Pharmacokinetics

Part V: Pharmacogenetics

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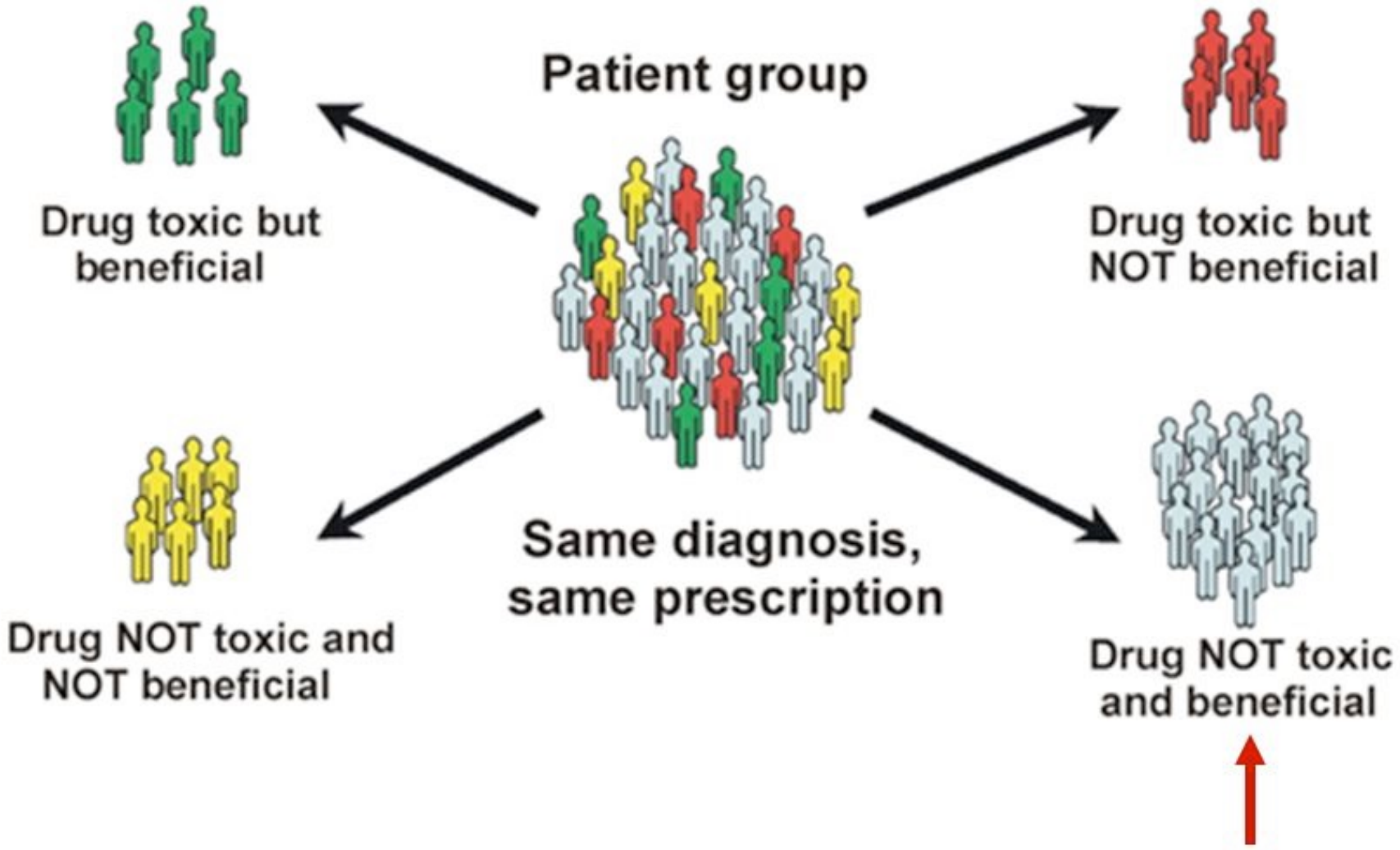
Inter-individual variability in drug response



Pharmacogenetics definition:

Pharmacogenetics is the study of how an individual (patient) will respond to particular medical treatments based on personal genetic profile.

The aim of pharmacogenetics is to tailor drug therapy to the genetic make-up of an individual, in order to avoid adverse drug reactions and gain the maximum therapeutic benefit.

➔ development of personalized therapies

Candidate genes in pharmacogenetics:

Genes responsible for variable drug effects are involved either in

PHARMACOKINETICS

- plasma drug carrier proteins (Distribution, Excretion)
- drug transporters(Absorption, Excretion, Distribution)
- metabolizing enzymes (Metabolism)

or in PHARMACODYNAMICS of the drug

- receptors
- ion channels, transporters
- enzymes
- immune molecules….

Plasma drug carrier protein

(Distribution, Excretion)

Principle: only unbound, or free drug, is pharmacologically active.

Most of the drugs are extensively bound to plasma proteins:

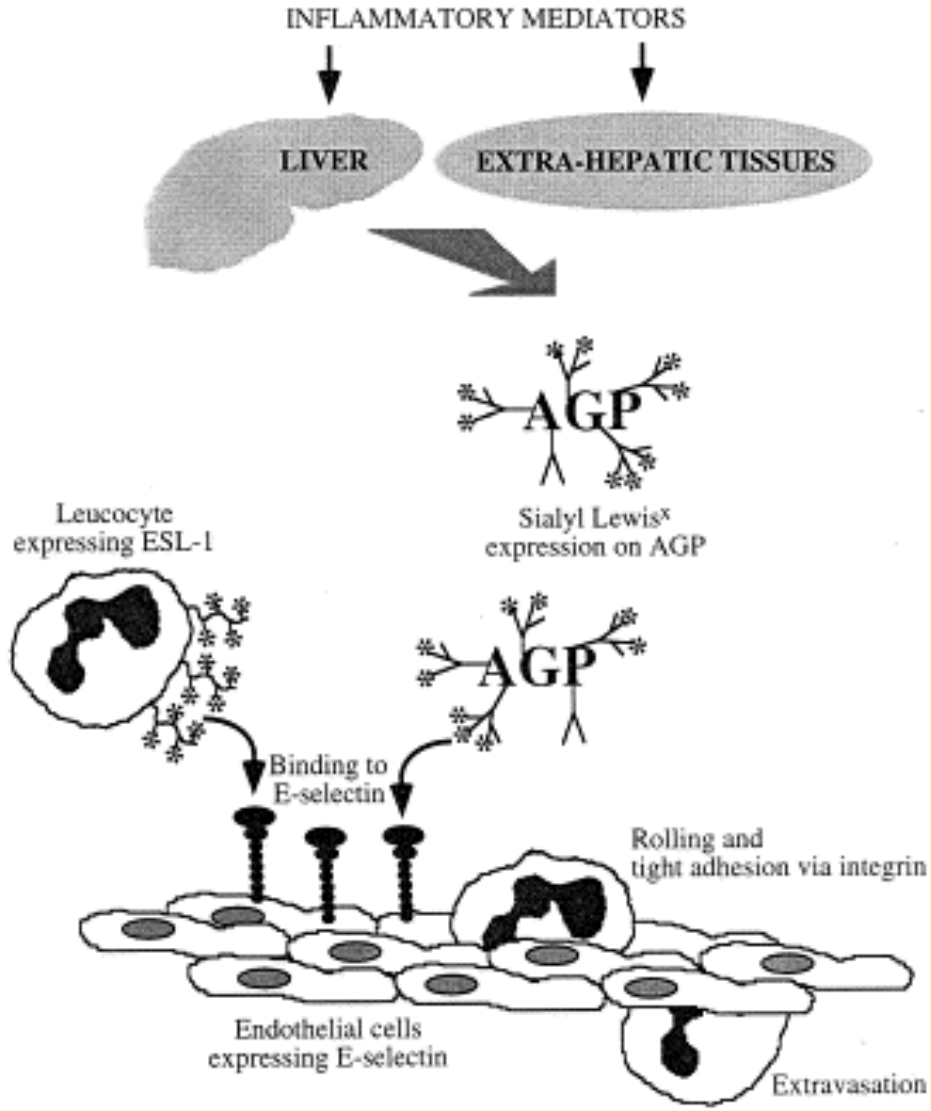
- albumin
- beta globulins
- lipoproteins
- alpha-1-acid glycoprotein (AGP)
- many other...

Binding of different drugs to serum proteins

Drug	Percent Protein Bound		
	Neonate	Infant	Adult
Ampicillin	7% to 10%	10% to 12%	18% to 30%
Caffeine	25%		30% to 40%
Diazepam	84% to 86%	98%	94% to 99%
Digoxin	14% to 26%		23% to 40%
Lidocaine	20%		70%
Indomethacin	95% to 98%		90% to 95%
Morphine	18% to 22%	31%	33% to 37%
Phenobarbital	20% to 25%	28% to 36%	45% to 50%
Phenytoin	70% to 80%	80%	89% to 93%
Theophylline	36% to 50%		50% to 65%
Vancomycin	36%		50% to 56%

Reiter, 2002, NeoReviews

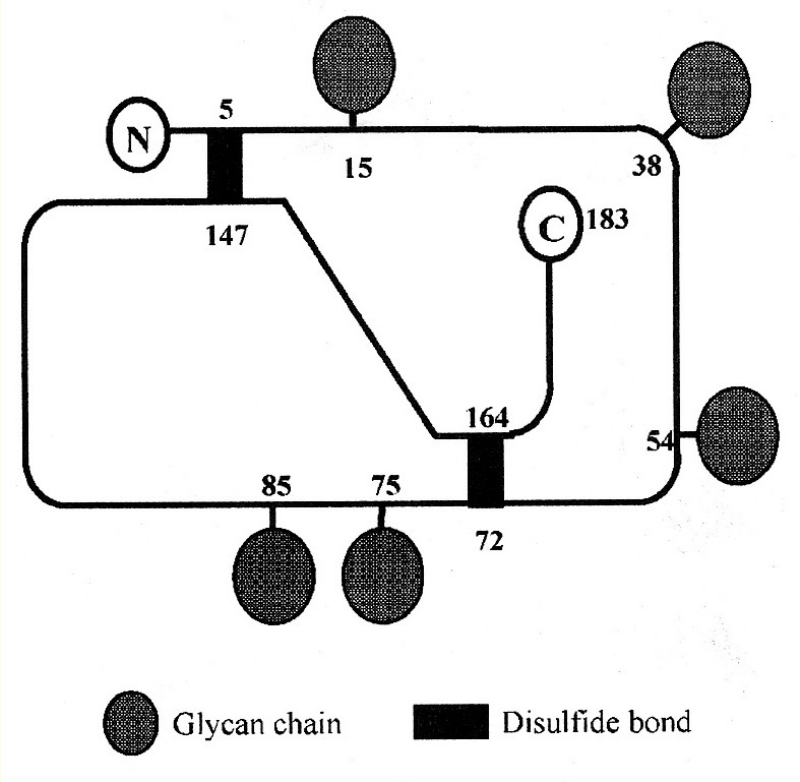
Example: α1- acid glycoprotein (AGP) (major role - immune response)



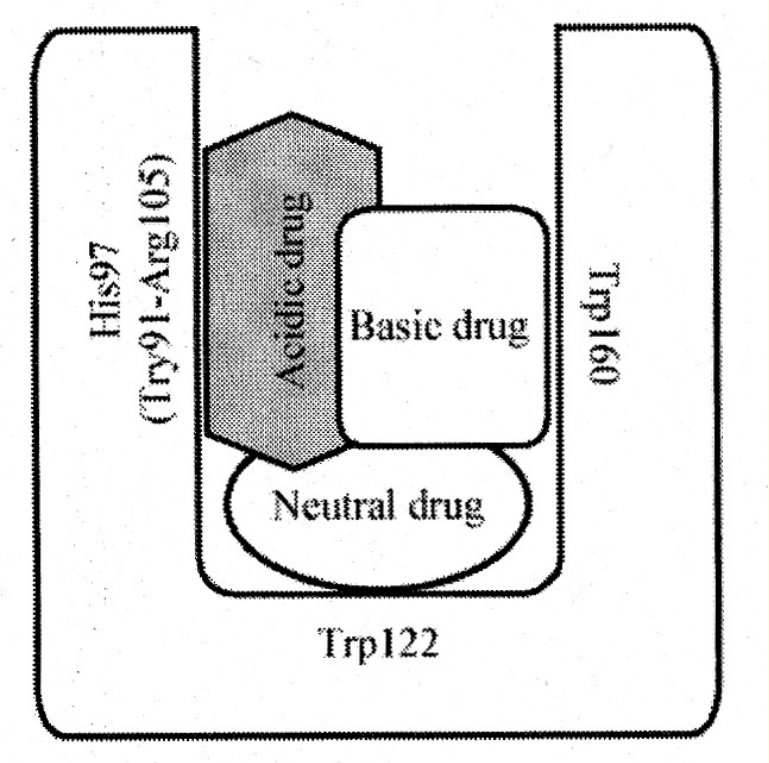
- AGP is a plasma protein synthesized in the liver
- plasma concentration of AGP is ~ 2.5 mg/ml (albumin ~ 40 mg/ml)
- this concentration rises two- to fivefold in response to inflammation, infection, surgery, cancer,....

Fournier et al, 2000, BBA

AGP binds many drugs (warfarin, disopyramide, quinidine, amitriptyline...)



