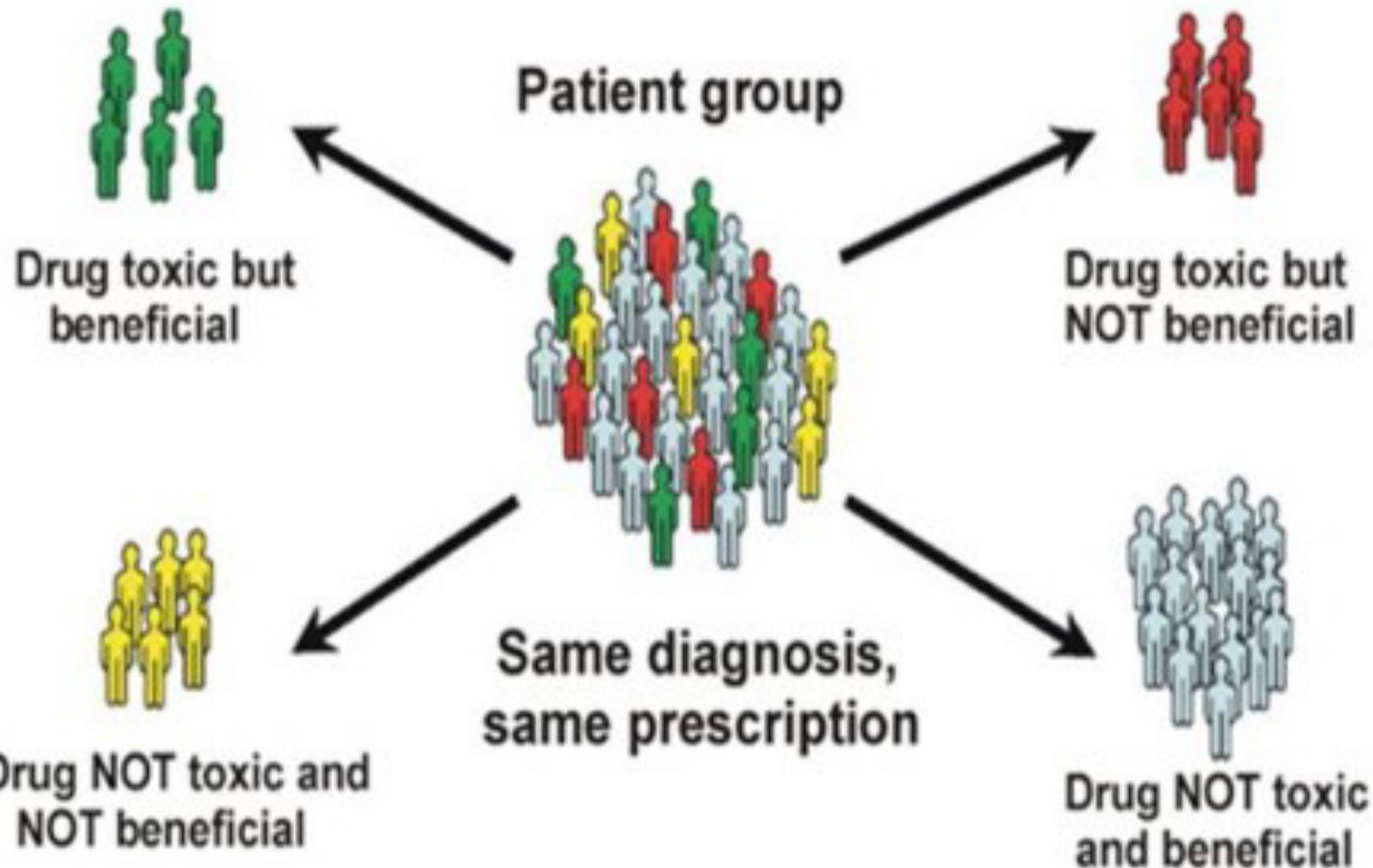
- Is harm (side effects) resulting from administrating a medication at its normal dosage during its normal use
- Different types of ADR Pirmohamed et al., 1998
- ADR cost US \$177.4 billion a year → which is high Ernst et al., 2001
- There is 2 million severe ADRs yearly in US and 100,000 deaths Giacomni et al., 2007
- The FDA has approved the labeling of more than a 500 drugs for Pharmacogenetic testing

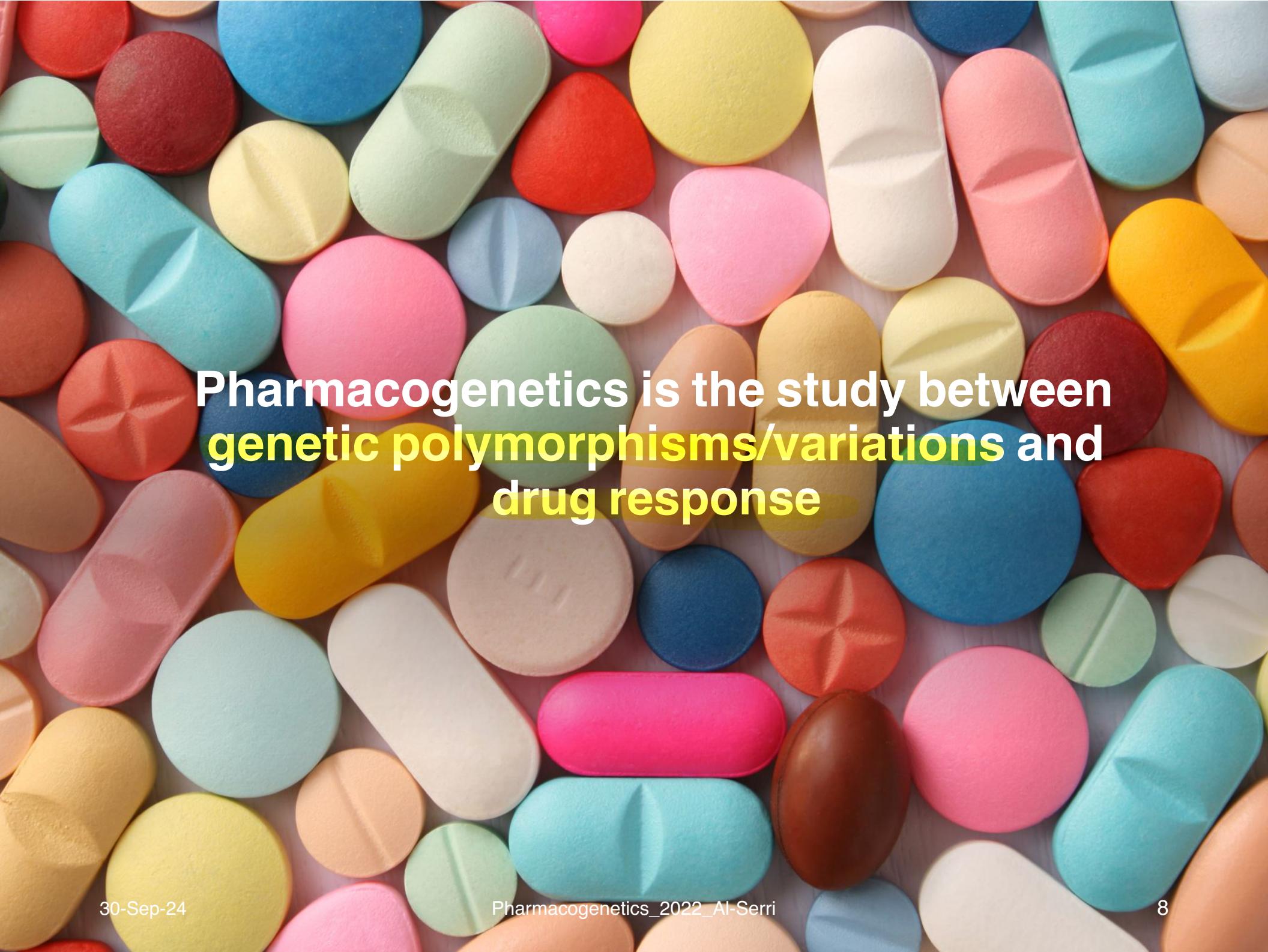
Drug Metabolic Variation – what are the factors?

