Pharmacogenetics of cytochrome P450 and its application and value in drug therapy – the past, present and future

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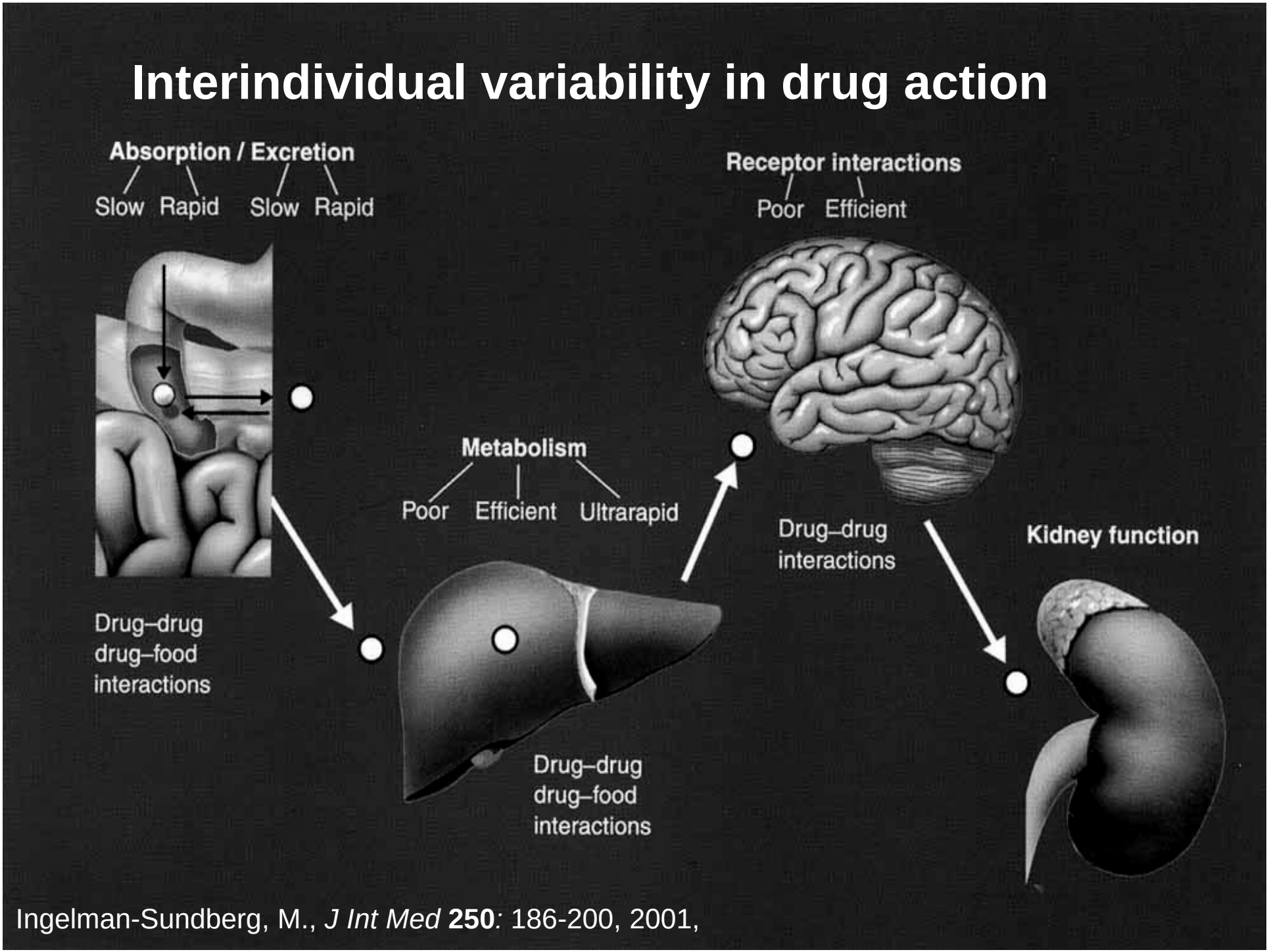
The human genome

- 3,120,000,000 nucleotides
- 23,000 genes
- >100 000 transcripts (!)
- up to 100,000 aa differences between two proteomes
- 10,000,000 SNPs in databases today

The majority of the human genome is transcribed and has an unknown function

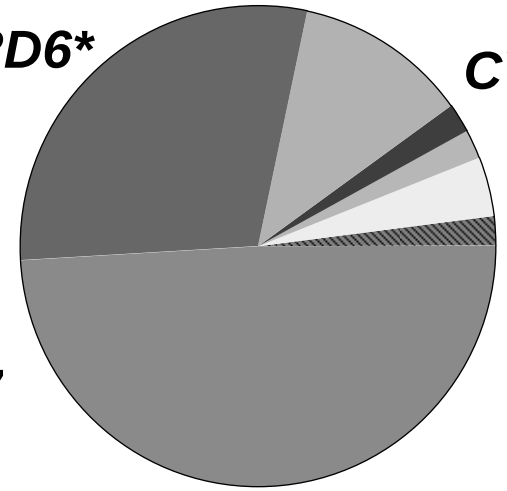
RIKEN consortium *Science* 7 Sep 2005

Interindividual variability in drug action



Ingelman-Sundberg, M., *J Int Med* **250***:* 186-200, 2001,

CYP dependent metabolism of drugs (80 % of all phase I metabolism of drugs)



Beta blokers
Antidepressants
Antipsychotics
Dextromethorphan
Codeine
Debrisoquine