Structure of human AGP



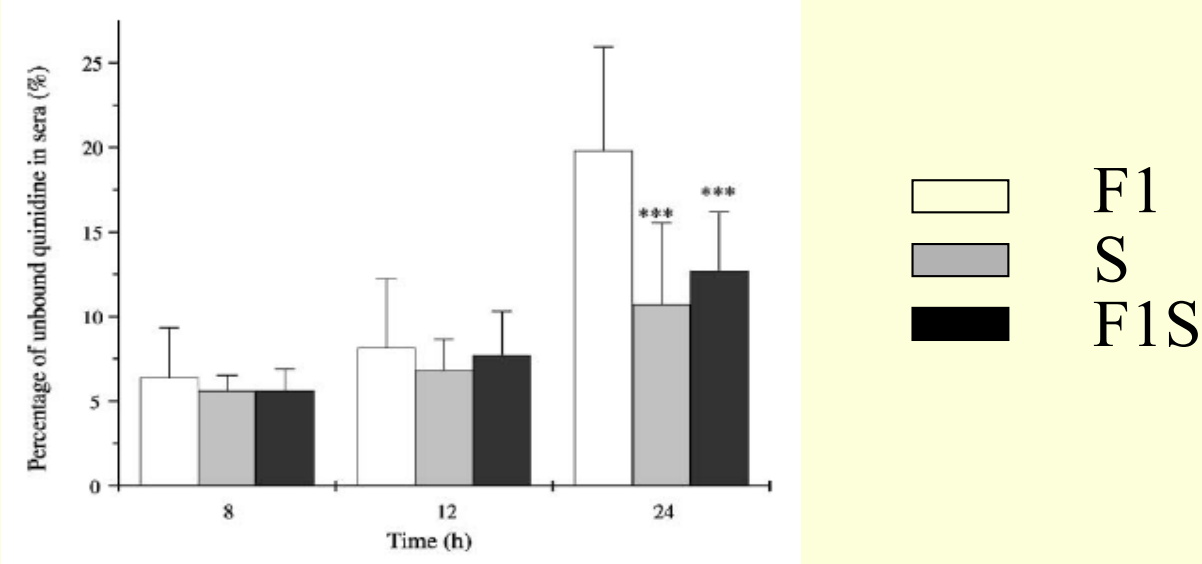
drug-binding regions of AGP

Otagiri, 2005, Drug Metab Pharmacokinet

Polymorphism in AGP gene (F1 and S alleles) results in different drug binding capacity of AGP protein variants

Protein binding percentage (%) of serum quinidine after a single oral dose of 200 mg quinidine sulfate in the healthy male subjects with the three **AGP** phenotypes

AGP phenotypes	*n*	Time after dosing (h)		
		8	12	24
F1	10	93.64±2.98	91.88±4.11	80.21±6.13
S	8	94.38±0.89	93.18±1.82	89.31±4.83***
F1S	10	94.38±1.27	92.26±2.57	87.26±3.42***



Li et al, 2002, Clin Chim Acta

Candidate genes for variable drug response

PHARMACOKINETICS:

- plasma drug carrier proteins (Distribution, Excretion)
- drug transporters (Absorption, Excretion, Distribution)
- metabolizing enzymes (Metabolism)

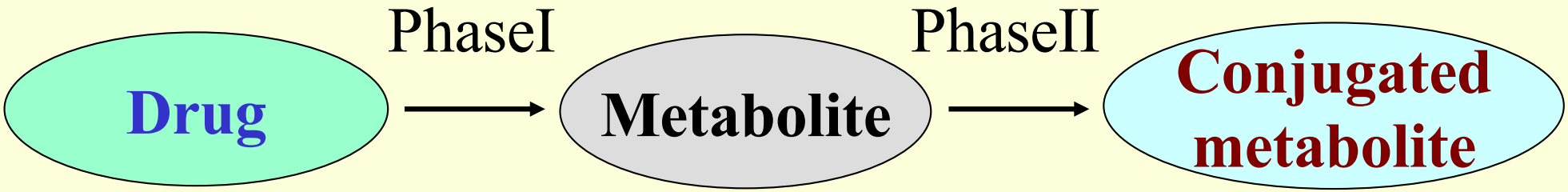
PHARMACODYNAMICS

- receptors
- ion channels, transporters
- enzymes
- immune molecules….

Drugs metabolism:

- Drug = Xenobiotic
- Biotransformation (metabolism) of xenobiotics =

  = protection of organism
- Two phases of drug metabolism:



R-H ⟶ **R-OH**, **R-COOH**, **$R-NH_2$** ⟶ **R-conjugated**

Genetic polymorphism in metabolizing enzymes (Phase I and Phase II) generates four main phenotypes:

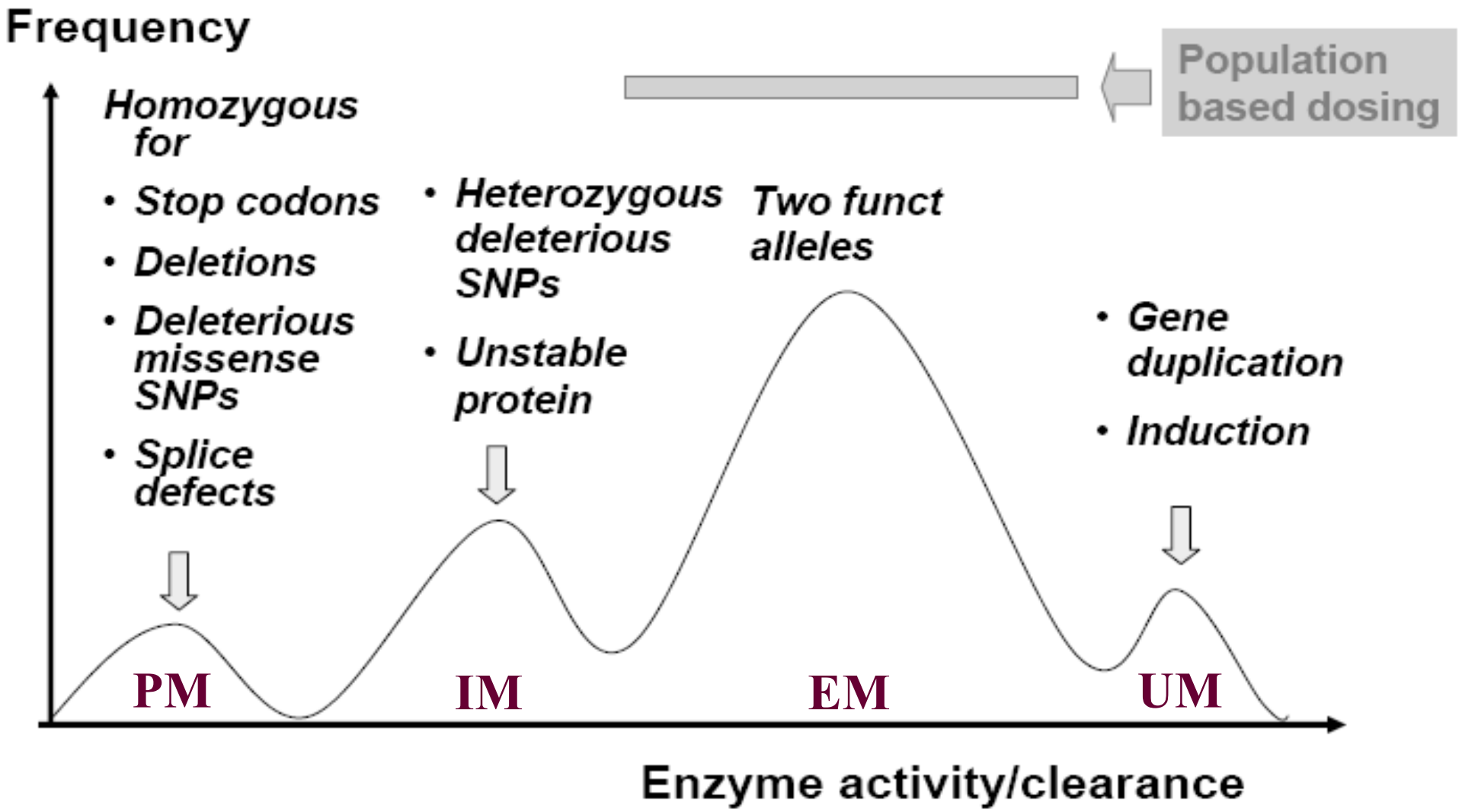
PM – poor metabolizers

IM – intermediate metabolizers

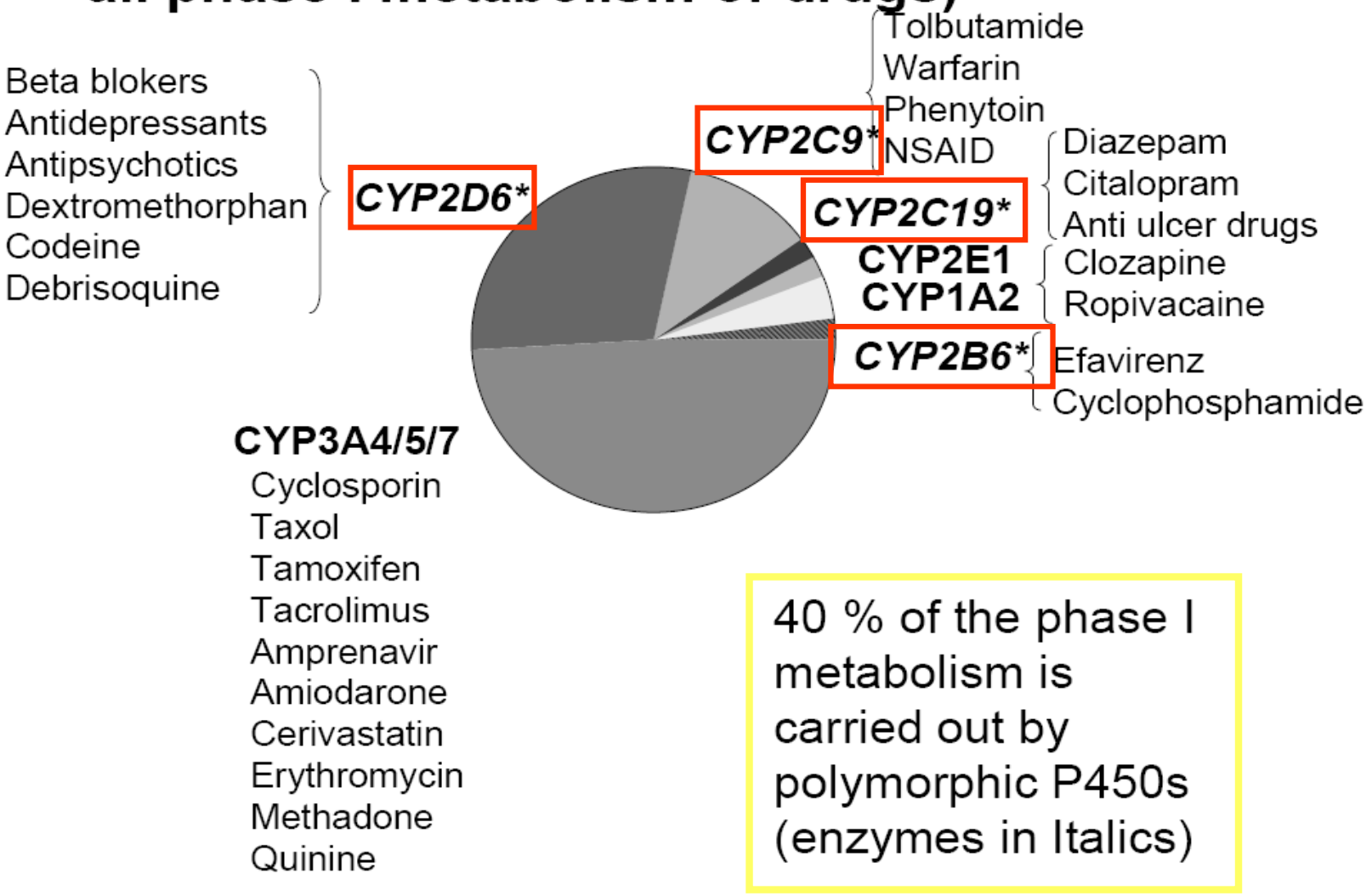
EM – efficient metabolizers

UM – ultrarapid metabolizers

Possible genetic causes of PM, IM, EM or UM phenotypes



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



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

Polymorphic = frequency of at least **one percent**

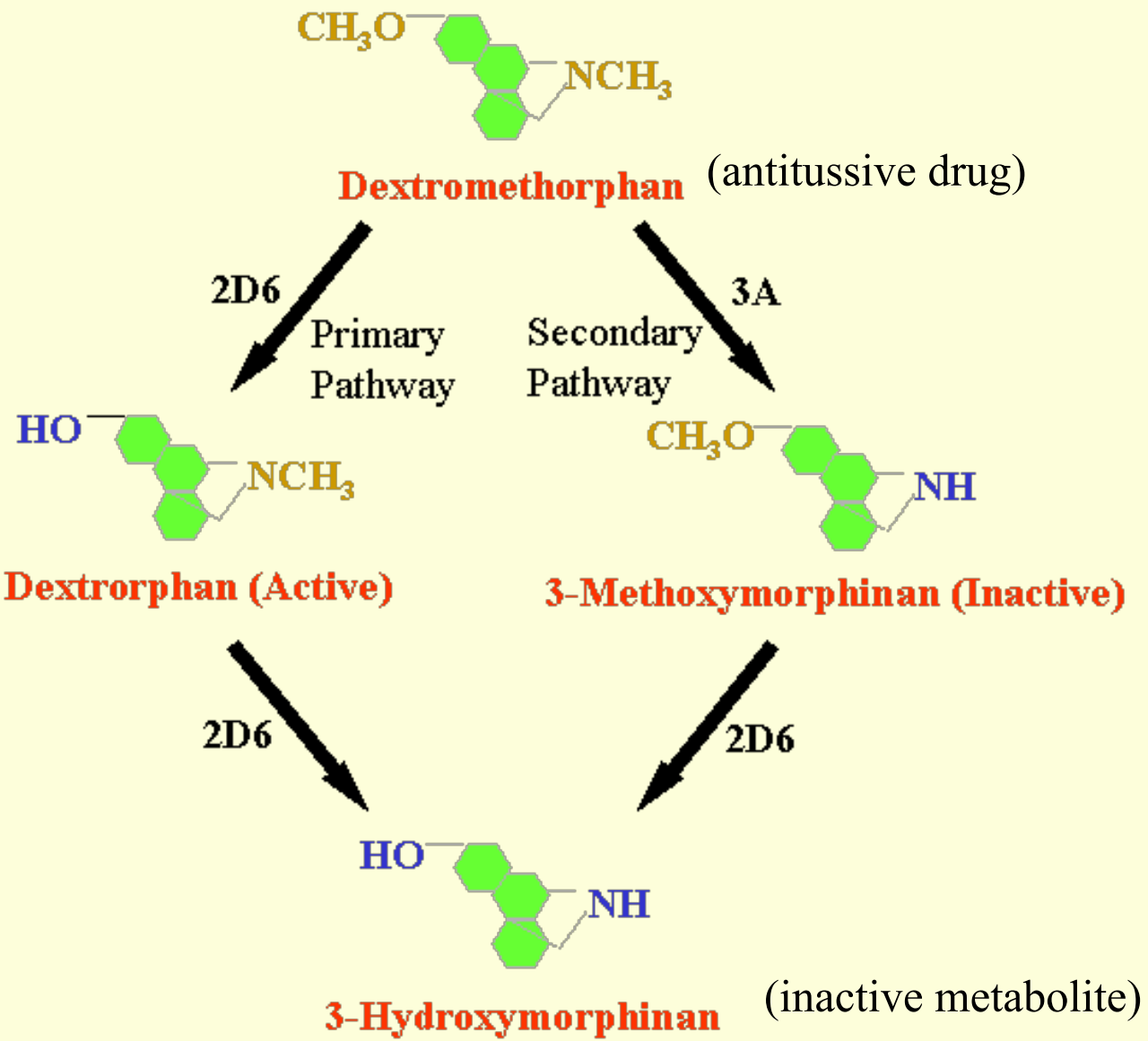
***CYP2D6* and pharmacogenetics:**

- 20-25% of clinically used drugs are metabolized by this enzyme

- more than 50 drugs are identified as substrates of CYP2D6

- CYP2D6 substrates are lipophilic bases with a protonable nitrogen atom

An example of CYP2D6 reaction



CYP2D6 polymorphisms

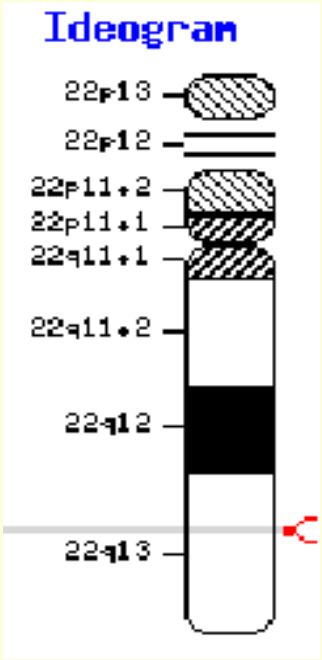
- more than 75 alleles (46 alleles are responsible for 99% of polymorphisms)
- 24 alleles have no activity
- 6 have decreased activity
- the *2 variant can have 1, 2, 3, 4, 5 or 13 copies (i.e. increased activity)
- CYP2D6 is involved in ~ 40% of all ADR

Origins of CYP2D6 polymorphism:

1. Genomic aspects
2. Evolutionary aspects

Genetic aspects:

- CYP2D6 gene is located on chromosome 22q13.1
- the 22q13.1 locus also contains two CYP2D pseudogenes, CYP2D7 and CYP2D8
- this results in a high frequency of crossover reactions



Chromosome 22

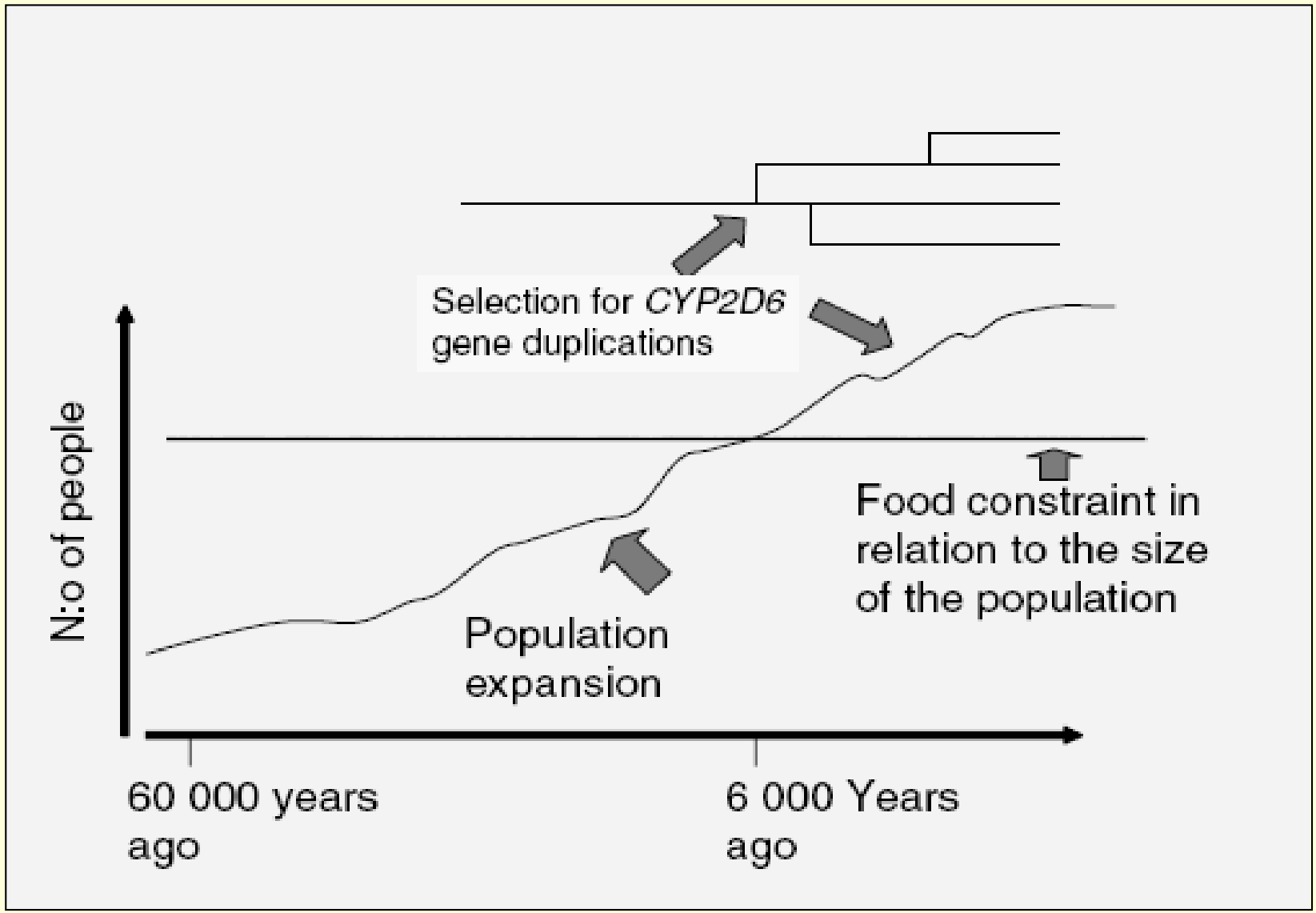
Evolutionary aspects:

- CYP2D6 is largely involved in metabolism of various xenobiotics, including plant toxins

- thus multiple CYP2D6 copies is a beneficial factor during starvation periods (increase the number of plants being able to provide useful food)

- example: high percentage of individuals with multiple CYP2D6 copies in North East Africa population

Duplication of CYP2D6 gene copies is Ethiopia is believed to have happened about 5’000-10’000 years ago

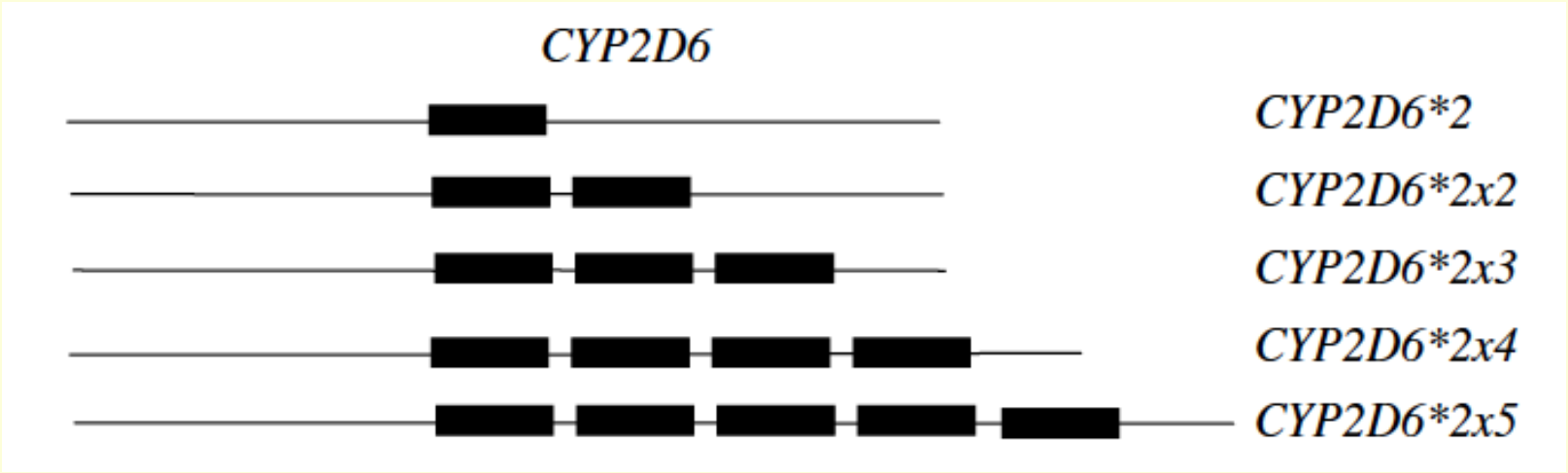


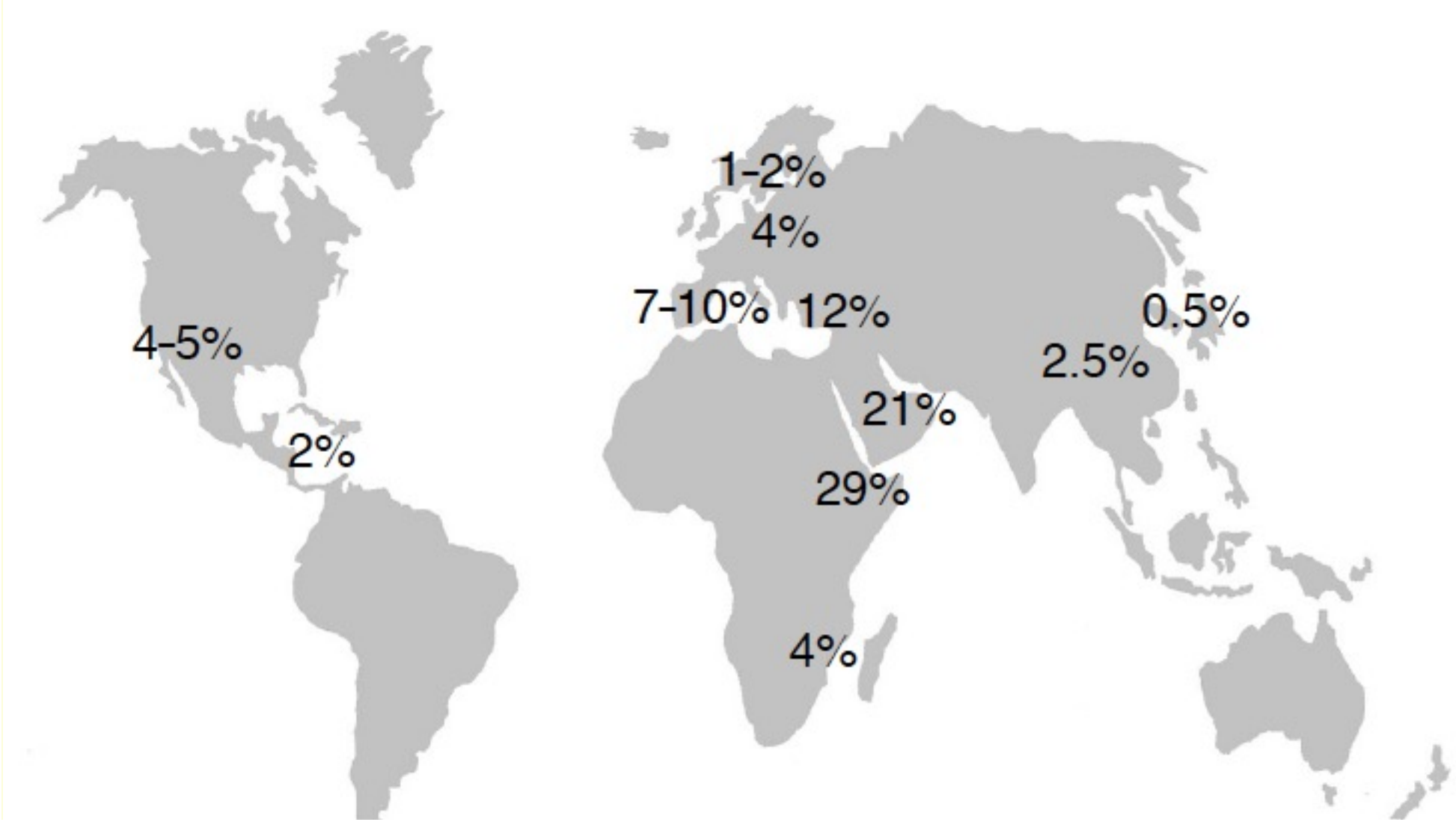
Ingelman-Sundberg, 2005

Major human polymorphic variant *CYP2D6* alleles and their global distribution

Table 3 Major human polymorphic variant *CYP2D6* alleles and their global distribution. For a complete list, see http://www.imm.ki.se/cypalleles/cyp2d6.htm