age
lifeStyle
genetics
enzymes
environments

→ you may have gene that's make you poor metabolizer regardless your age, your health status and every thing else





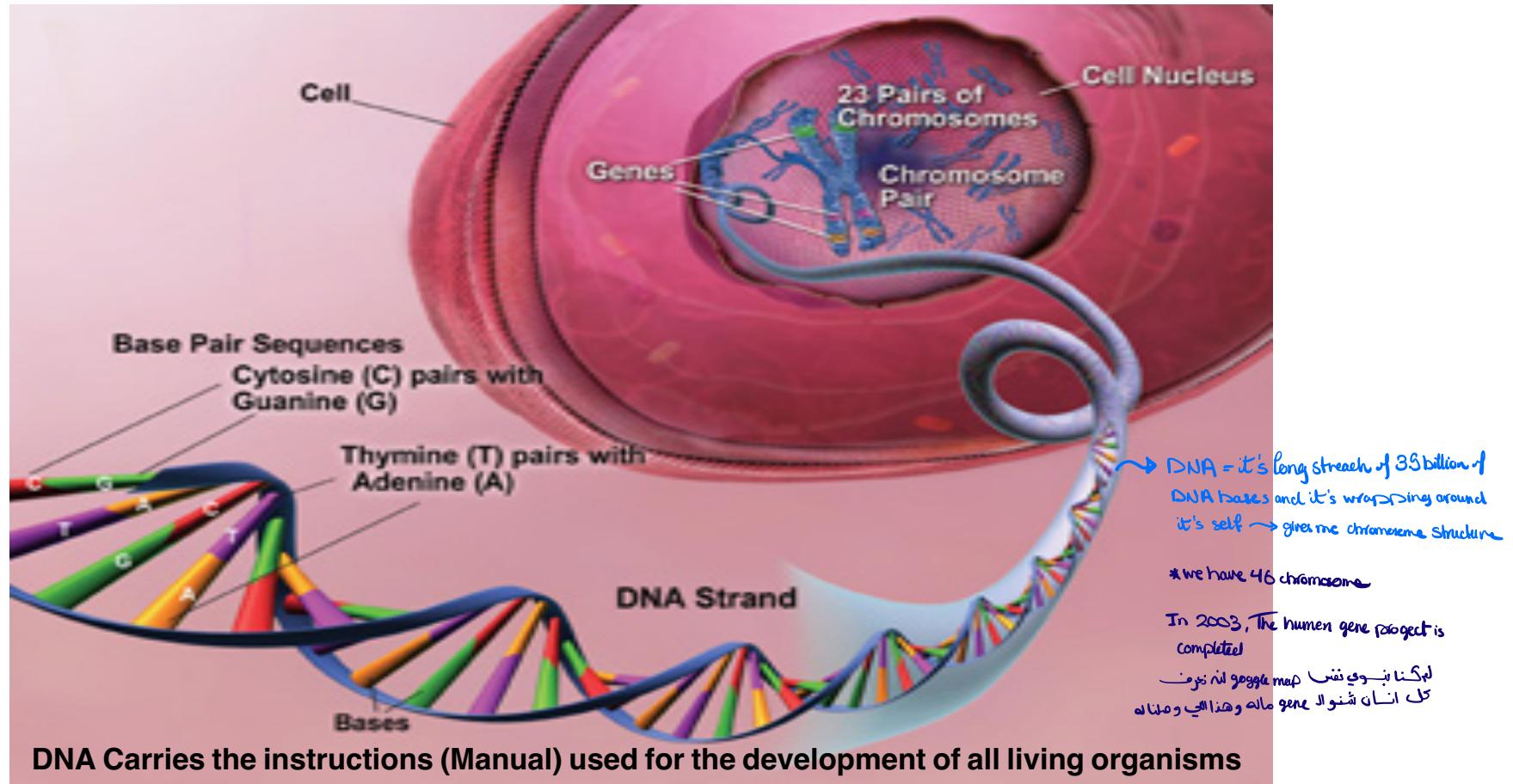


**Pharmacogenetics is the study between
genetic polymorphisms/variations and
drug response**

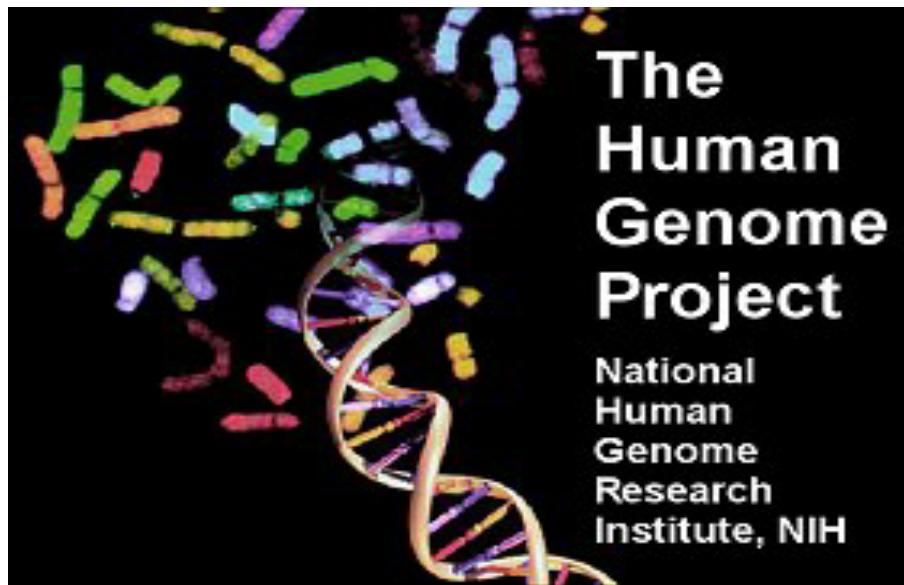
46 chromosomes we have

what's the genetic Polymorphisms / variation (markers)
↳ diff code = diff sequence of the bases

Genetics 101



Basic facts in genetics



1990 - 2003

To sequence 3.5 billion nucleotides (A, G, C, and T)