CYP2D6*

Tolbutamide
Warfarin
Phenytoin
NSAID

CYP2C9*

Diazepam
Citalopram
Anti ulcer drugs

CYP2C19*

CYP2E1
Clozapine

CYP1A2
Ropivacaine

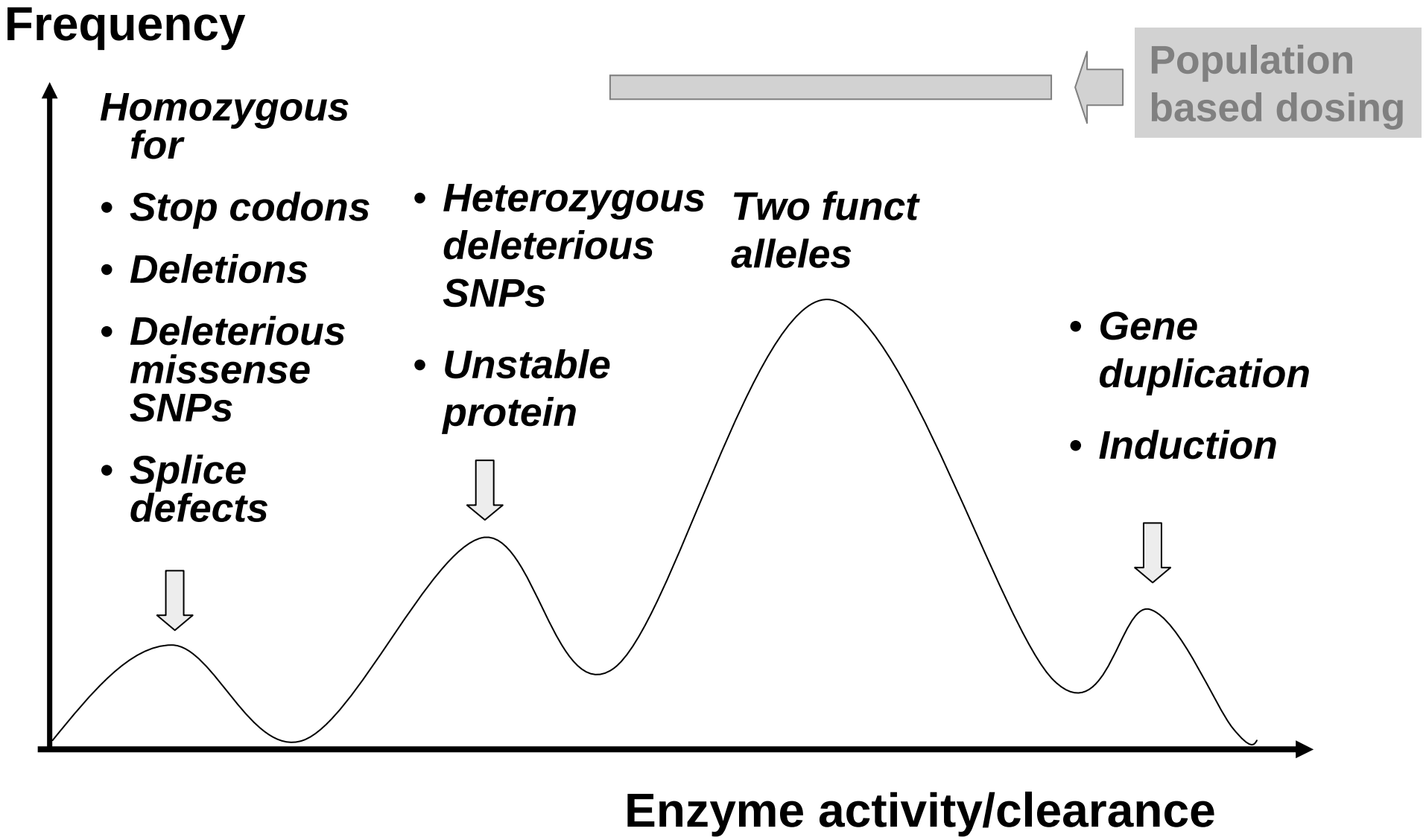
CYP2B6*
Efavirenz
Cyclophosphamide

CYP3A4/5/7
Cyclosporin
Taxol
Tamoxifen
Tacrolimus
Amprenavir
Amiodarone
Cerivastatin
Erythromycin
Methadone
Quinine

40 % of the phase I metabolism is carried out by polymorphic P450s (enzymes in Italics)

Phenotypes and mutations

PM, poor metabolizers; IM, intermediate met;
EM, efficient met; UM, ultrarapid met



The Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee

http://www.imm.ki.se/CYPalleles/

Webmaster: Sarah C Sim

Editors: Magnus Ingelman-Sundberg, Ann K. Daly, Daniel W. Nebert

Advisory Board: Jürgen Brockmöller, Michel Eichelbaum, Seymour Garte, Joyce A. Goldstein, Frank J. Gonzalez, Fred F. Kadlubar, Tetsuya Kamataki, Urs A. Meyer, David R. Nelson, Michael R. Waterman, Ulrich M. Zanger.

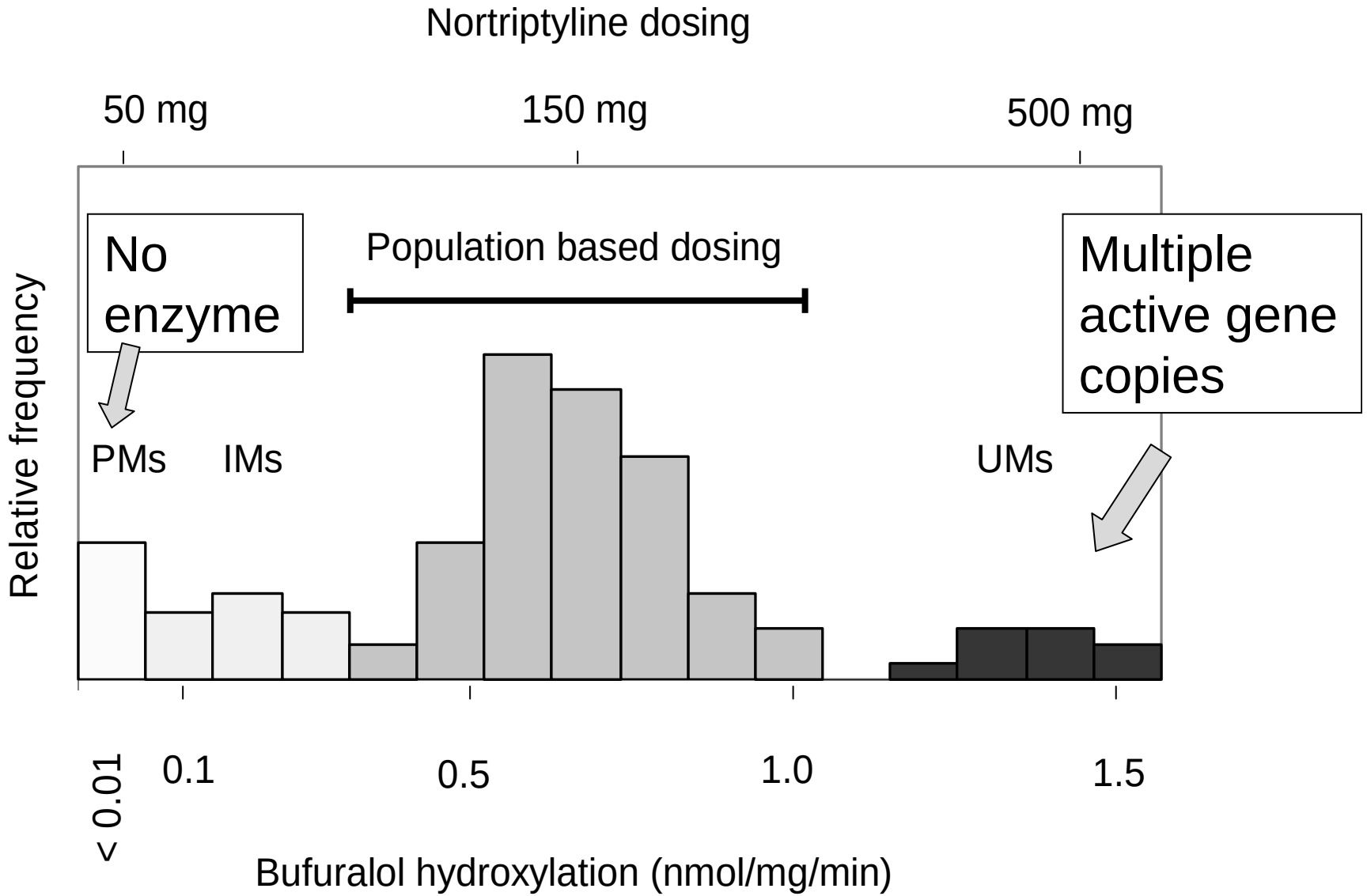
Nomenclature files for human cytochrome P450 alleles:
CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A7, CYP5A1, CYP8A1, CYP21.