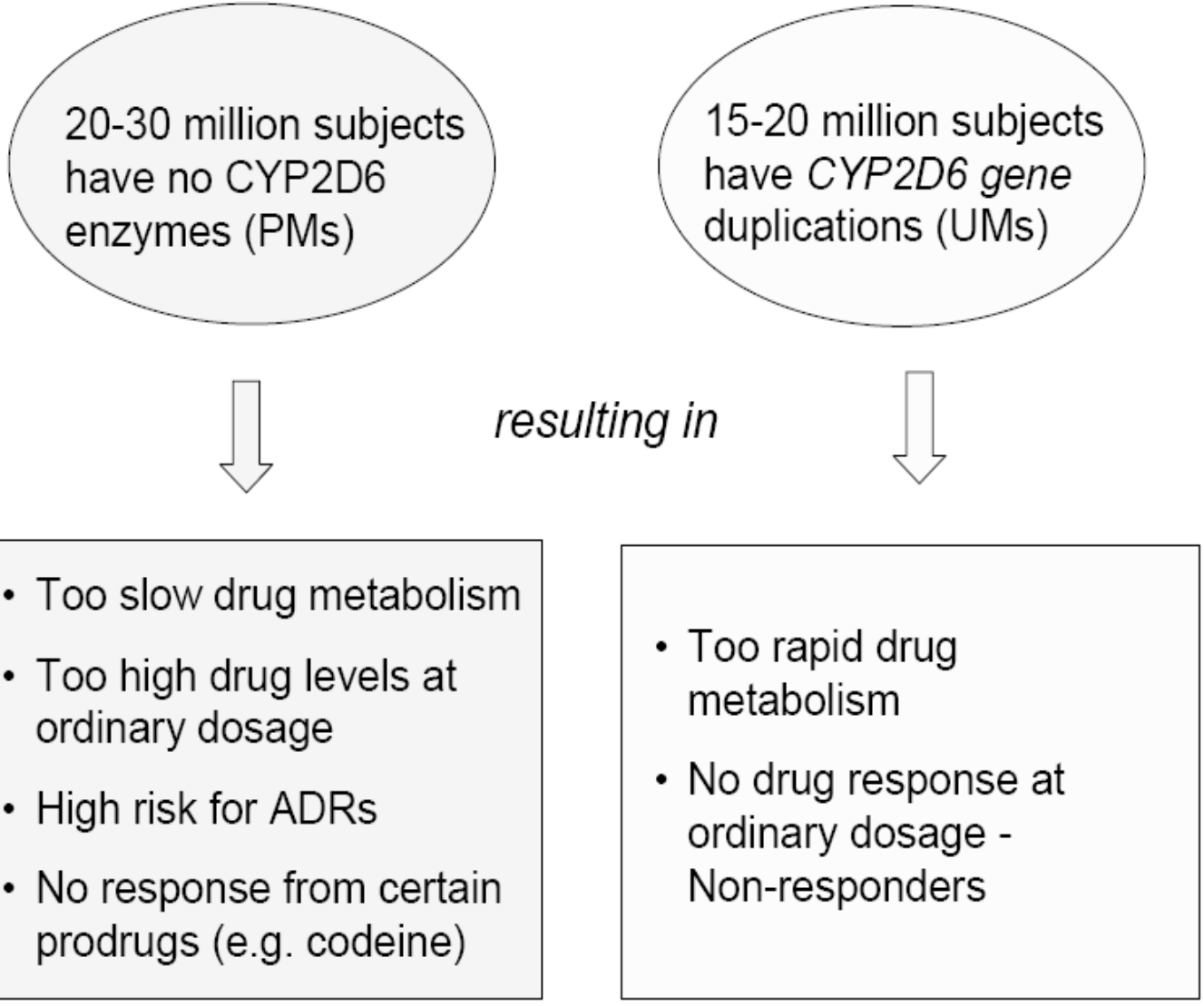
Major variant alleles	*Mutation*	*Consequence*	*Allele frequencies (%)*			
			Caucasians	*Asians*	*Black Africans*	*Ethiopians and Saudi Arabians*
*CYP2D6*2xn*	Gene duplication/ multiduplication	Increased enzyme activity	1–5	0–2	2	10–16
*CYP2D6*4*	Defective splicing	Inactive enzyme	12–21	1	2	1–4
*CYP2D6*5*	Gene deletion	No enzyme	2–7	6	4	1–3
*CYP2D6*10*	P34S, S486T	Unstable enzyme	1–2	51	6	3–9
*CYP2D6*17*	T107I, R296C, S486T	Altered affinity for substrates	0	0	20–35	3–9



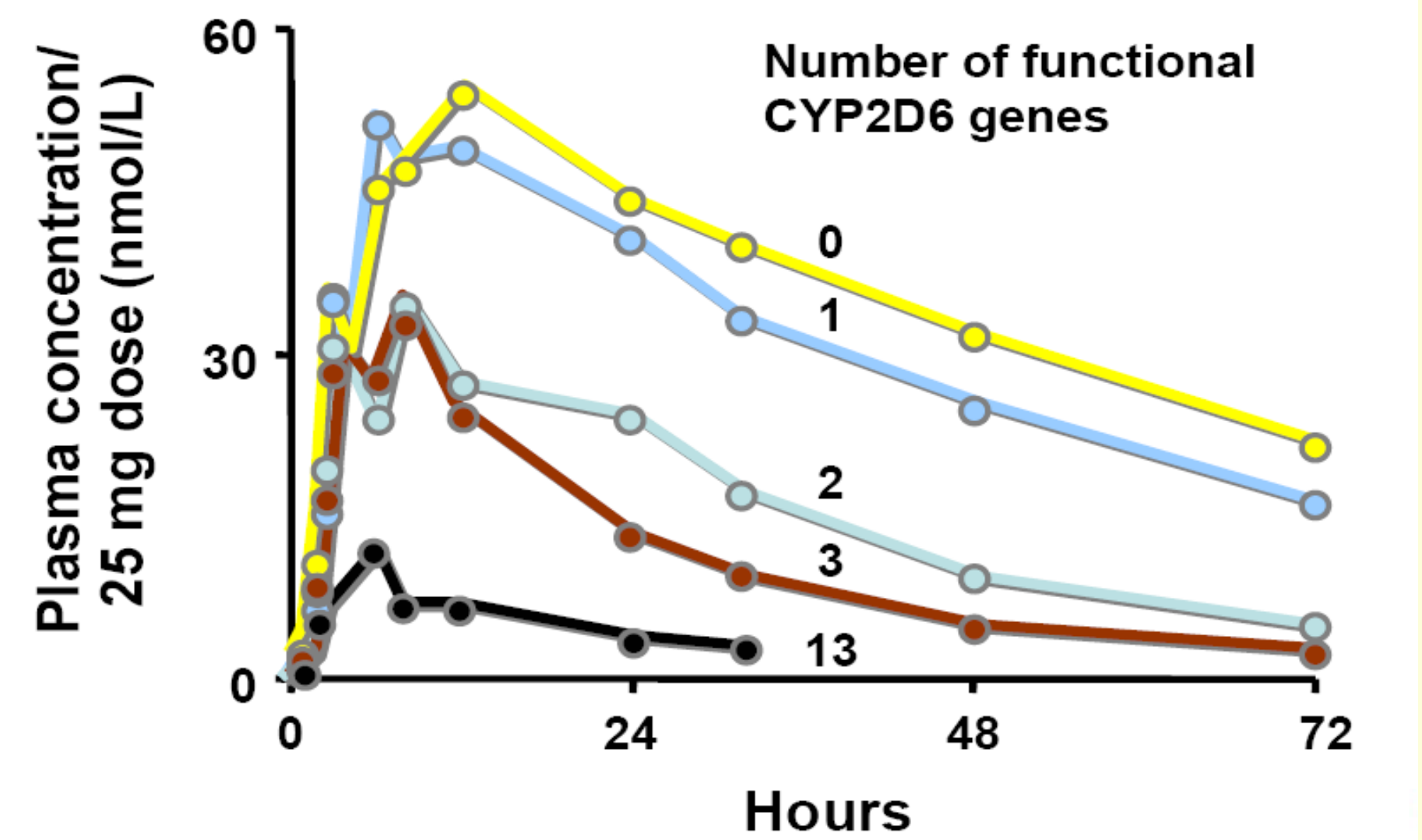


Frequency of individuals carrying alleles with multiple *CYP2D6* gene copies in different parts of the world (another study). A particularly high frequency can be observed in the Ethiopian and Saudi Arabian populations. The Muslim migration around 700 AD probably explains the high prevalence in the Mediterranean area.

CYP2D6 and the European population

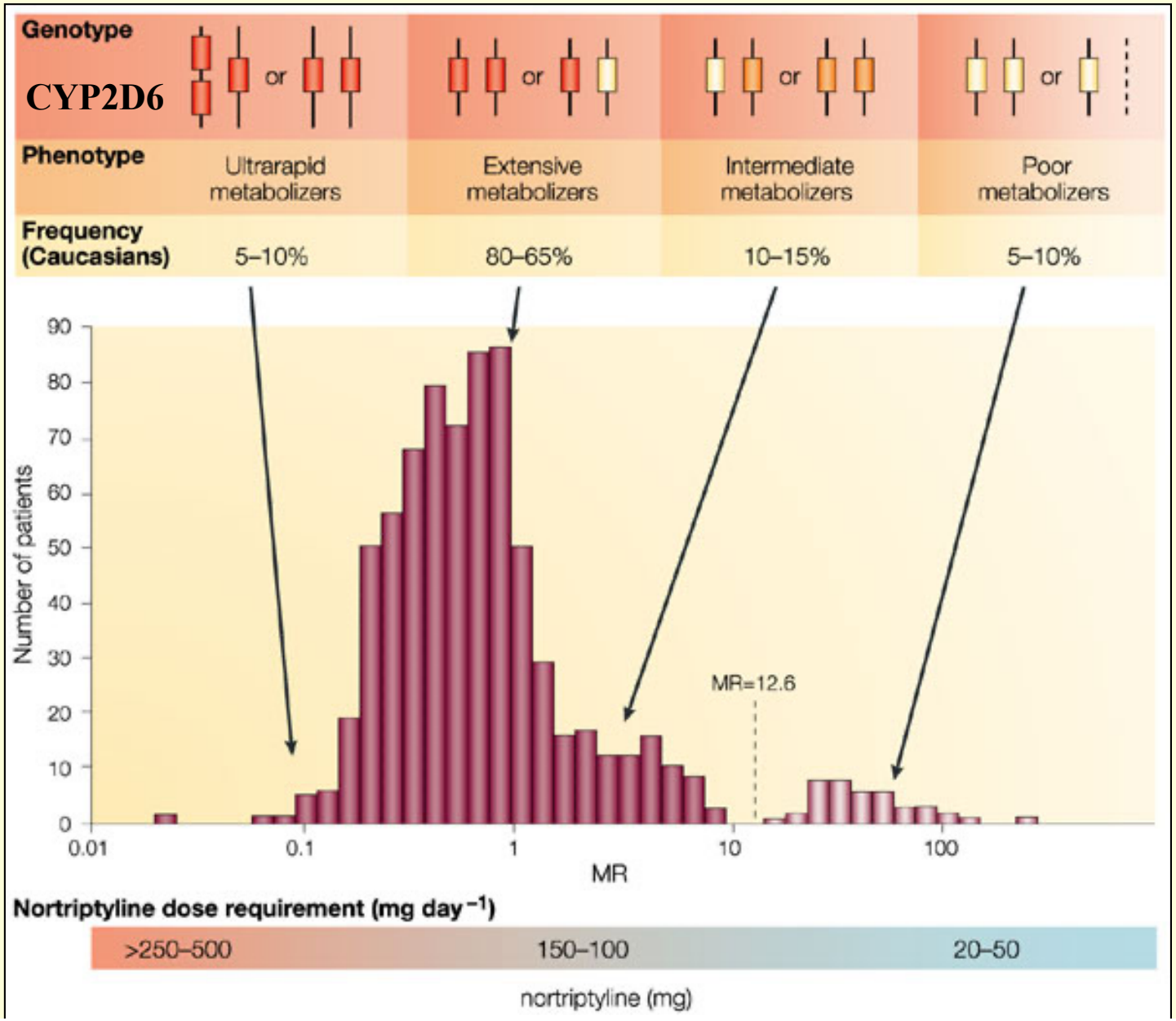


Example: metabolism of Nortriptyline (antidepressant)