To know the sequences that represent ~50,000 genes

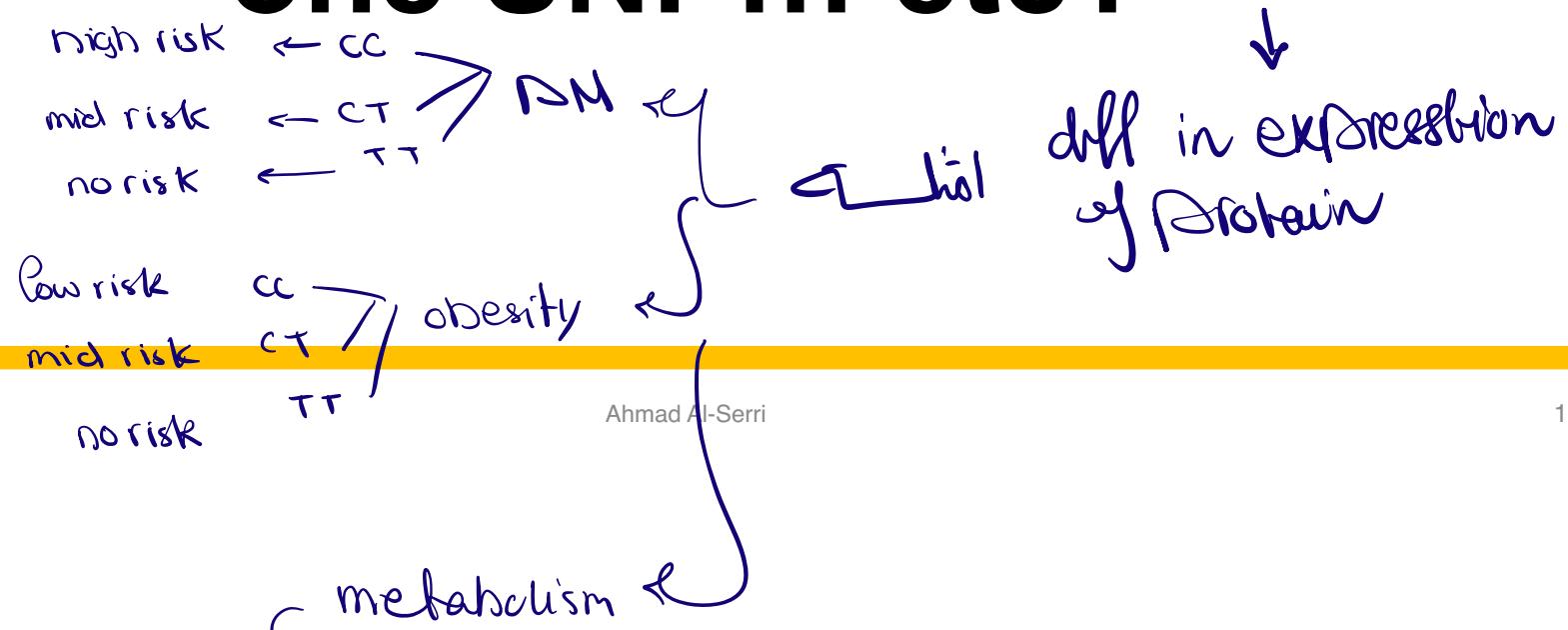
Navigate - To create a map of all this and to access it using easily developed tools

Think of google maps!

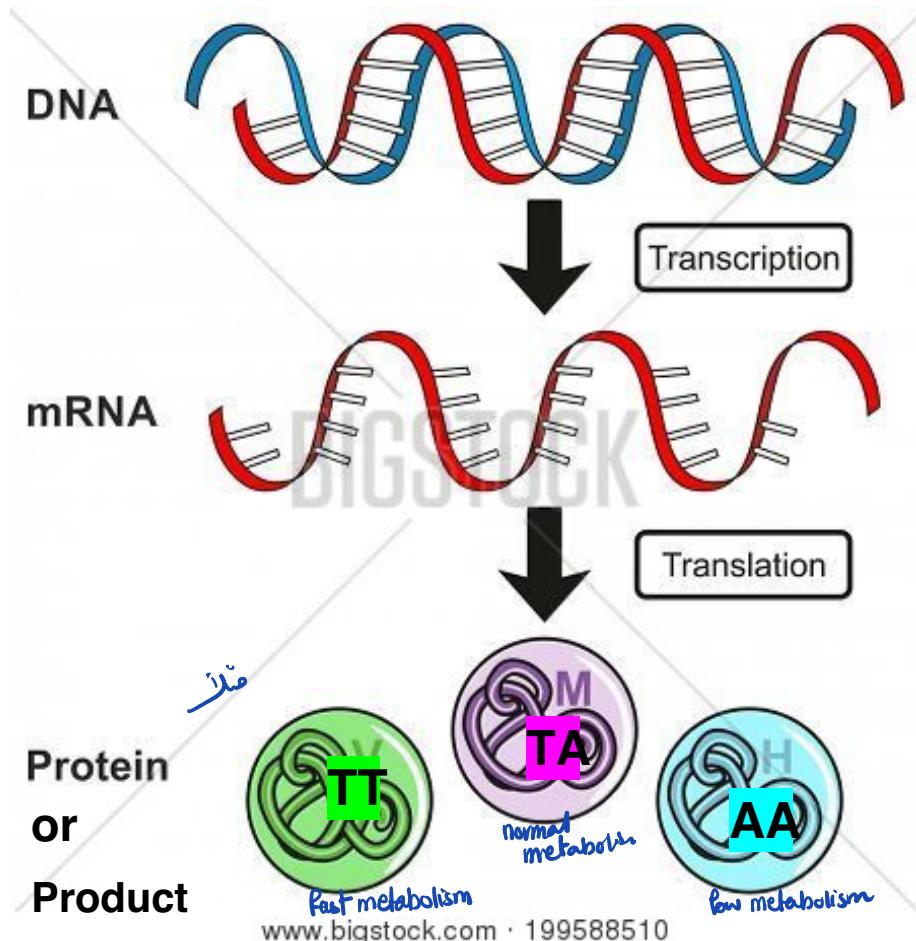
<https://pubmed.ncbi.nlm.nih.gov/31798046/>

↓
مُو شرط يكون
حالی یکون می خواهد + Population میں
اوہنڈا عالیہ کام متان و قصار فتح
حال اقتدارت عین رعن ابادی

So what does it mean biologically if you have a “CC” or “CT” or “TT” for one SNP... etc?



Central Dogma – variation



فیعد هالس اسے کہنا نکریں ایسا This Pt has slow metabolism رام اوری انہیں this SNP

* الدكتور ياب طري انه قبل 20 yrs كان سعر
والي عالي (100 مليون) بحالته قادره على برمجة حاسوب
الذين سعراً دهار (1000) مل (cost)
what is the adv of that?
every one can do research

Research on SNPs

Genetic association studies

– candidate gene approach

- Case/control study (ADR vs normal)
- Requires knowledge of the gene being involved
 - CYP2C9 gene, selecting a SNP of interest (rs1122608 A/G)
 - Statistical analysis showing significance ($p < 0.05$)
 - A susceptibility gene/SNP
 - Replication!

Based on what we choose this gene?
based on the functional studies we didn't before
and from pharmacokinetic and pharmacodynamic of the drug!
So we know which gene we want to look at!

Genotype	Cases (side effects) n=100	Controls (no side effects) n=100
AA	20 (22%)	72 (78%)
AG	43 (44%)	54 (46%)
GG	80 (74%)	27 (26%)

$$P = 0.003 \text{ OR } 2.3 (1.5-3-2)$$

SE جل واحد جل اقل واحد جل
نفع و نفع
از ترجمة جل
OE

so G is a marker that indicate who will has SE
يس العيب في جل واحد جل او جل
so which is mean there are other factors that associated with Pte (other SNP, age, gender)
بس اجيب من جل واحد جل او جل
so which is mean there are other factors that associated with Pte (other SNP, age, gender)

↳ which is mean there are other SNPs as the opposite function
↳ SNP causes fast metabolism so he will has normal metabolism
↳ SNP cause slow metabolism

PubMed®

pharmacogenetics of clopidogrel

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Best match

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572 results

<< < Page 1 of 58 > >>

RESULTS BY YEAR

2001 2024

Pharmacogenetics of clopidogrel.