Cytochrome P450s and ADRs

- **59 % of drugs cited in ADR-studies are metabolised by polymorphic phase 1 enzymes - P450s account for 86 % of those**
- **Only 20 % of drugs which were substrates for nonpolymorphic enzymes were in the ADR reports**
- **CYP2D6 was involved in 38 % of all ADR reports**

Phillips et al *JAMA* **286**:2270-2279, 2001

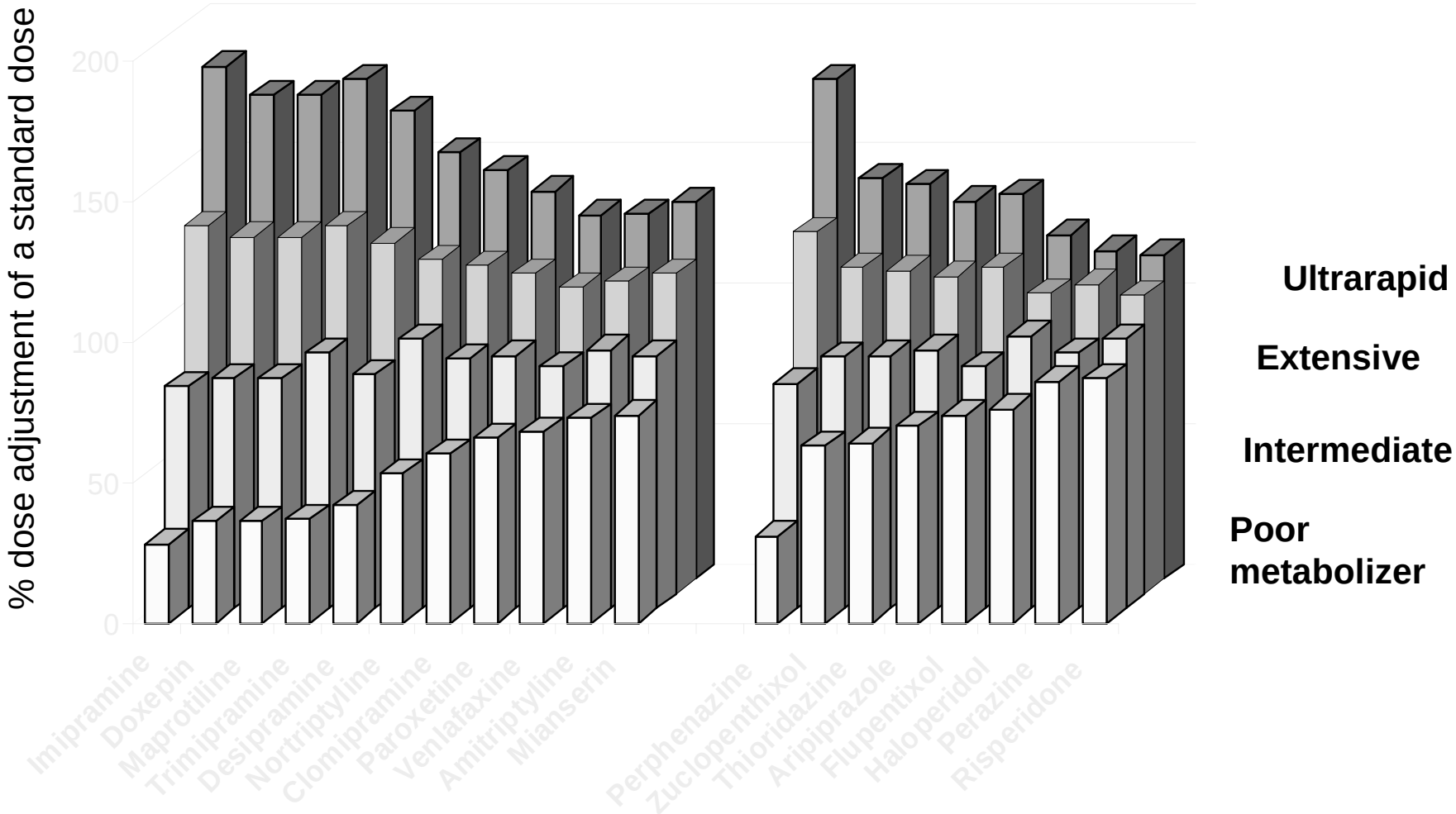
CYP2D6 and rate of metabolism in the European population



Based on the European population with 7 % PMs and 5.5% UMs overall

Ingelman-Sundberg, M. *Trends Pharmacol Sci* 2004, **25**:193-200

CYP2D6-based dose adjustments for antidepressants and antipsychotics



Kirchheiner et al., Mol Psychiatry 2004

CYP2D6 and the European population

20-30 million subjects have no CYP2D6 enzymes (PMs)

15-20 million subjects have *CYP2D6 gene* duplications (UMs)