Dalen et al, 1998

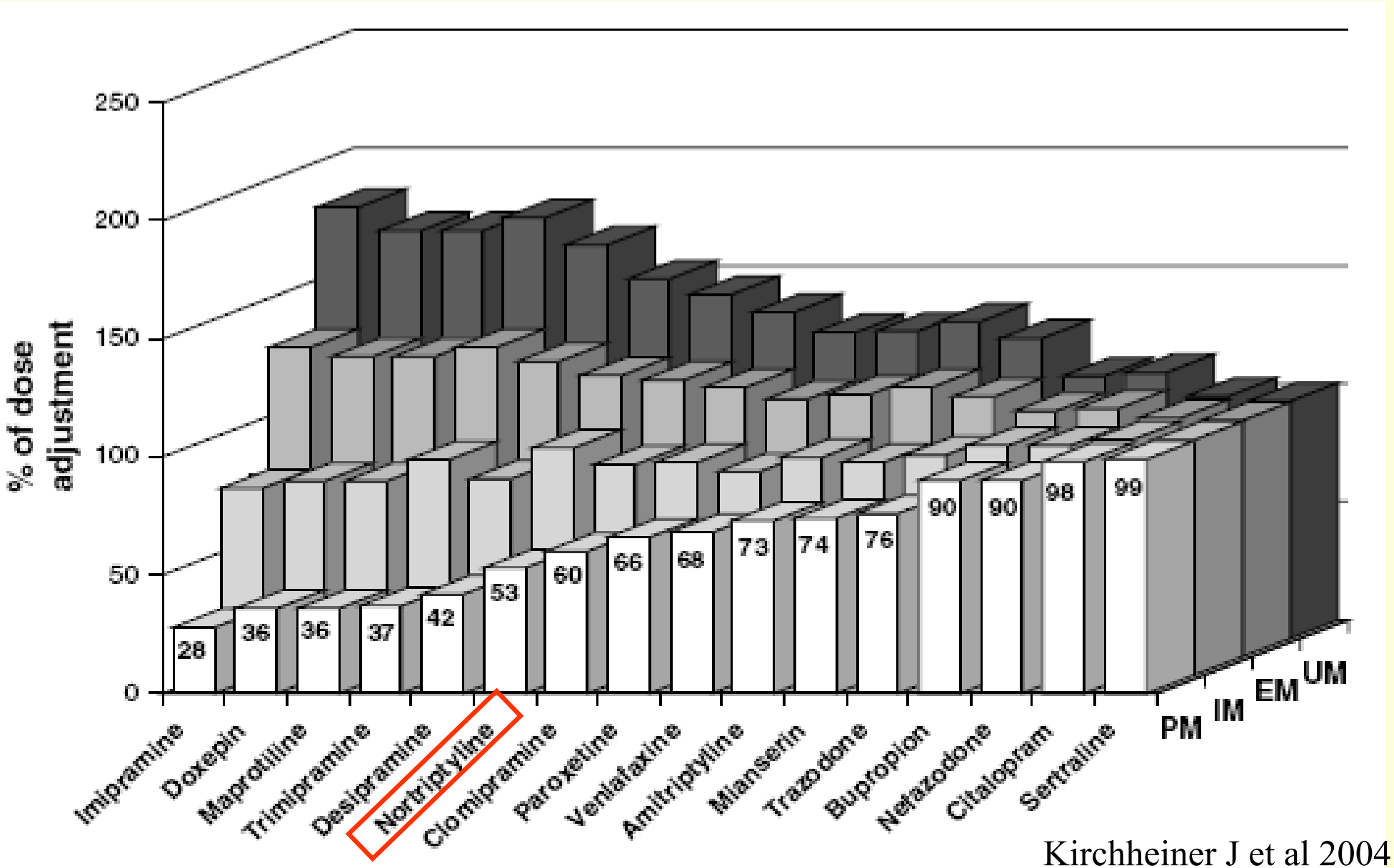
Nortriptyline metabolism in caucasians



Meyer, 2004

MR – metabolic ratio = [drug]/[metabolite]

CYP2D6-based dose adjustments for antidepressants



Kirchheiner J et al 2004

Example: codeine intoxication associated with ultrarapid CYP2D6 metabolism

The NEW ENGLAND JOURNAL of MEDICINE

- a case report

Gasche et al, N Engl J Med. 2004

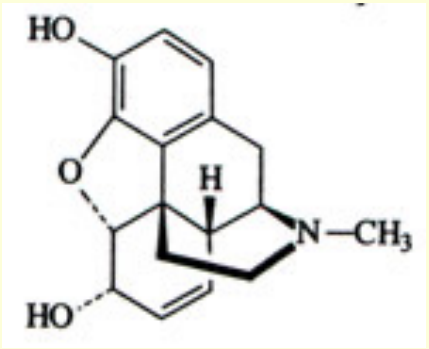
- 62 year old man hospitalized for pneumonia
- treated with standard doses of codeine as a cough suppressant, clarithromycin (antibiotic) and voriconazole (antifungal)
- coma – morphine levels 20 times expected levels
- rapidly recovered with naloxone, μ-opioid receptor antagonist
- diagonstics: UM genotype for CYP2D6

Codeine metabolism

codeine

CYP2D6

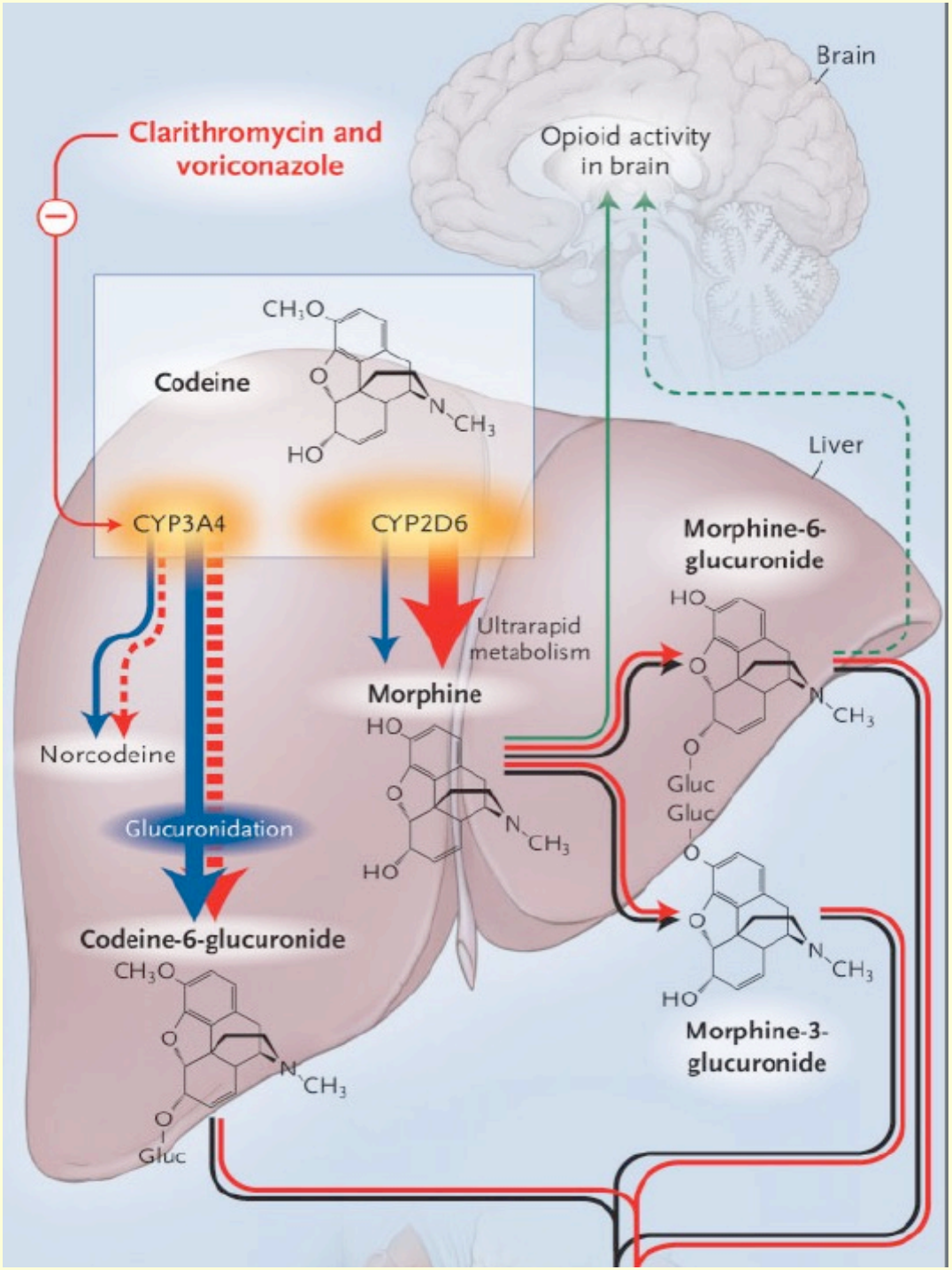
morphine



CYP3A4

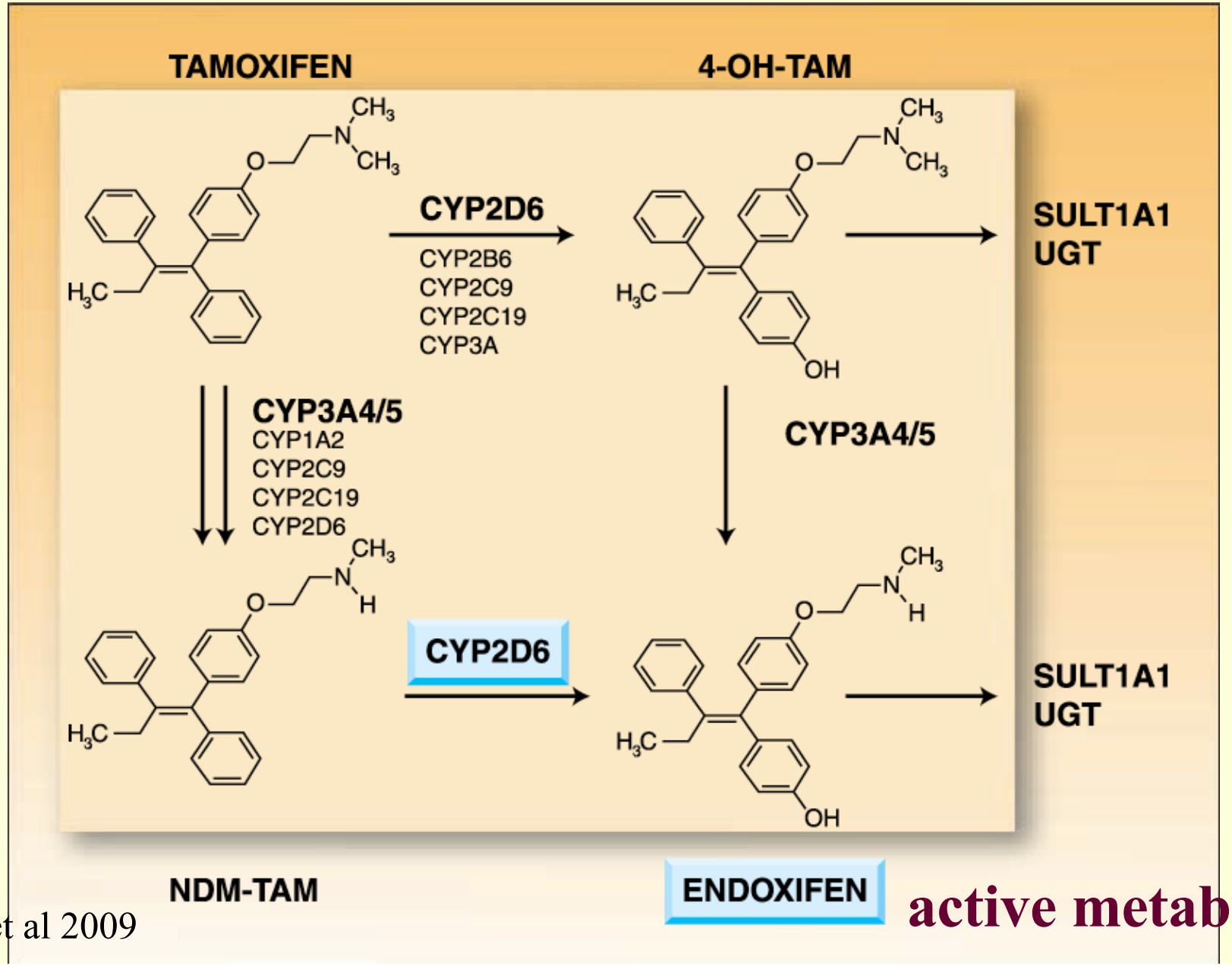
norcodeine

conjugation
and/or
elimination



Inhibition of CYP3A4 and UM phenotype for CYP2D6 are responsible for the abnormal accumulation of morphine

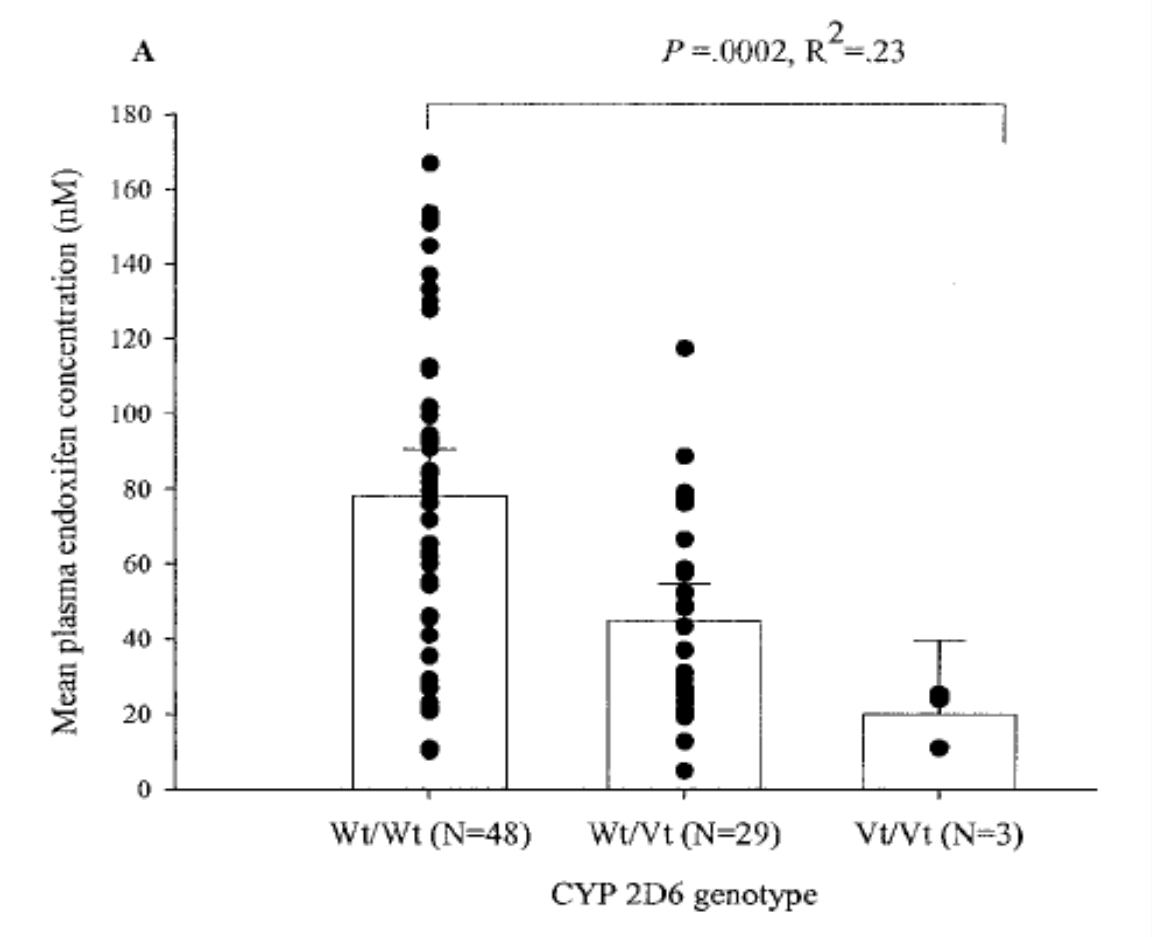
Example 2: tamoxifen therapy for breast cancer



active metabolite

Dezentje et al 2009

- about 35% women do not respond to tamoxifen treatment
- this correlates with the low levels of endoxifen in patients with inactive CYP2D6 alleles (*3, *4, *5 and *6)