O'Connor SA, Hulot JS, Silvain J, Cayla G, Montalescot G, Collet JP.

Cite

Curr Pharm Des. 2012;18(33):5309-27. doi: 10.2174/138161212803251880.

Share

PMID: 22724417 Review.

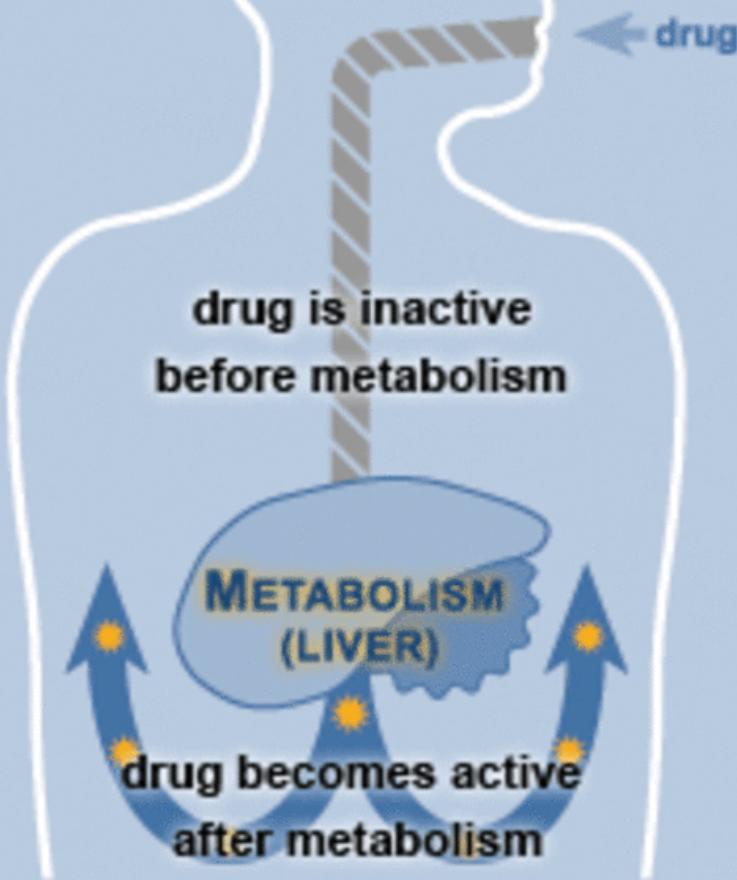
Clopidogrel used in conjunction with aspirin has a central role in the treatment of patients with an acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI).

...Pharmacogenomic analyses have identified loss-of-function variant alleles of CY ...

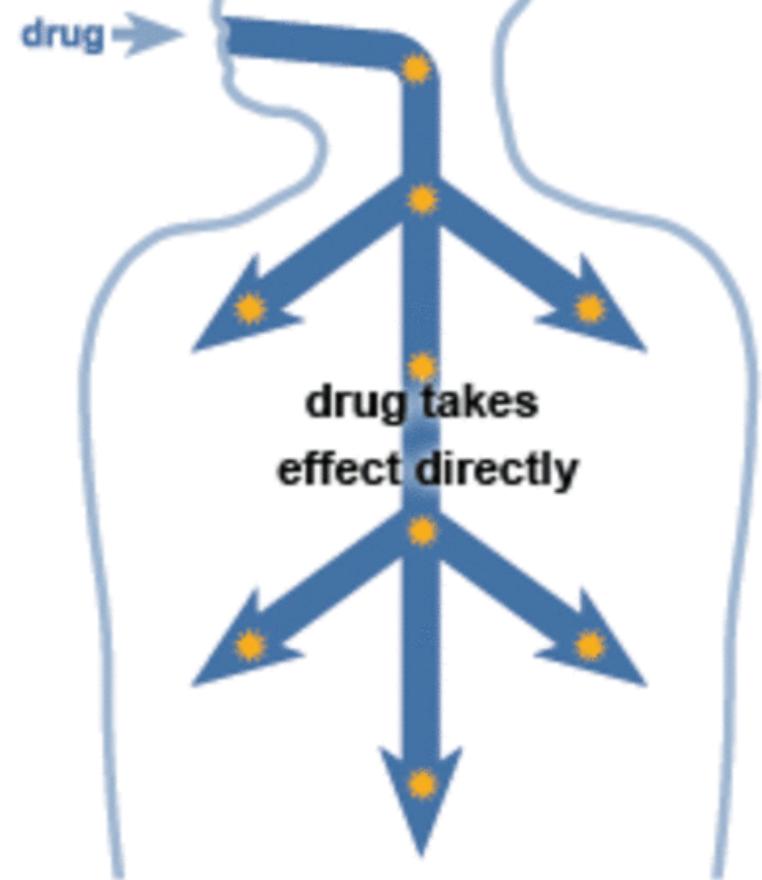
**So, we have ~25000
genes – which genes
are involved in
Pharmacogenetics?**