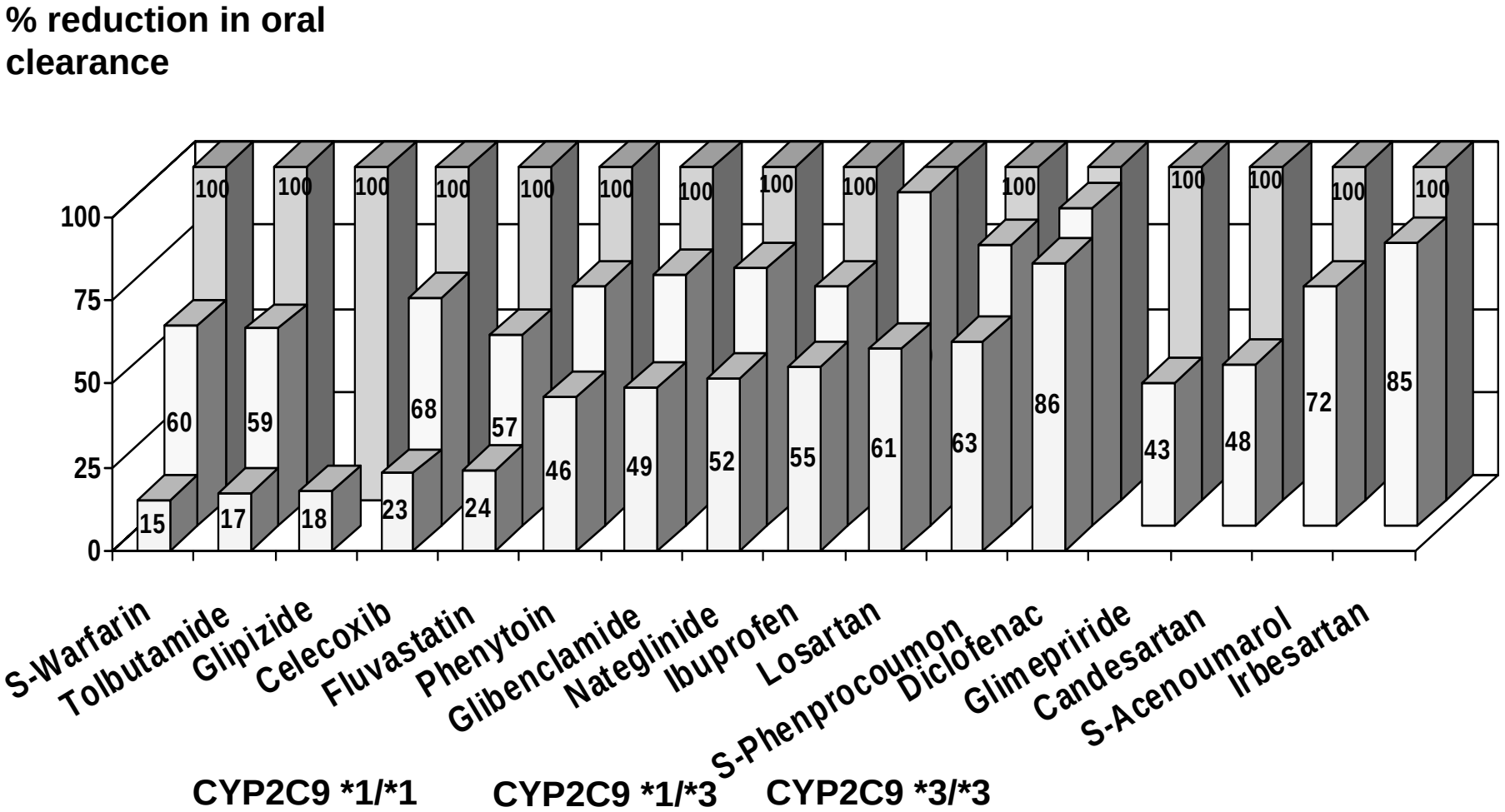
resulting in

- Too slow drug metabolism
- Too high drug levels at ordinary dosage
- High risk for ADRs
- No response from certain prodrugs (e.g. codeine)

- Too rapid drug metabolism
- No drug response at ordinary dosage - Non-responders