CYP2C19 and pharmacogenetics:

CYP2C19 substrates:

proton pump inhibitors: omeprazole, lansoprazole, rabeprazole, pantoprazole (role in control of gastric pH)

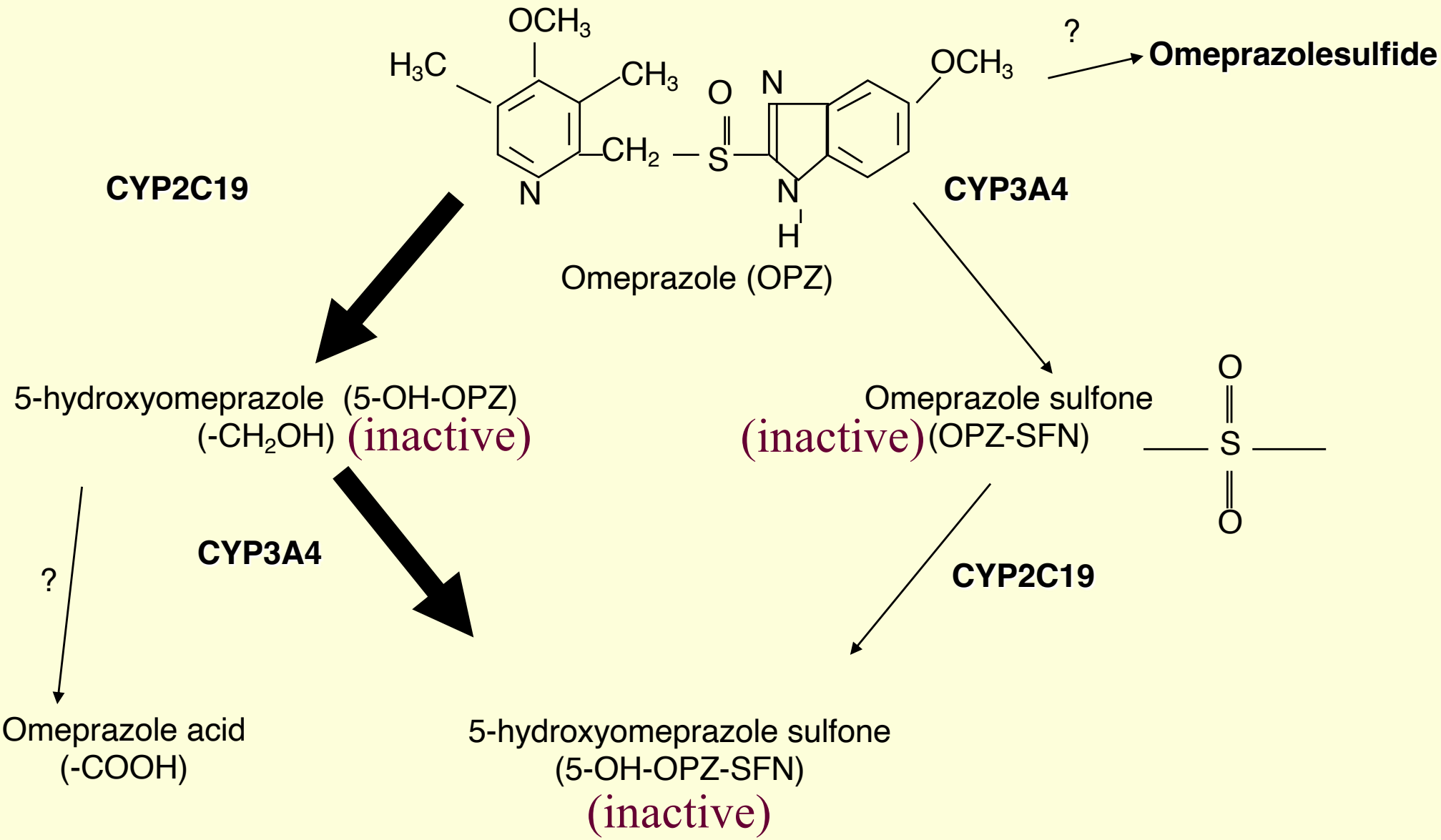
antidepressants: fluoxetine, sertraline

antiretroviral (HIV): nelfinavir

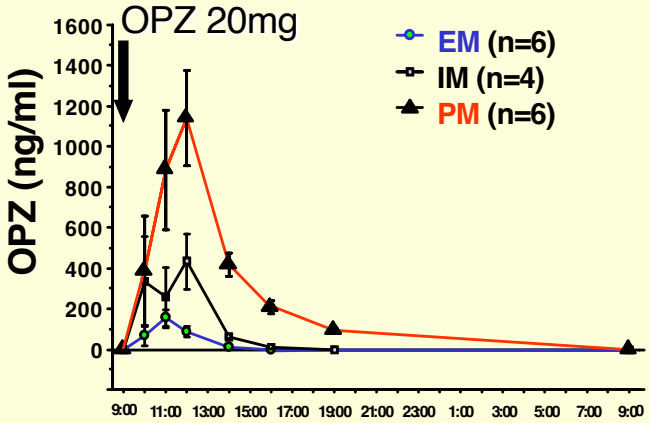
All known CYP2C19 polymorphisms lead to enzyme inactivation

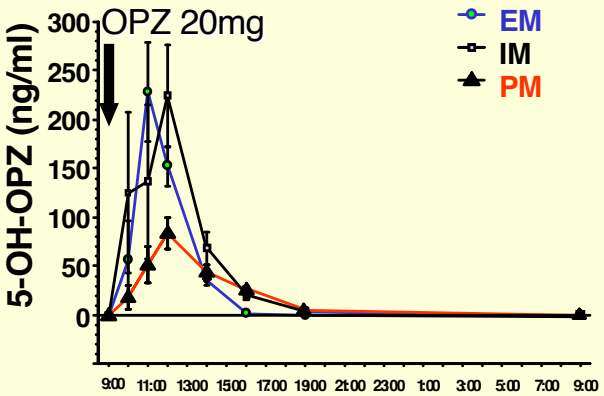
CYP2C19 allele	Critical nucleotide change	Reason allele affects CYP2C19	Frequency of each allele in various racial groups (n = total alleles tested)		
			Caucasians	Blacks	Chinese
*1	none	wild type	0.844 (n = 2,712)	0.823 (n = 1,932)	0.65 (n = 1,368)
*2	681G→A	splicing defect in exon #5	0.147 (n = 2,712)	0.173 (n = 1,932)	0.30 (n = 1,368)
*3	636G→A	premature stop codon	0.0004 (n = 2,712)	0.004 (n = 1,932)	0.05 (n = 1,368)
*4	1A→G	mutation of initiation codon	0.006 (n = 344)	–	0.002 (n = 606)
*5	1297C→T	Arg(433)→Trp structure and stability	0.000 (n = 344)	–	0.001 (n = 844)
*6	395G→A	Arg(132)→Gln structure and stability	0.000 (n = 344)	–	–
*7	T→A inversion at 5′ splice site of intron 5	intron #5 splicing defect	0.000 (n = 344)	–	–
*8	358T→C	Trp(120)→Arg structure and stability	0.000 (n = 344)	–	–
Others	unknown	unknown	<0.003	–	–

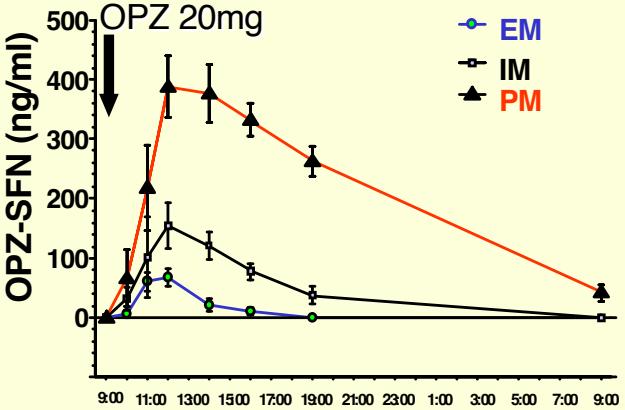
Example: metabolism of omeprazole (H^+/K^+-ATPase inhibitor)

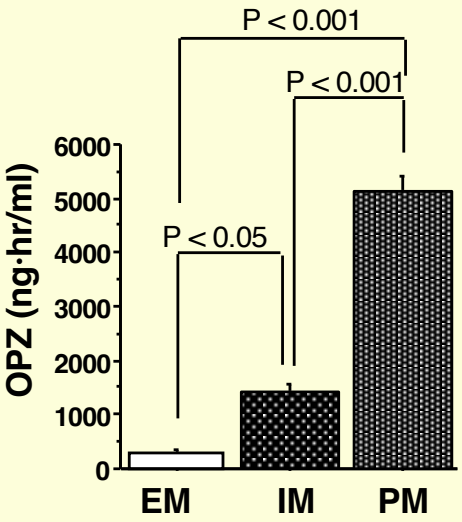


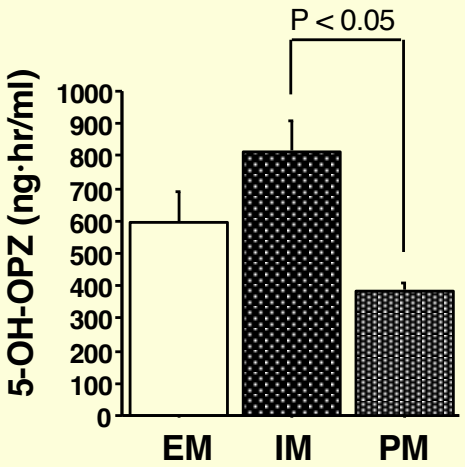
Omeprazole metabolism in EM, IM and PM patients