By understanding / Studying the drug and disease

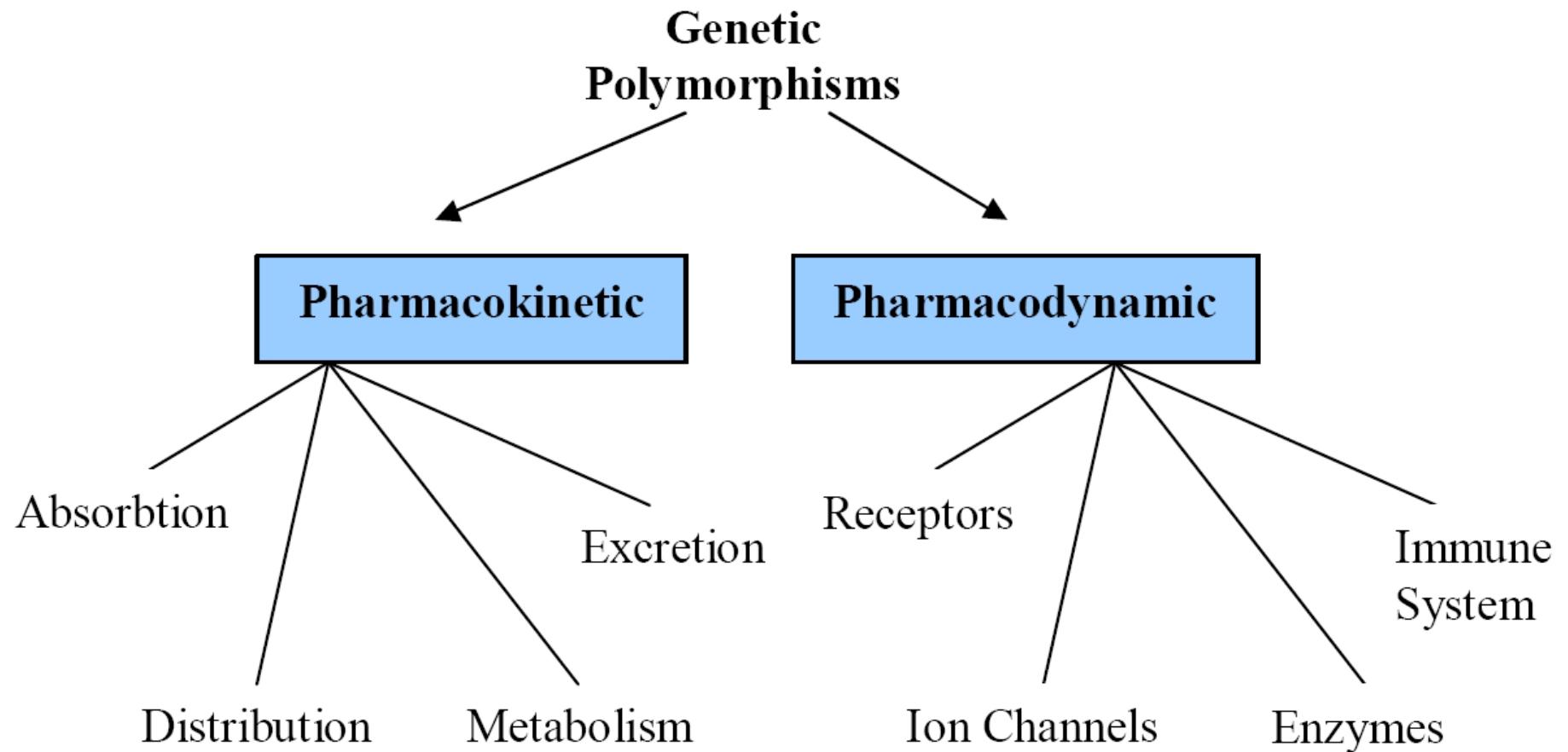
Pro Drug



Active Drug



Understanding the drug mechanism of action



Cytochrome P450 (CYP)

one of common drugs responsible of drug metabolism

- Most studied enzyme system involved in drug metabolism
- Primary found in the liver
- More than 60 genes in the CYP family

Carvedilol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions, Clinical Pharmacology
Clopidogrel	Cardiology	CYP2C19	CYP2C19 intermediate or poor metabolizers	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Isosorbide and Hydralazine	Cardiology	NAT1-2	Slow acetylators	Clinical Pharmacology
Metoprolol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Precautions, Clinical Pharmacology
Prasugrel	Cardiology	CYP2C19	CYP2C19 poor metabolizers	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Propafenone	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Propranolol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	Precautions, Drug Interactions, Clinical Pharmacology

Pharmacogenetics of Warfarin

On Anticoagulant drug ch1
pharmacogenetics

anticoagulation

- Most common anti-coagulant (Blood thinner) used
- Used to prevent for thrombosis and embolism in **early 1950s**
- Conventional dosing is based on **international normalized ratio (INR) 2-3** → standard
- **Narrow therapeutic index** is a challenge in clinical care
- **Bleeding** is the most common adverse effect due to overdosing
- There are many factors that interfere with warfarin anticoagulation effect
- Large inter-individual variation

to find right dose is an issue
to give someone dose and suddenly
he suffer from bleeding (SE)

so we want to know
if there is genetic
test makes me
know the the
accurate dose

↓
First we want to
understand
pharmacokinetic /
dynamic of
the drug and
we found out

↓ ↓
cyp2c9 VKORC1
are involved mainly

so we need higher dose
of warfarin

* CYP2C9 → warfarin metabolism
(inactivating warfarin)
* ↑ VKORC1 → ↑ higher coagulation

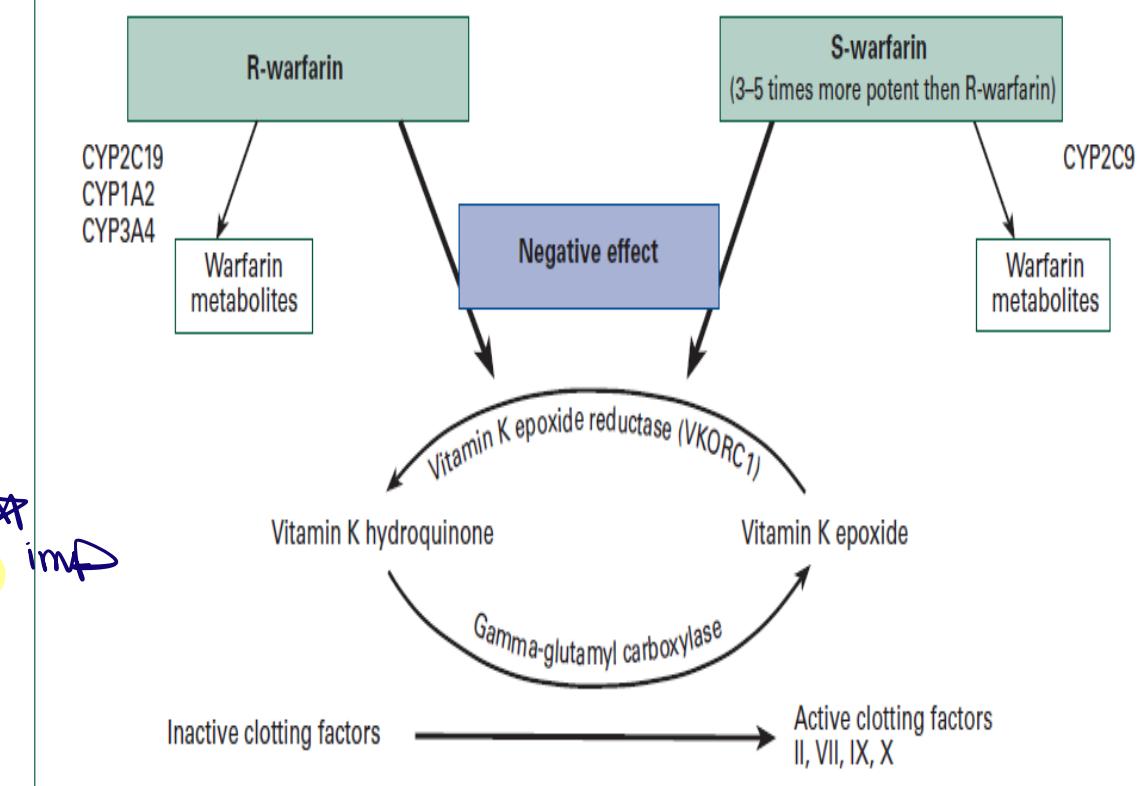
Pharmacogenetics of Warfarin

- Warfarin is a specific inhibitor of vitamin K epoxide reductase (VKOR) which is involved in Vitamin K-dependent clotting factors
- Encoded by the gene (VKORC1)
- CYP2C9 gene encodes for one of the main enzymes involved in warfarin metabolism
- **CYP2C9 works on inactivating Warfarin**
- The higher the CYP2C9 enzyme activity and VKORC1 enzyme activity the more dosage of warfarin is needed

Fig. 1

Schematic diagram of the action of warfarin

Warfarin is administered as a racemic mixture of S and R enantiomers. Cytochrome P450 2C9 inactivates the more potent S-warfarin enantiomer. Warfarin inhibits vitamin K epoxide reductase, preventing recycling of vitamin K leading to partially carboxylated sub- or non-functional coagulation proteins.