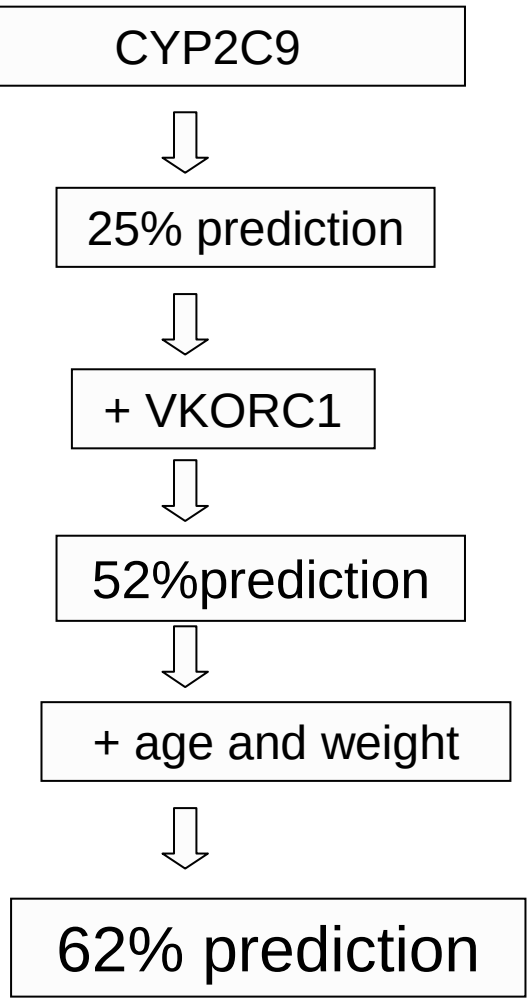
Relevant for 15 % of all drugs used

Pharmacogenetics based dose adjustments: *CYP2C9*3*



Kirchheiner & Brockmöller, 2005

Warfarin dosage variation: 0.5-8 mg/day

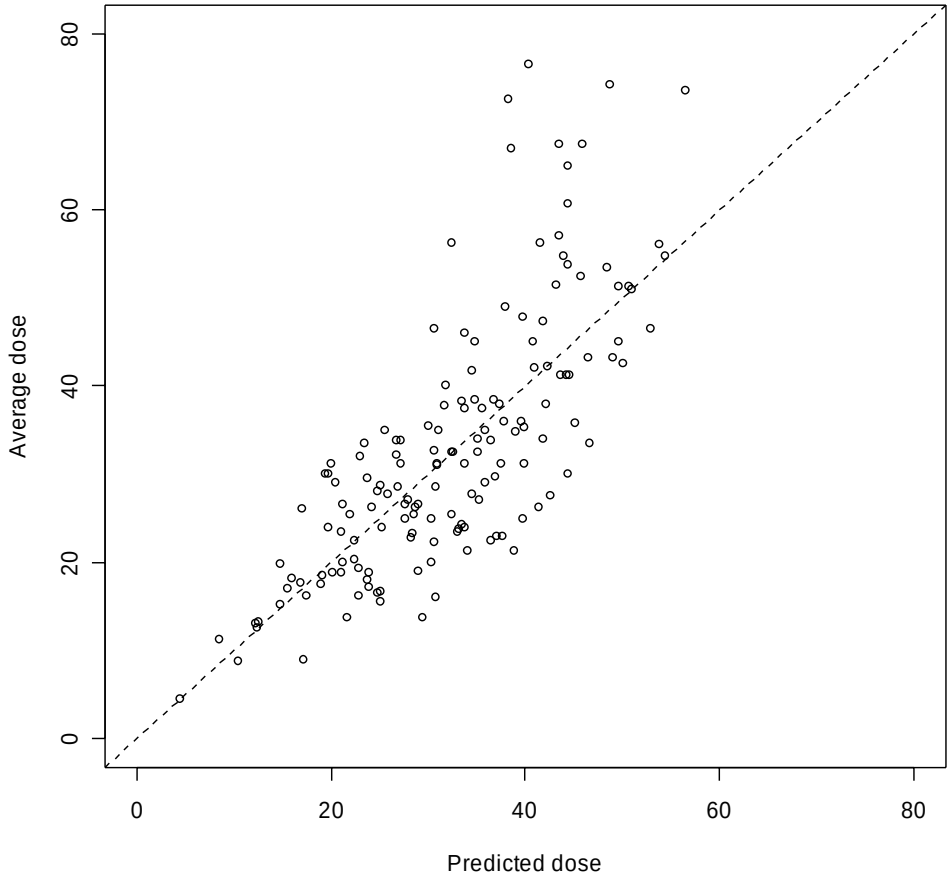


VKOR = vit K epoxide reductase

Multiple regression model explains 61% of variance in warfarin dose

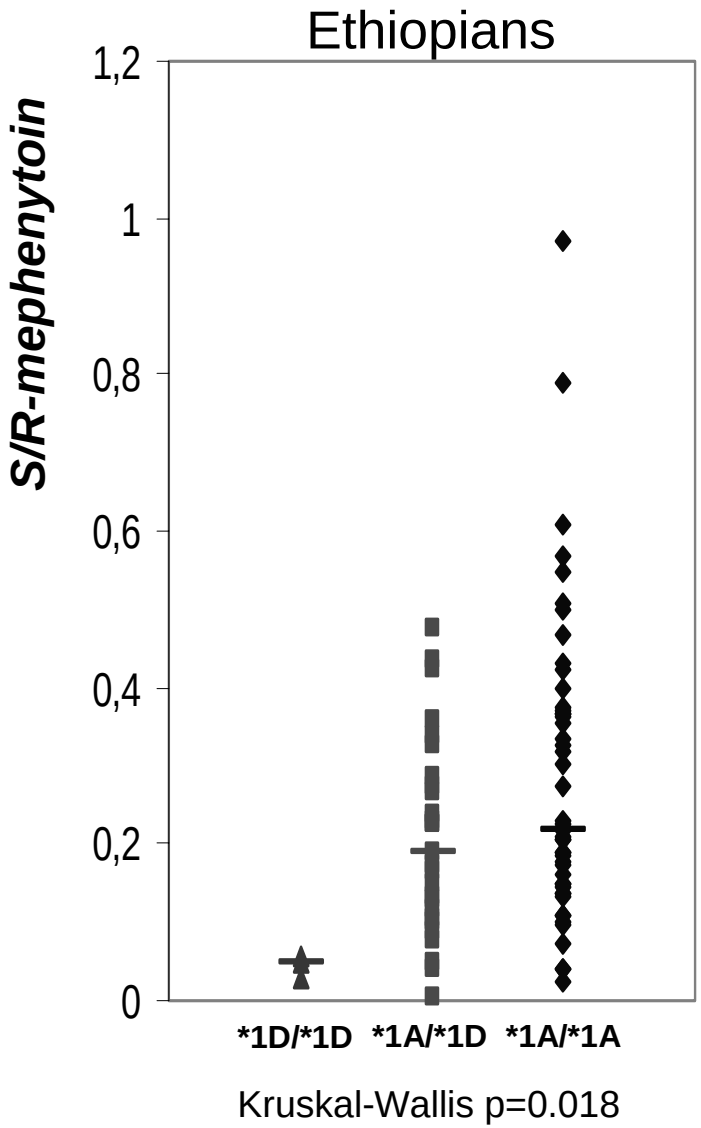
Variables	*Dose p*
VKORC1	<.0001
CYP2C9	<.0001
PROC	0.0541
Age	0.0002
Bodyweight	0.0002
Indication	0.0406
Interaction	0.1018

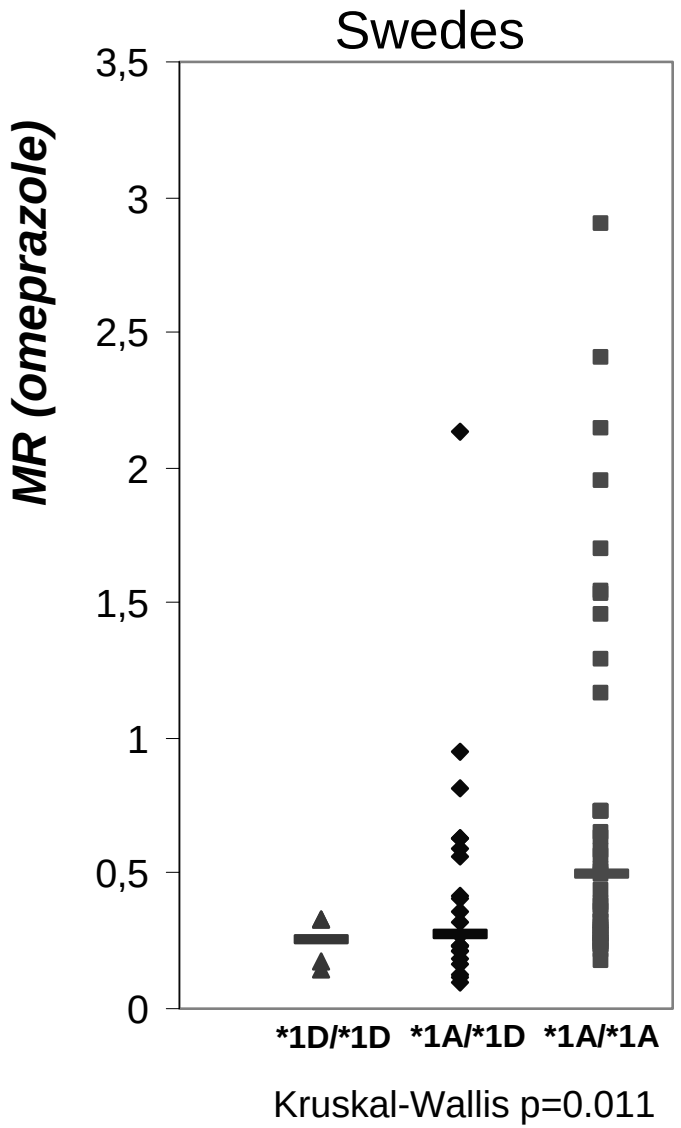
Total r^2 for the model = 0.614



Wadelius M, Chen LY, Eriksson N, Ghori J, Wadelius C, Bentley D, McGinnis R, Deloukas P.
Uppsala University, Sweden and the Wellcome Trust Sanger Institute, UK.