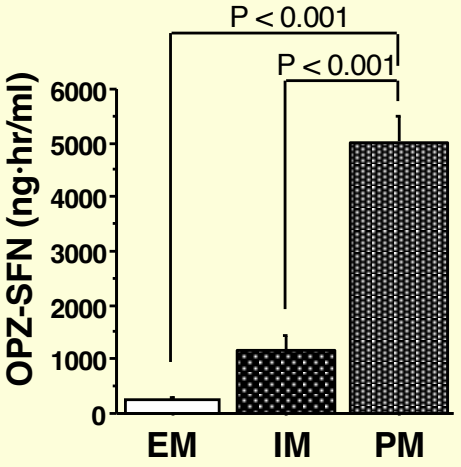




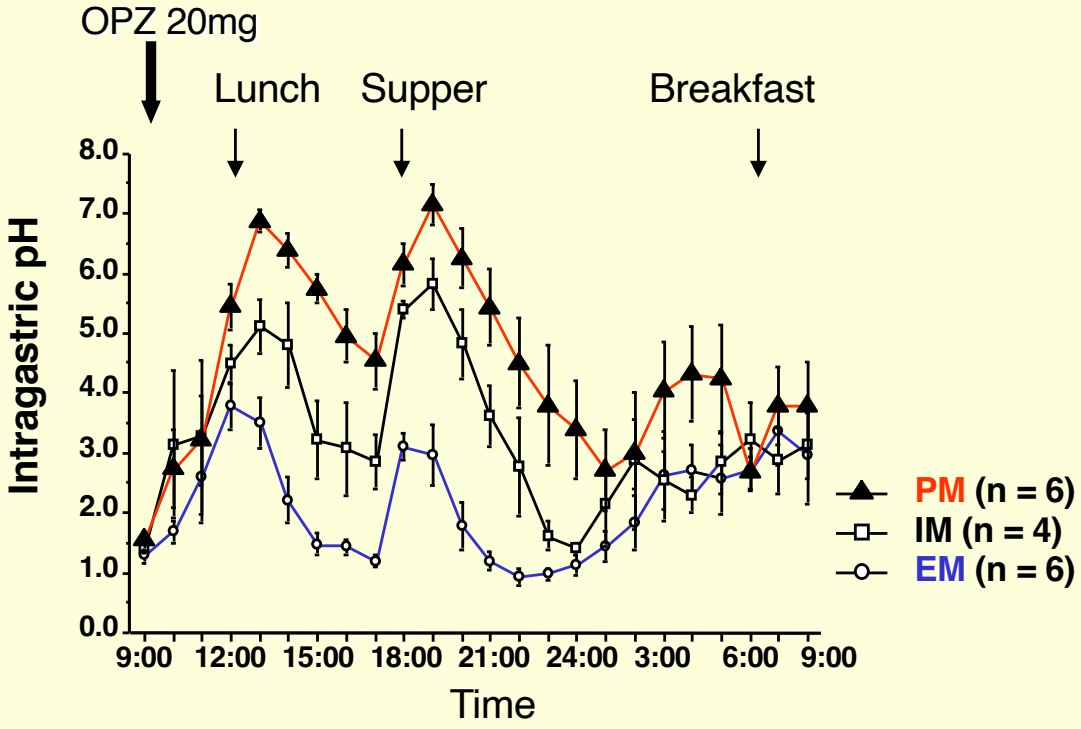


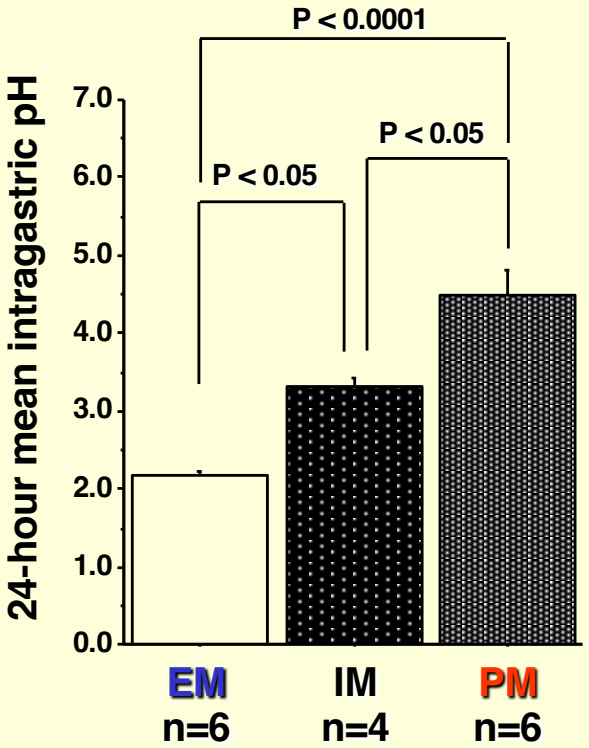




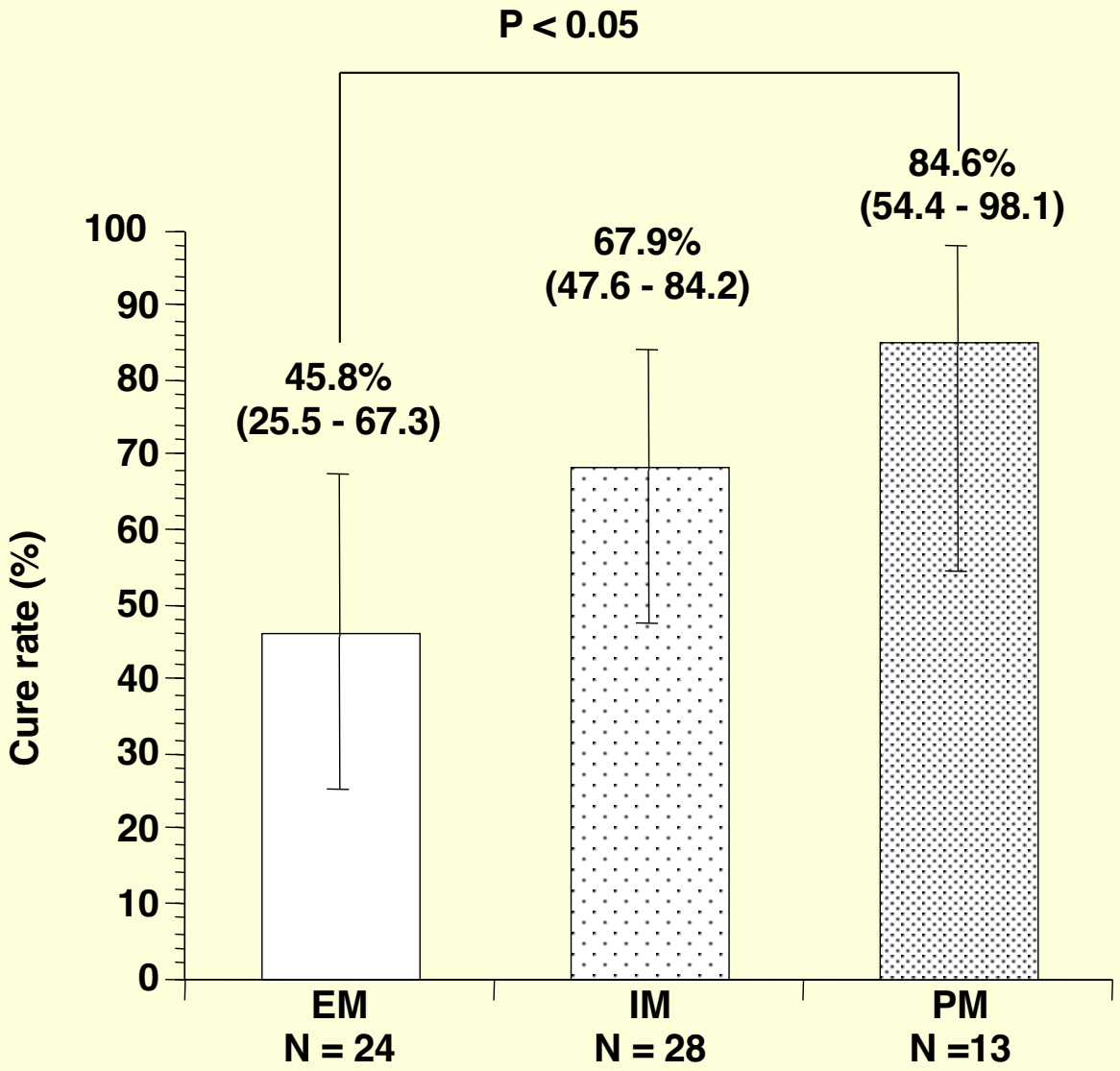


Profiles of intragastric pH values as a function of CYP2C19 genotype status

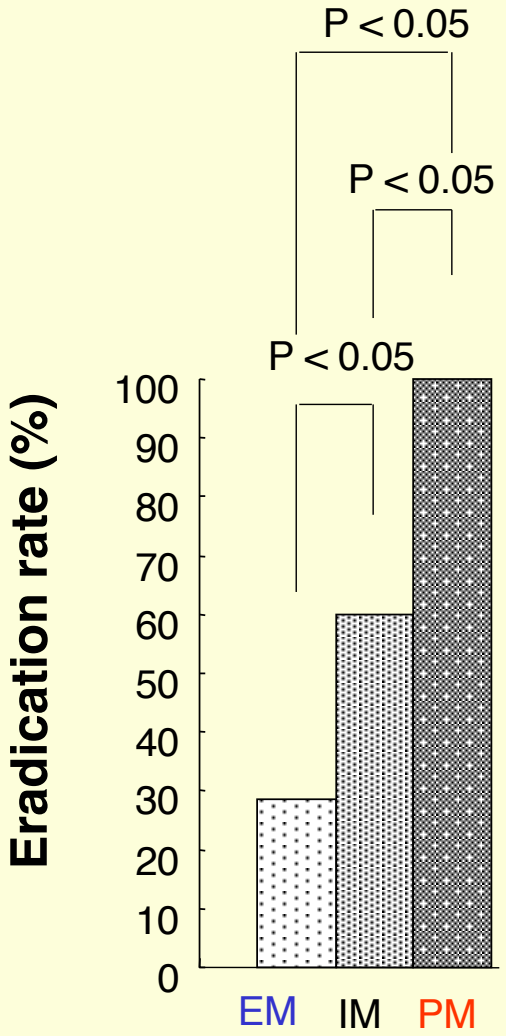




Cure rate with a daily dose of 30 mg of lansoprazole (omeprazole) for 8 weeks



Influence of CYP2C19 polymorphisms on omeprazole-based eradication of *Helicobacter pylori*



- omeprazole makes antibiotics more stable by raising intragastric pH
- neutralization on intragastric pH allows *H.pylori* to reach at the growth phase and thus becomes more sensitive to antibiotics

Inter-ethnic differences in the frequency of CYP2C19 poor metabolizers (PMs)

White Americans	~ 2.5 %
African Americans	~ 2.0 %
White Europeans	~ 3.5 %
Zimambweans	~ 4.8 %
Chinese	~ 20.0 %
Korean	~ 12.6 %
Japanese	~ 20.0 %

CYP2C9 and pharmacogenetics:

CYP2C9 substrates:

tolbutamide
phenytoin
S-warfarin
glipizide
tamoxifen
diclofenac
ibuprofen
piroxicam
suprofen
S-naproxen
sulfamethoxazole
torsemide
losartan
busipirone

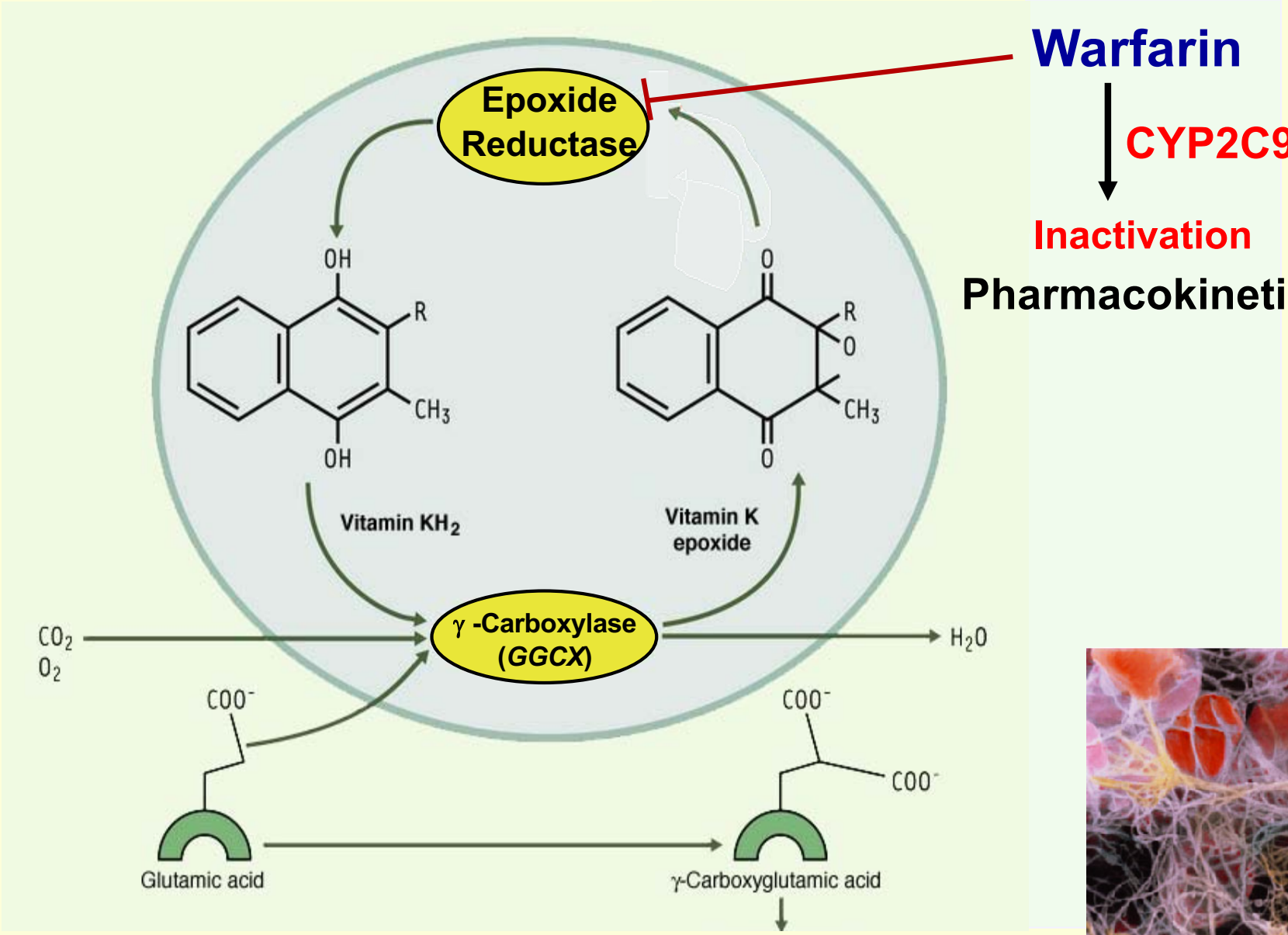
Warfarin Background

- Commonly prescribed oral anti-coagulant and acts as an inhibitor of the vitamin K cycle
- In 2018, 31 million prescriptions were issued for warfarin (Coumadin™)
- Prescribed following MI, atrial fibrillation, stroke, venous thrombosis, prosthetic heart valve replacement, and following major surgery
- Difficult to determine effective dosage
  - Narrow therapeutic range, risk of bleeding
  - Large inter-individual variation

Vitamin K Cycle

- Vitamin K synthesized by plants and bacteria e.g. leafy green vegetables and intestinal flora
- Vitamin K - discovered from defects in blood "koagulation"
- Vitamin K - required coenzyme for γ-carboxylation of glutamic acid (Glu) conversion to γ-carboxy-glutamic acid (Gla)
- Glu --> Gla modification needed for Ca^{2+} binding, clot formation