CYP2C9

- Several variants in CYP2C9 are associated with reduced enzyme activity and lower clearance rates of warfarin
- Two well studied SNPs (rs1799853 and rs1057910) which change the amino acids
some has CC and some CT and some TT
- rs1799853 C to T substitution resulting in Arginine to Cysteine
- Possible genotypes are Wild-type homozygous CC, heterozygous CT or homozygous mutant TT
- rs1057910 A to C substitution resulting in Isoleucine to Leucine
- Possible genotypes are wild-type homozygous AA, heterozygous AC or homozygous mutant CC
- Of course, different combination of genotypes (Haplotypes) mean different enzyme activity – see next slide

Enzyme activity based on Genotype combinations

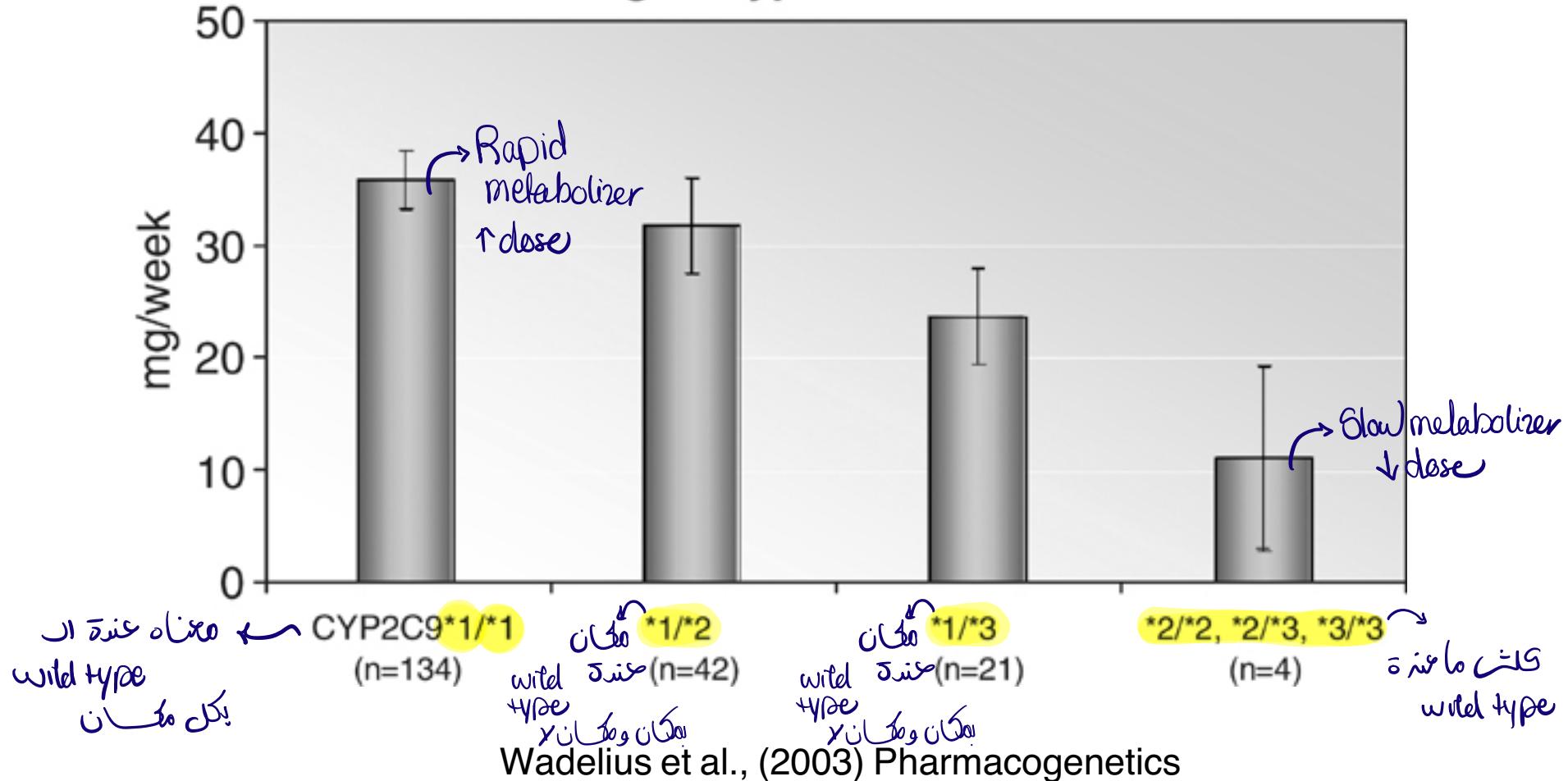
Gene	Phenotype CC, CT, TT <i>Up to 4%</i>	Advice
CYP2C9	Extended Metaboliser	Reference enzyme activity patient should respond well to recommended dose
CYP2C9	Intermediate Metabolizer	Intermediate enzyme activity lower starting dose is recommended and extra monitoring for bleeding events. Consider acenocumarol as alternative.
CYP2C9	Poor Metabolizer	Low enzyme activity. Low starting dose and low maintenance dose should be considered. Monitor carefully for bleeding events. Consider acenocumarol as alternative.

CYP2C9 genotype vs Dosage

1* → wild type (homozygote CC or AA)