A novel ultrarapid *CYP2C19* allele (*CYP2C19*17*)





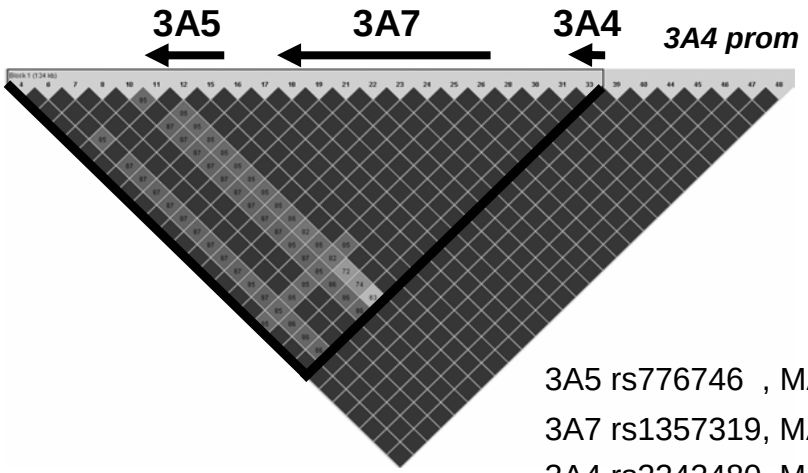
Frequency and effect of *CYP2C19*17* on clinical parameters

Population	**Allele frequency**	***1/*1***	***1/*17***	***17/*17***
Swedes	20.1	155	80	9
Ethiopians	17.9	126	60	4
Tanzanians	16.3	63	23	3
Chinese*	5.0	54	6	0

	17/*17	***1/*17***	***1/*1***	***1/*2***
n	4	23	38	16
Omeprazole MR	0.25±0.10	0.44±0.44	0.77±0.70	1.17±0.75
Pred omeprazole AUC	742±93	926±410	1240±658	1620±710
Predicted intragastric pH	3.50	3.75	4.20	4.50

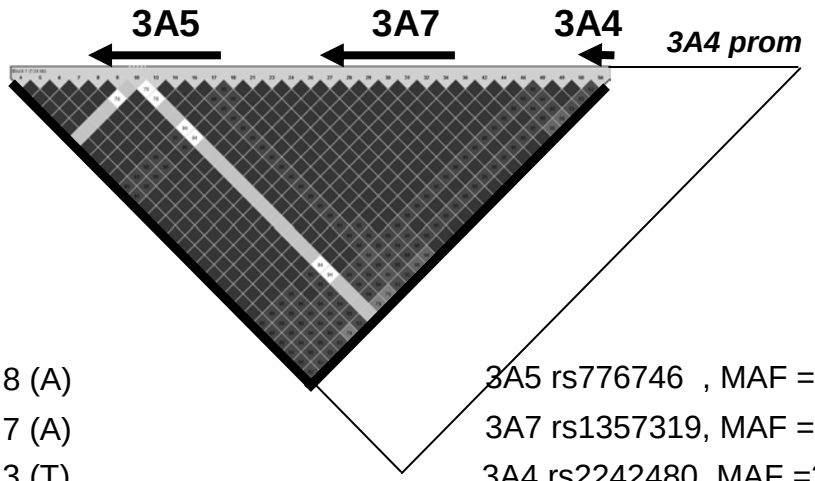
CYP3A locus: INTERETHNIC DIFFERENCES

European



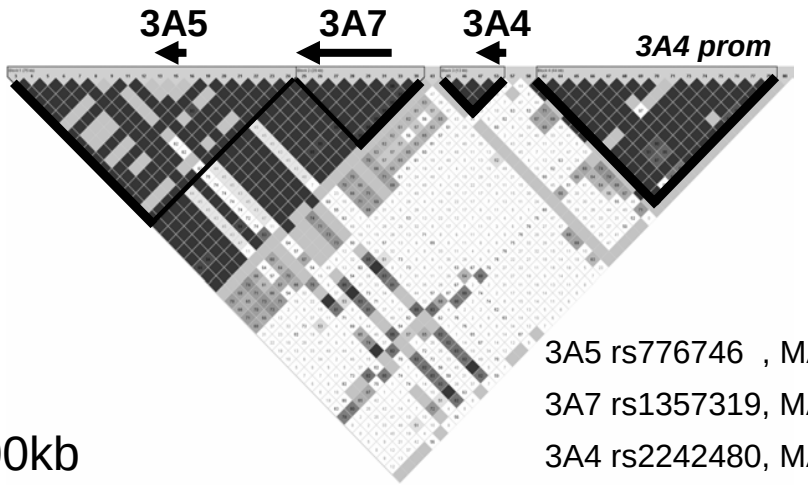
3A5 rs776746 , MAF =5.8 (A)
3A7 rs1357319, MAF =6.7 (A)
3A4 rs2242480, MAF =8.3 (T)

Chinese



3A5 rs776746 , MAF =33 (A)
3A7 rs1357319, MAF =34 (A)
3A4 rs2242480, MAF =26 (T)

African

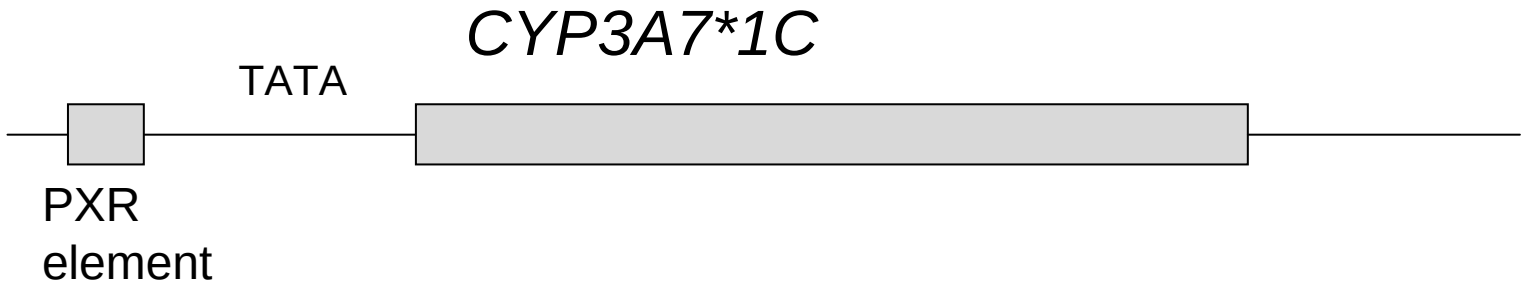


3A5 rs776746 , MAF =15 (G)
3A7 rs1357319, MAF =35 (C)
3A4 rs2242480, MAF =11 (C)