2*, 3* → not wild type

CYP2C9 genotype vs. warfarin dose



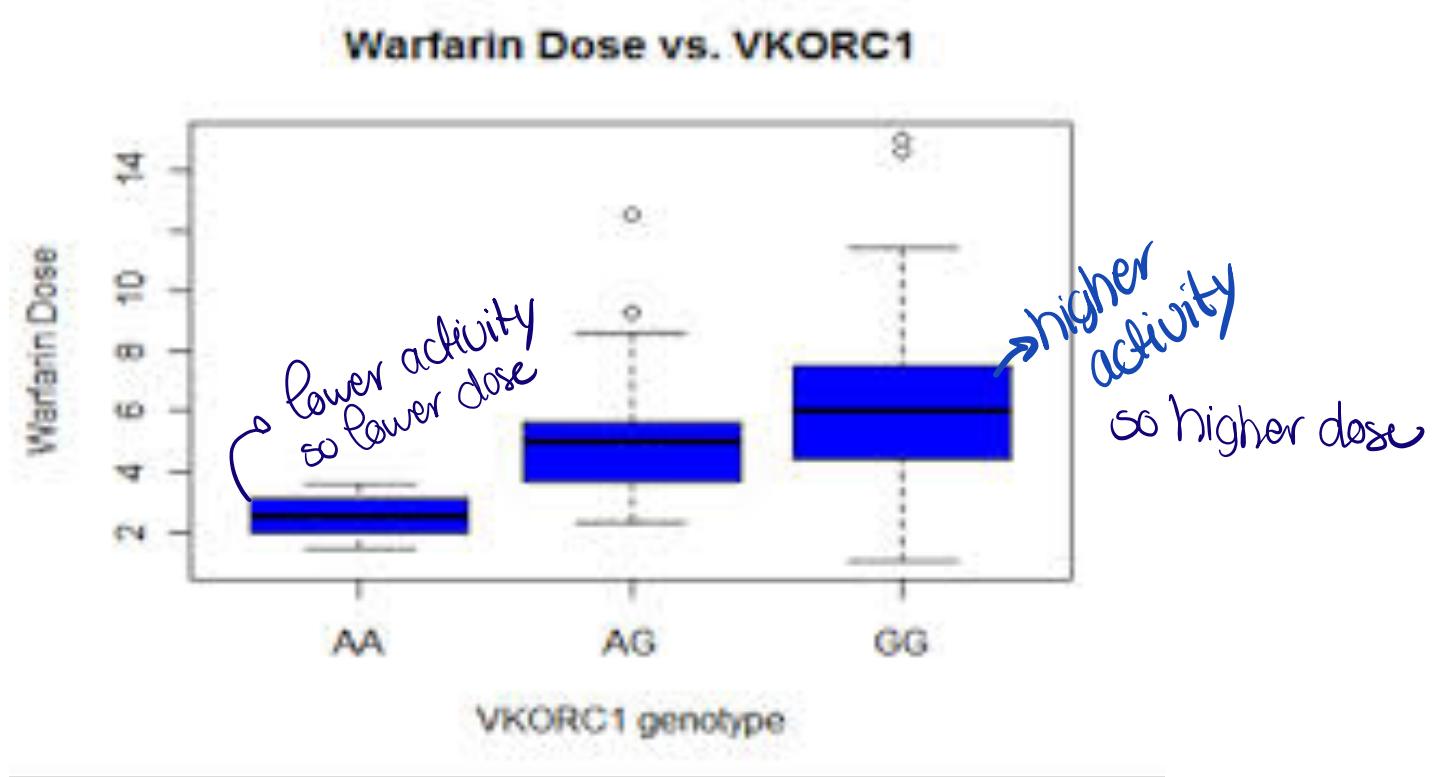
VKORC1

- Vitamin K epoxide reductase (VKORC1)
- Involved in activating blood clotting factors
- Warfarin is a Vitamin K-antagonist
- levels of expression is relevant to drug dosing
- Too much enzyme means increase in clotting (ie. increase dosage)
- SNP rs9923231 (G-1639A)
- Three possible genotypes GG, GA and AA
- Carriers of GG genotypes have 30% more active enzyme than AA genotype carriers → So who has

GG genotype → needs higher dose due to increasing in clotting

AA genotype → needs lower dose than who has GG genotype

VKORC1 genotype vs Dosage



<http://www.stanford.edu/class/gene210/web/html/schedule.html>

Combination of CYP2C9 and VKORC1 genotype vs Dosage

حال ماضيكم حفظون

حال بس ابيكم نعمون
الغقرة

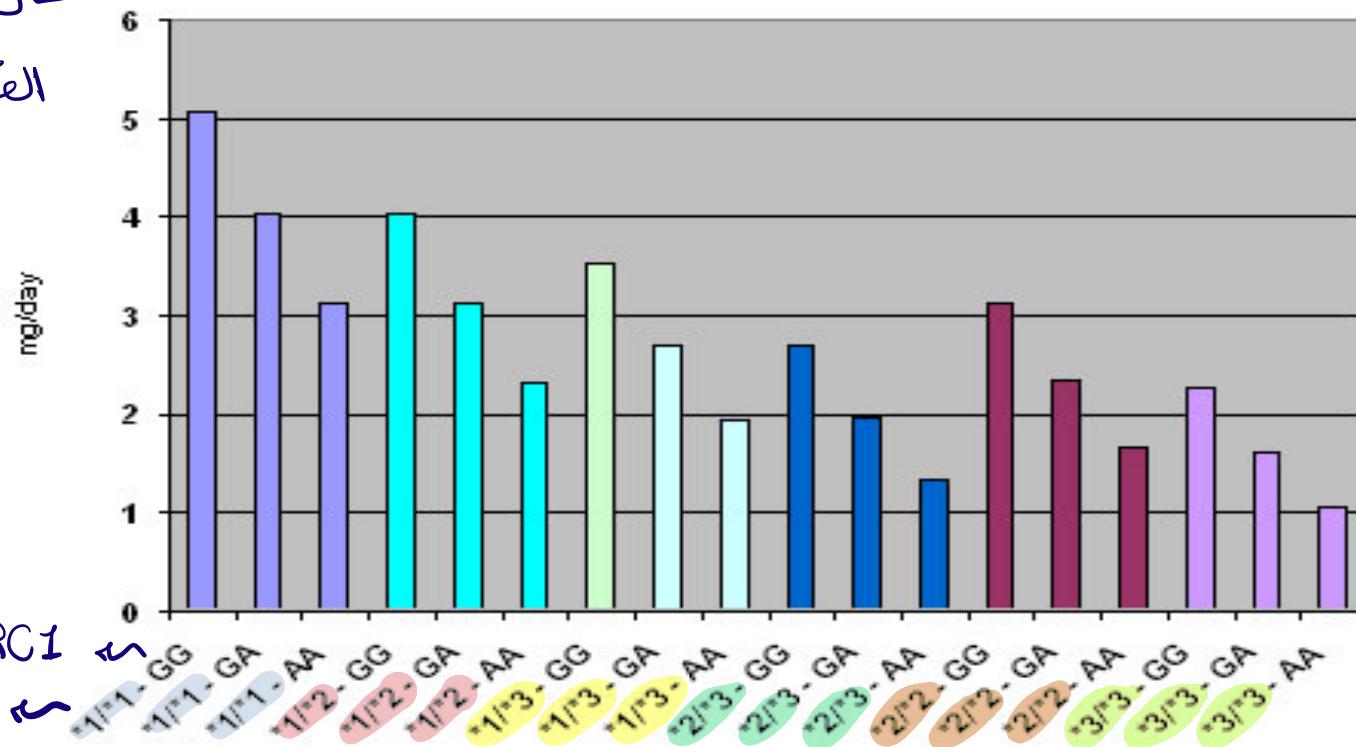
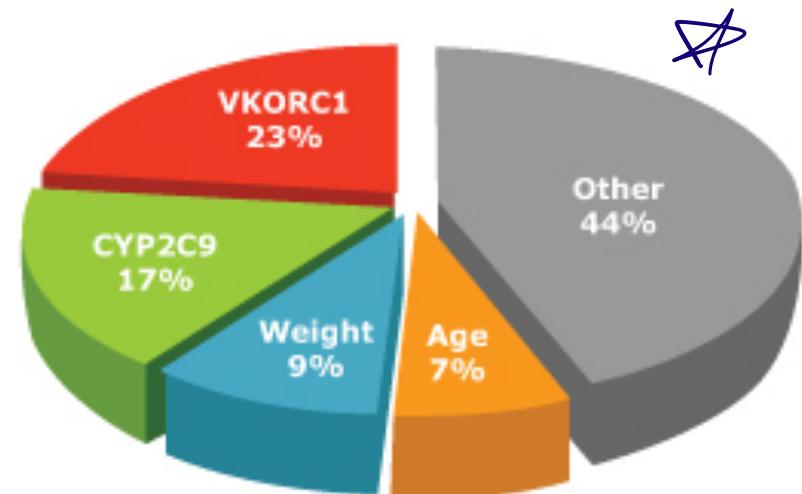


Table 1: Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on CYP2C9 and VKORC1 genotype using the warfarin product insert approved by the United States Food and Drug Administration:

VKORC1 Genotype (-1639G>A, rs9923231)	CYP2C9*1/*1	CYP2C9*1/*2	CYP2C9*1/*3	CYP2C9*2/*2	CYP2C9*2/*3	CYP2C9*3/*3
GG	5.7	5.7	3.4	3.4	3.4	0.5-2
GA	5.7	3.4	3.4	3.4	0.5-2	0.5-2
AA	3.4	3.4	0.5-2	0.5-2	0.5-2	0.5-2

Pharmacogenetics of Warfarin

- At least to date there are more than 20 genes found associated with warfarin
 - About 70 SNPs
 - It took more than 20 years to discover these SNPs and still counting!
 - CYP2C9 and VKORC1 is estimated to account to 40% of variability in response and used for genetic testing
 - www.Pharmgkb.org
 - Many factors other than genetics are involved in dose requirement; age, weight, ethnicity, smoking, other Medications and diet (intake of Vitamin K).
 - Age and weight is estimated to account to 15% of variability in drug response
- The hardest*



McClain MR, Palomaki GE, Piper M, Haddow JE. Genet Med. 2008 Feb;10(2):89-98

- > [Warfarin Dosing](#)
- > [Clinical Trial](#)
- > [Outcomes](#)
- > [Hemorrhage Risk](#)
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User:
Patient:
[Version 2.34](#)
Build : Oct 30, 2011
30-Sep-24

Required Patient Information

Age: Sex: -Select- Ethnicity: -Select-

Race: -Select-

Weight: lbs or kgs

Height: (feet and inches) or (cms)

Smokes: -Select- Liver Disease: -Select-

Indication: -Select-

Baseline INR: Target INR: Randomize & Blind

Amiodarone/Cordarone® Dose: mg/day

Statin/HMG CoA Reductase Inhibitor: -Select-

Any azole (eg. Fluconazole): -Select-

Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: -Select-

Genetic Information

[VKORC1-1639/3673:](#) Not available/pending

[CYP4F2 V433M:](#) Not available/pending

[GGCX rs11676382:](#) Not available/pending

[CYP2C9*2:](#) Not available/pending

[CYP2C9*3:](#) Not available/pending

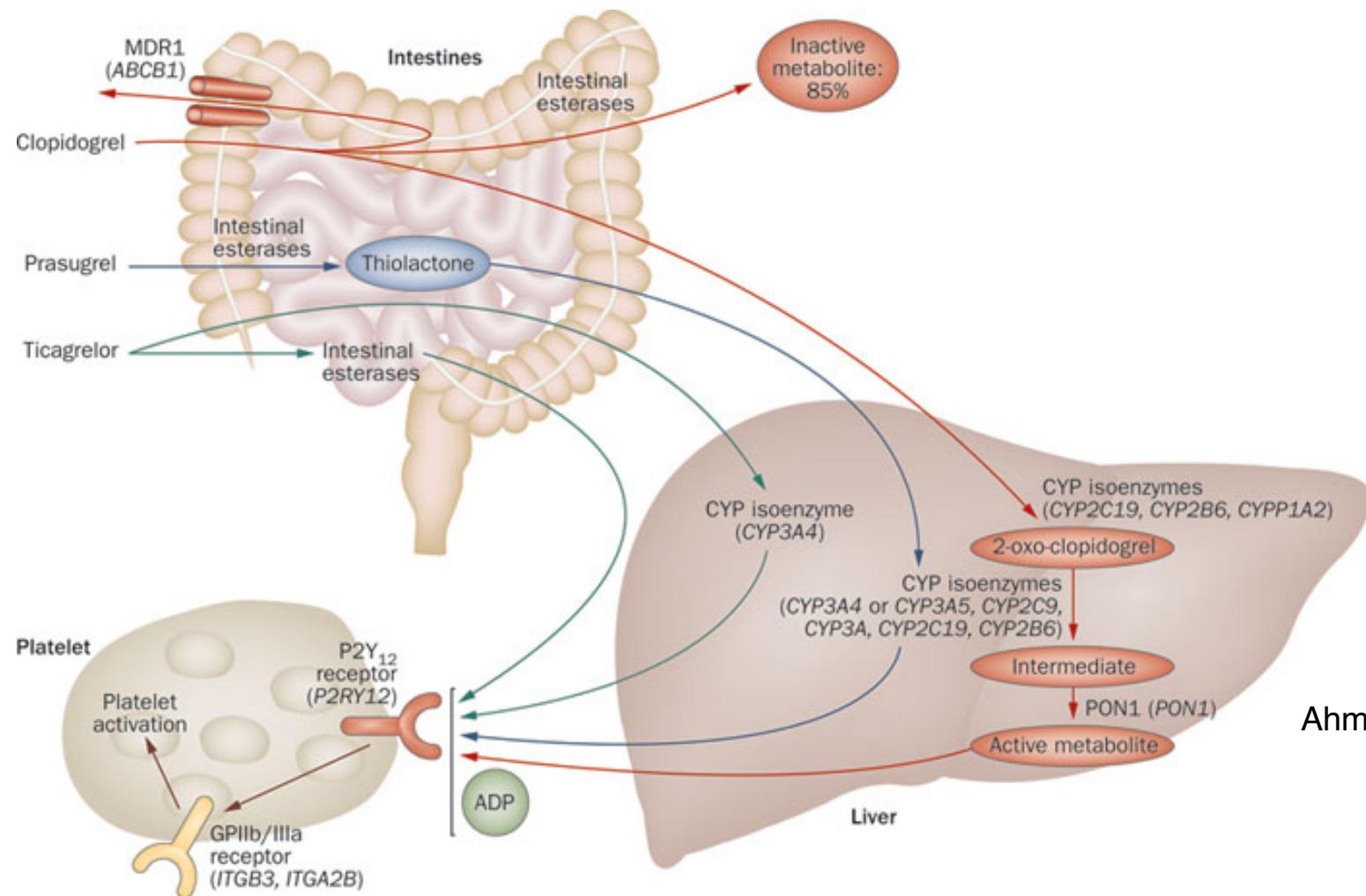
Pharmacogenetics of Clopidogrel

الافضل قبل الاختبار
انه يجري genetic test وابو الكستور واحد من

عمرنا 50+
genes and involved SNPs
in 5 years!

- Known as Plavix and approved in 2002
- Inhibits platelet activation (cell fragments that form clots) to inhibit thrombosis
- Used for acute coronary syndrome (ACS) and coronary artery stent placement
- Anti-platelet effect is variable among patients
- Issue:** 30% taking the drug show no response and may result in recurrence of cardiac events

Clopidogrel pharmacokinetics and dynamics



- about 85 % of the drug is hydrolyzed to an inactive form
- The remaining must be metabolized into an active metabolite by liver cytochrome P-450 enzymes

CYP

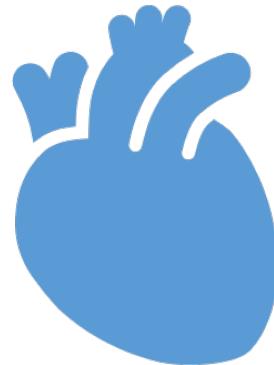
- Multiple enzyme involved in the metabolism (CYP1A2, CYP2B6, CYP2C9, CYP3A4 and CYP2C19)
- CYP2C19 is said to have the most important role
- Multiple Genetic polymorphisms in CYP2C19 found to be associated with response to Clopidogrel
- More than 25 SNPs found
- Three common SNPs rs4244285 (*2), rs4986893 (*3) and rs1224860 (*17) in the CYP2C19 is found involved in enzyme activity creating three categories of metabolism
- Having CYP2C19*2 and *3 (ie having reduced enzyme efficacy compared with CYP2C19*17)
- **Carriers of the CYP2C19*2 receiving clopidogrel are found to be associated with 42% of higher risk of major adverse cardiac events**
- The FDA in 2010 issued a “black box” warning for CYP2C19
- Alternative medications should be considered (e.g. Brilinta (Ticagrelor))



Take home message

End 11.31

- Adverse drug reaction is a world-wide issue
- Understanding a drugs Pharmacokinetics and pharmacodynamics is important for Pharmacogenetics research
- CYP2C9 and VKORC1 are mainly tested for Warfarin Pharmacogenetics. CYP2C19 is mainly tested for Clopidogrel Pharmacogenetics.
- However, there are still more genes and variations to be discovered



Is Pharmacogenetic testing being applied regularly for CVD? Should you test before applying the drug? Or after an ADR?

Before → But there is no clinical guideline