200kb

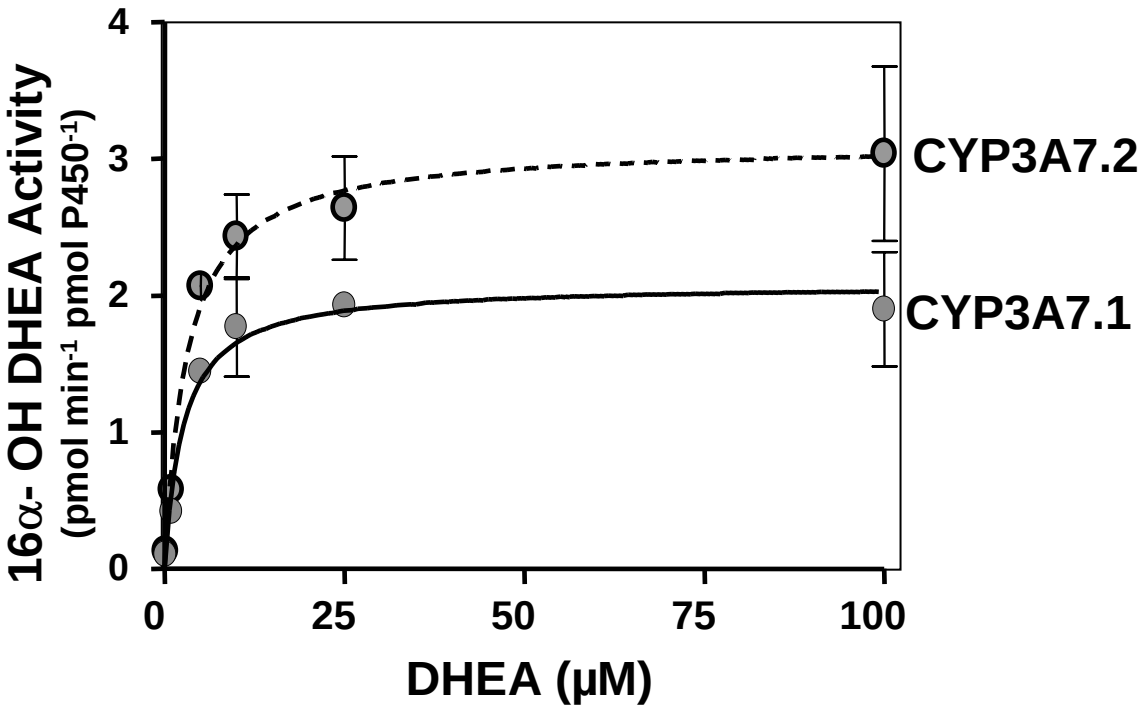
MAF (%)	**European**	**Chinese**	**Africans**
CYP3A5 rs776746	6 (**A**)	33 (**A**)	15 (**G**)
CYP3A7 rs1357319	7 (**A**)	34 (**A**)	35 (**C**)
CYP3A4 rs2242480	8 (**T**)	26 (**T**)	11 (**C**)

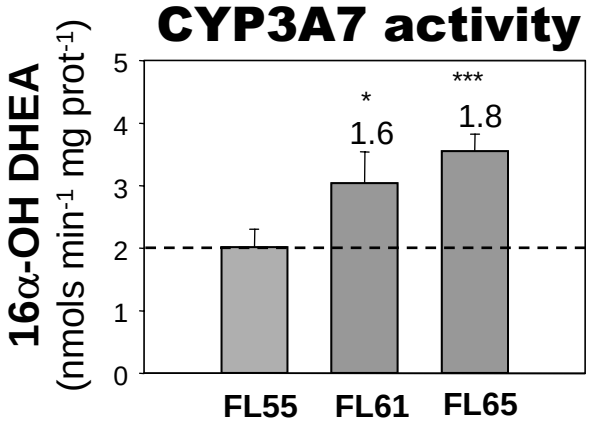
Polymorphically determined expression of CYP3A7 in human adult liver

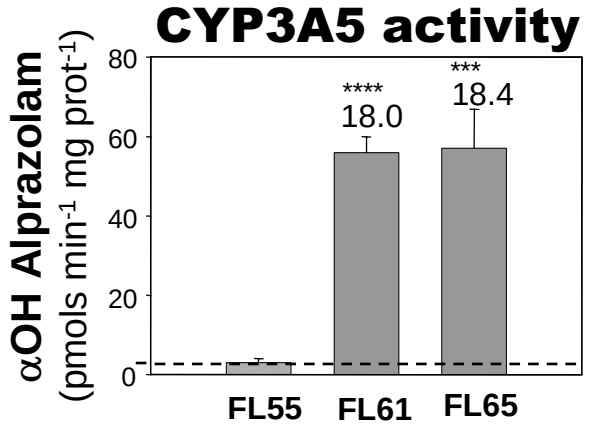


- one in 10 adult livers expressed CYP3A7 at 24-90 pmol/mg (9-36% to total CYP3A levels in these livers).
- 5/7 livers with *CYP3A7*1C* expressed CYP3A7 protein.
- In 57 livers CYP3A7 was present at 4 pmol/mg, *higher* than that of CYP3A5.

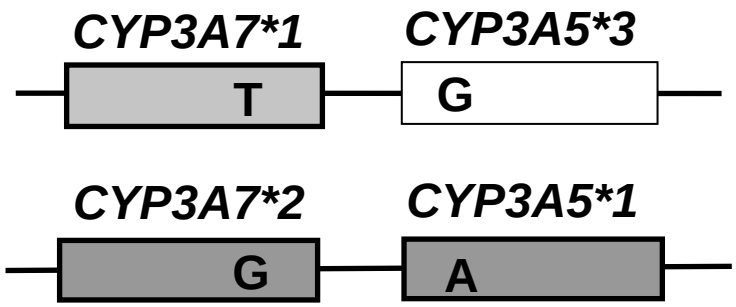
Sim SC et al. *Pharmacogenet Genomics.* 2005 Sep;15(9):625-31.







HAPLOTYPE



Estimated Frequency (%)

Caucasians	Chinese	Africans
90	**72**	**20**
7	**27**	**62**

Genotyping for CYPs

Enzyme	substrates	phenotypes
CYP2B6 –	cyclophosphamide, efavirenz	IM/EM
CYP2C9 –	warfarin, antidiabetics, phenytoin, celecoxib	PM/IM/EM
CYP2C19 –	antiulcer drugs, citalopram	PM/EM/UM
CYP2D6 –	antidepressants, antipsychotics, codeine, tramadol, perhexiline, antiemetic drugs,	PM/IM/EM/UM

Examples of clinical impact of cytochrome P450 pharmacogenetics

		Dose % of ctrl		
Disease	**Enzyme**	**UMs**	**PMs**	**Examples**
Depression	CYP2C9			Bipolar disorders and valproate
	CYP2C19		40	PMs and SSRIs
	CYP2D6	200	30	Non-responders (UMs) and side effects of tricyclics (PMs)
Psychosis	CYP2D6	160	30	Haloperidol and parkinsonian side effects
Ulcer	CYP2C19		20	Dosing of PPIs pH and gastrin changes
Cancer	CYP2B6			Cyclophosphamide metabolism
	CYP2D6	250	60	Non-response of antiemetic drugs (UMs)
CV	CYP2C9		30	warfarin dosing (acenocoumarol) Irbesartan and blood pressure response;
	CYP2D6	160	30	Perhexiline neuropathy and hepatotoxicity,
Pain	CYP2D6			Codeine no response (PMs)
Epilepsia	CYP2C9			Phenytoin pharmacokinetics and side effects

Conclusions, pharmacogenetics in future drug treatment

- In 15-25 % of the cases of drug treatment genotyping w be very important for prediction of drug efficacy and drug toxicity
- For certain drugs genotyping will be relavant in 100 % of the cases
- Predictive genotyping might prevent 10-20 % of serious and fatal adverse drug reactions
- In 15-35 % drug metabolism is influenced by pylogenic factors and difficult to foresee by genotyping
- In 50 % of the cases genetic factors are of limited importance

Drug Reaction Testing

Do not alter the dosage amount or schedule of any drug you are taking without first consulting your doctor or pharmacists.

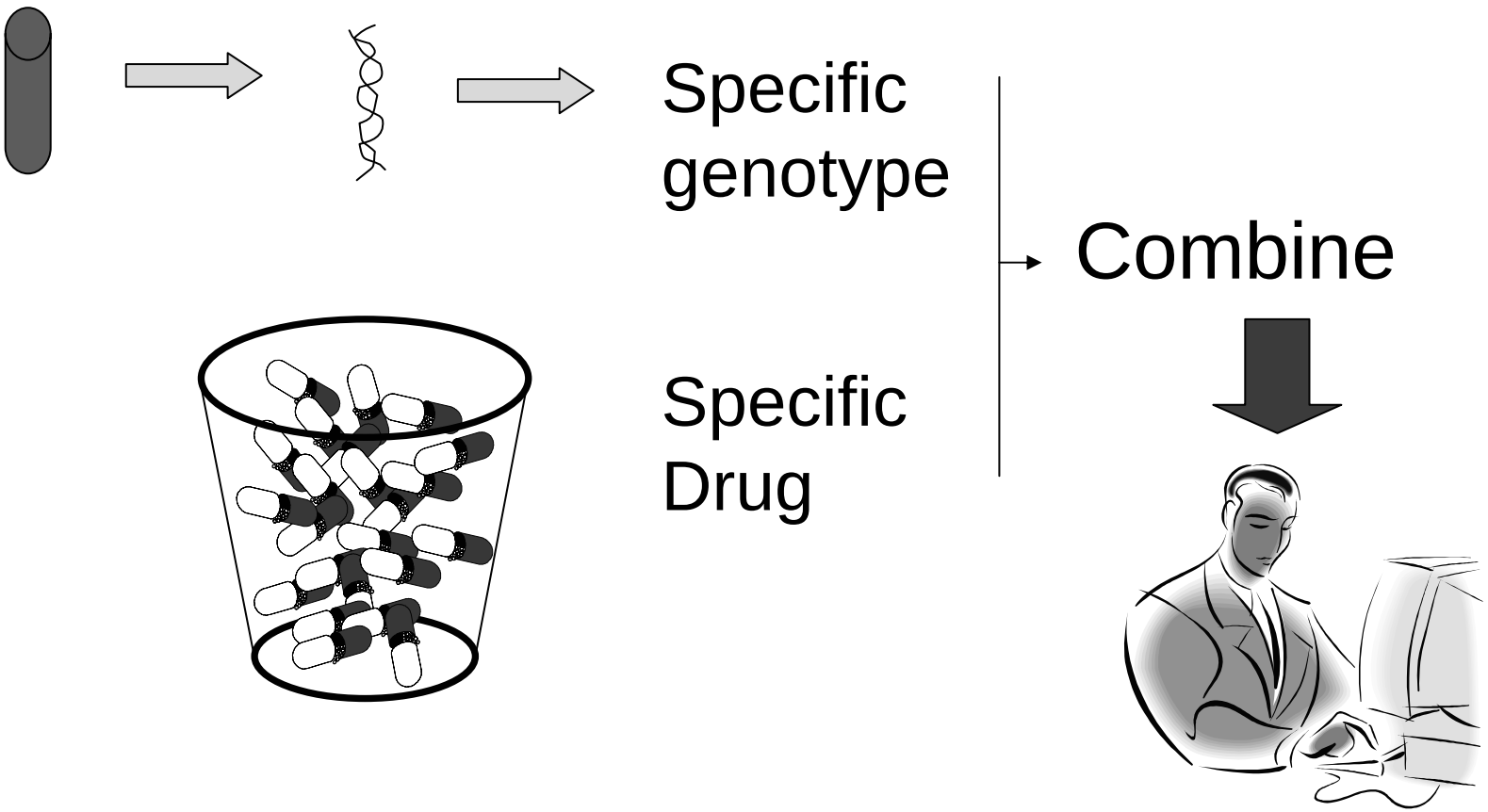
Research shows that of all the clinical factors such as age, sex, weight, general health and liver function that alter a patient's response to drugs, genetic factors are the most important. This information becomes even more crucial when you consider the fact that adverse reactions to prescription drugs are killing about 106,000 Americans each year -- roughly three times as many as are killed by automobiles. This makes prescription drugs the fourth leading killer in the U.S., after heart disease, cancer, and stroke.

We currently offer CYP2D6, CYP2C9, CYP2C19, and CYP1A2 screens that can help your physician or pharmacist predict your particular response to many prescription, OTC (over-the-counter) and herbal medicines including those used to treat depression, anxiety, seizures and psychoses; blood pressure, anticoagulation and other heart medicines; anti-diabetic agents, and many pain relievers. These include such important medications as Coumadin (Warfarin), Prozac, Zoloft, Paxil, Effexor, Hydrocodone, Amitriptyline, Claritin, Cyclobenzaprine, Haldol, Metoprolol, Rythmol, Tagamet, Tamoxifen, Valium, Carisoprodol, Diazepam, Dilantin, Premarin, and Prevacid (and the over-the-counter drugs, Allegra, Dytuss and Tusstat). **Click here to view a more complete list of drugs processed through these pathways.**

Approximately half of all Americans have genetic defects that affect how they process these drugs. There are four different types of metabolizers, and we all fall into one of these categories for the variable pathways in

Future (cont…)

- Large prospective studies with well characterized patients on monotherapy
- Pharmacogenetics is used during drug development
- The urgent need concerns old drugs – industry will not finance such studies
- Pharmacogenetics is not used in the clinics unless required by regulations
- Development of guidelines of critical importance
- Implementation in the clinics after guidelines will occur


Specific genotype
Specific Drug
Combine