Warfarin inhibits the vitamin K cycle

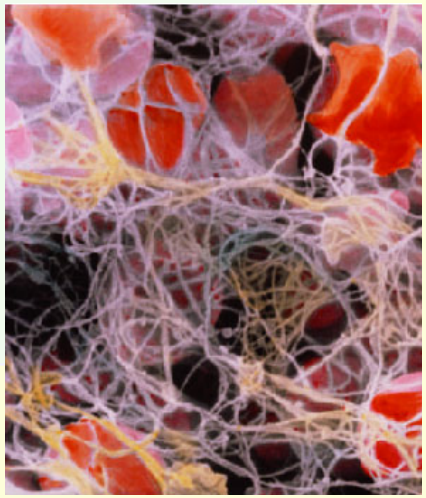


Warfarin

CYP2C9

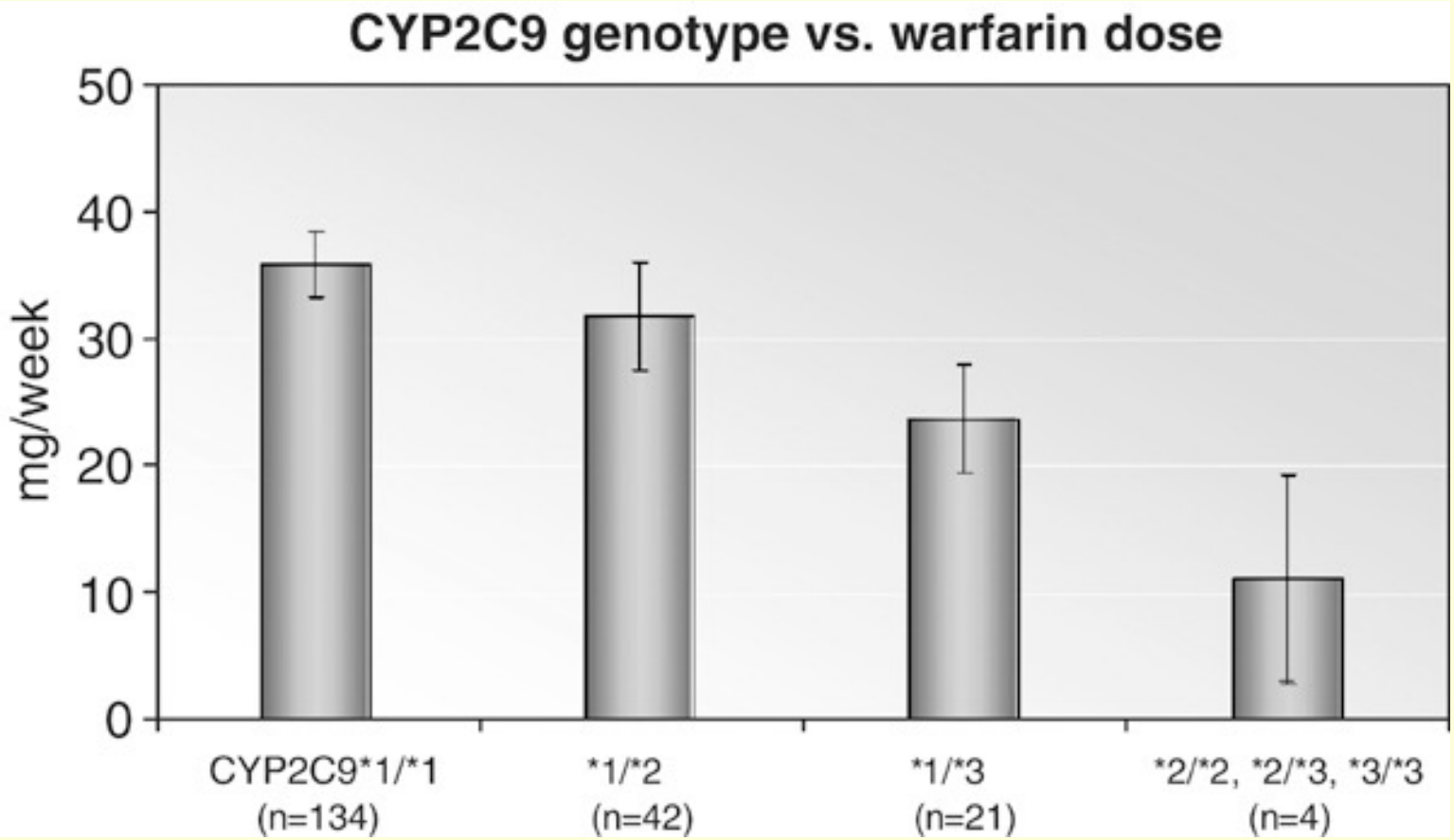
Inactivation

Pharmacokinetic



Vitamin K-dependent clotting factors
(FII, FVII, FIX, FX, Protein C/S/Z)

Effect of CYP2C9 Genotype on Anti-coagulation - Related Outcomes: Warfarin Maintenance Dosage



-Variant alleles that have significant clinical impact:

CYP2C9*1 (WT) - normal

CYP2C9*2 (Arg144Cys) - low/intermediate

CYP2C9*3 (Ile359Leu) - low

Frequency of the Defective *CYP2C9* Alleles in Different Ethnic Groups (loss-of-function mutations)

Population	*CYP2C9*2*	*CYP2C9*3*	*CYP2C9*5*
Caucasian-American	12.3%	5.6%	0%
Hispanic-American	12.0%	3.4%	0.5%
African-American	2.5%*	1.8%	1.6%
Chinese	0%*	4.1%	0%
Japanese	0%*	0%	0%

Phase I reactions may occur by oxidation, reduction or hydrolysis reactions

Oxidation

- cytochrome P450 monoxygenase system
- flavin-containing monooxygenase system
- alcohol dehydrogenase and aldehyde dehydrogenase

Reduction

- NADPH-cytochrome reductase
- reduced (ferrous) cytochrome P450

Hydrolysis

- esterases and amidases
- epoxide hydrolase

Alcohol statistics:

England

- 7-15% of all hospital admissions (offences + cirrhoses)
- 30’000 death/year
- cost 5’000’000’000 $/year

USA

- 17 million alcoholics
- cost 300’000’000’000 $/year

Proofs for deleterious effect of alcohol on public health:

prohibition in the US, periods of high taxes on alcohol

Phase I reactions – alcohol dehydrogenase and acetaldehyde dehydrogenases

- there is a high individual variability in ethanol metabolism, with alcohol elimination rates varying as much as three- to four-fold from person to person
- such an individual variability is mainly due to genetic variations in ethanol and acetaldehyde metabolizing enzymes

Genetic variation in alcohol metabolizing enzymes

- Alcohol Dehydrogenases (ADH), a family of cytosolic enzymes using NAD^+ as a cofactor
- There are five classes of human ADHs
- Under physiological conditions the main isoforms involved in ethanol metabolism are ADHs from classes I, II and IV
- Class I: 90% in the liver, Km for ethanol $< 5\ \mu M$
- ADH1 has several polymorphic variants

Genetic variations in alcohol metabolizing enzymes

- ADH1B*2 and ADH1B*3 alleles exhibit faster ethanol oxidation

Distribution of ADH1 alleles in different populations

	ADH1B*1	ADH1B*2	ADH1B*3	ADH1C*1	ADH1C*2
White American	**95%**	**<5%**	**<5%**	**50%**	**50%**
Black American	**85%**	**<5%**	**15%**	**85%**	**15%**
Asian	**15%**	**85%**	**<5%**	**95%**	**5%**

• 15% of Black Americans have ADH1B*3 allele → increased alcohol metabolic rate

• 85% of Asians have ADH1B*2 allele → increased alcohol metabolic rate → toxic accumulation of acetaldehyde → deterrent against heavy drinking

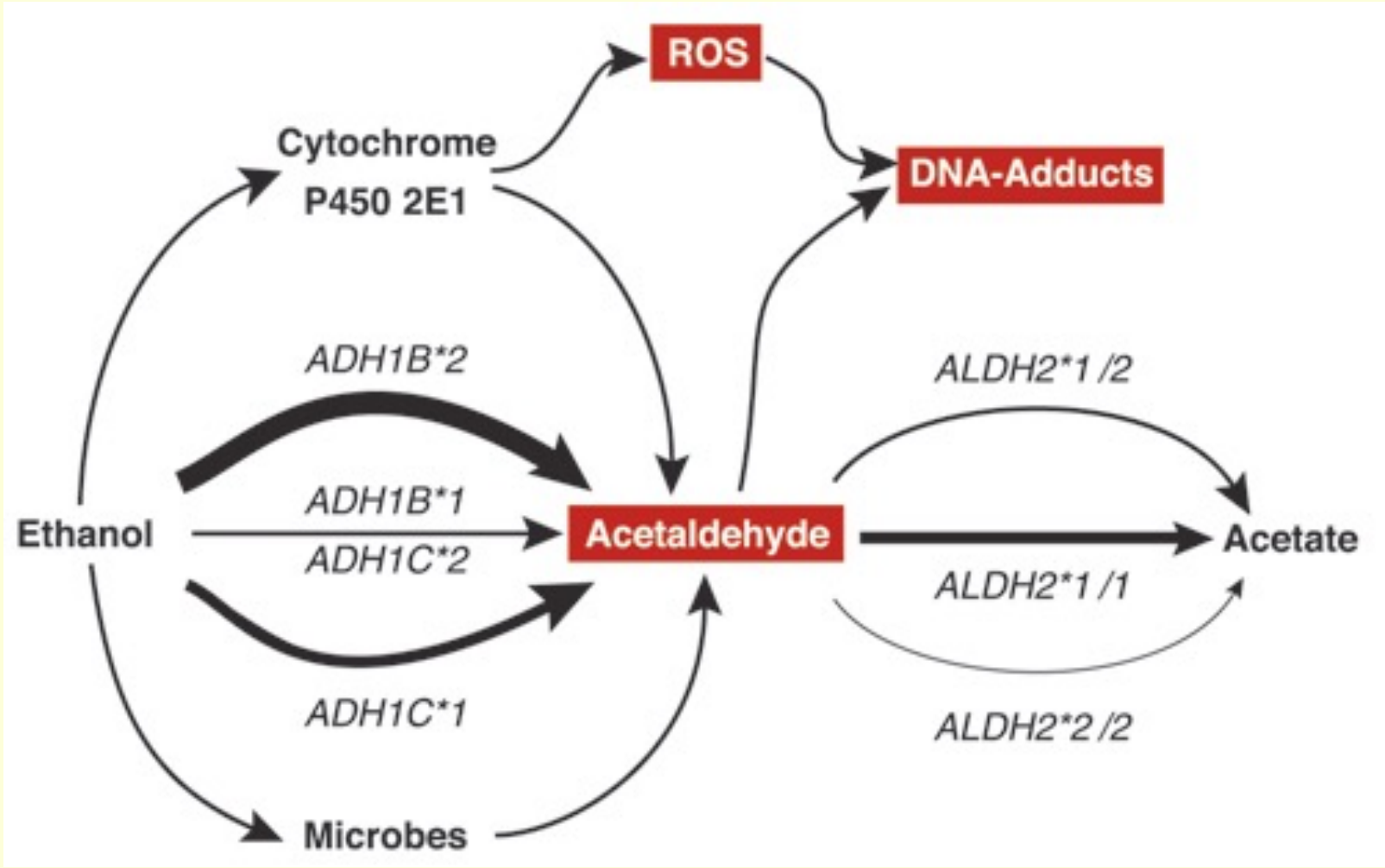
Genetic variation in acetaldehyde metabolizing enzymes

- Acetaldehyde Dehydrogenase (ALDH), a family of cytosolic/mitochondrial enzyme using NAD^+ as a cofactor
- There are nine major families of human ALDHs
- Under physiological conditions the main isoforms involved in acetaldehyde metabolism is mitochondrial ALDH2
- ALDH2 is highly expressed in the liver and stomach, as well as in other tissues; Km for acetaldehyde $< 5\ \mu M$
- ALDH2 have several polymorphic variants

Genetic variation in alcohol metabolizing enzymes

ALDH2*2 is a major polymorphic allele of ALDH2 resulting in catalytic inactivation of the enzyme

	ALDH2 Genotypes (%)		
	*1/*1	*2/*1	*2/*2
Caucasian	100[3]	0	0
Japanese	56.4	39.4	4.2
Filipino	87.3	12.7	0
Korean	71.6	26.6	1.8
Chinese	59.0	35.9	5.1
Vietnamese	43.0	57.0	



Seitz & Becker, NIH

ALDH2*2 is associated with lower tendency to drink excessively in Japanese population (acetaldehyde toxicity)

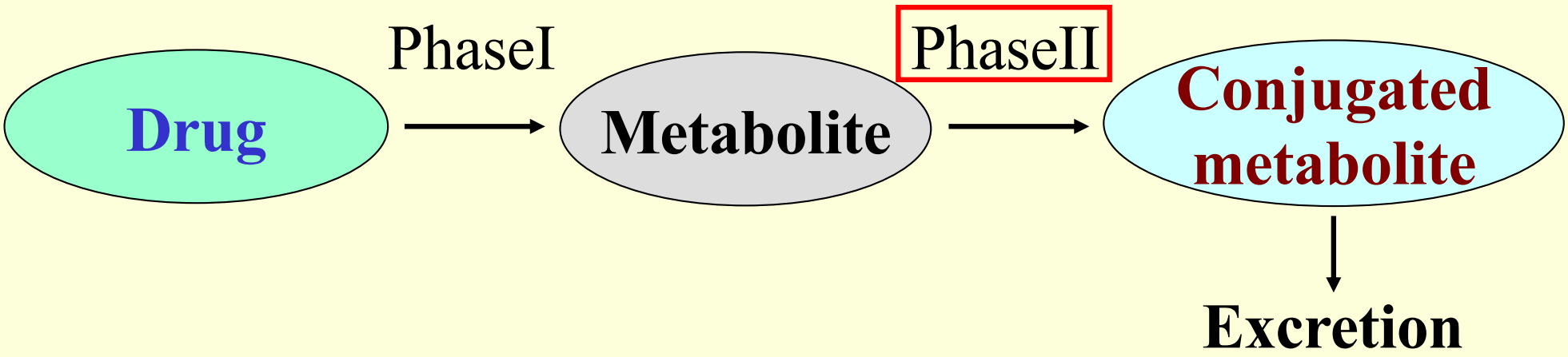
Locus	Genotype	Controls (N=461) (%)	Alcoholics (N=655) (%)
ALDH2	*1 / *1	58	88
	*1 / *2	35	12
	*2 / *2	7	0

$p < .001$

Higushi, 1994, Alcohol Alcohol Suppl

Candidate genes **PHARMACOKINETICS**:

- metabolizing enzymes (two categories)
- metabolizing enzymes in PHASE I REACTIONS
- metabolizing enzymes in PHASE II REACTIONS

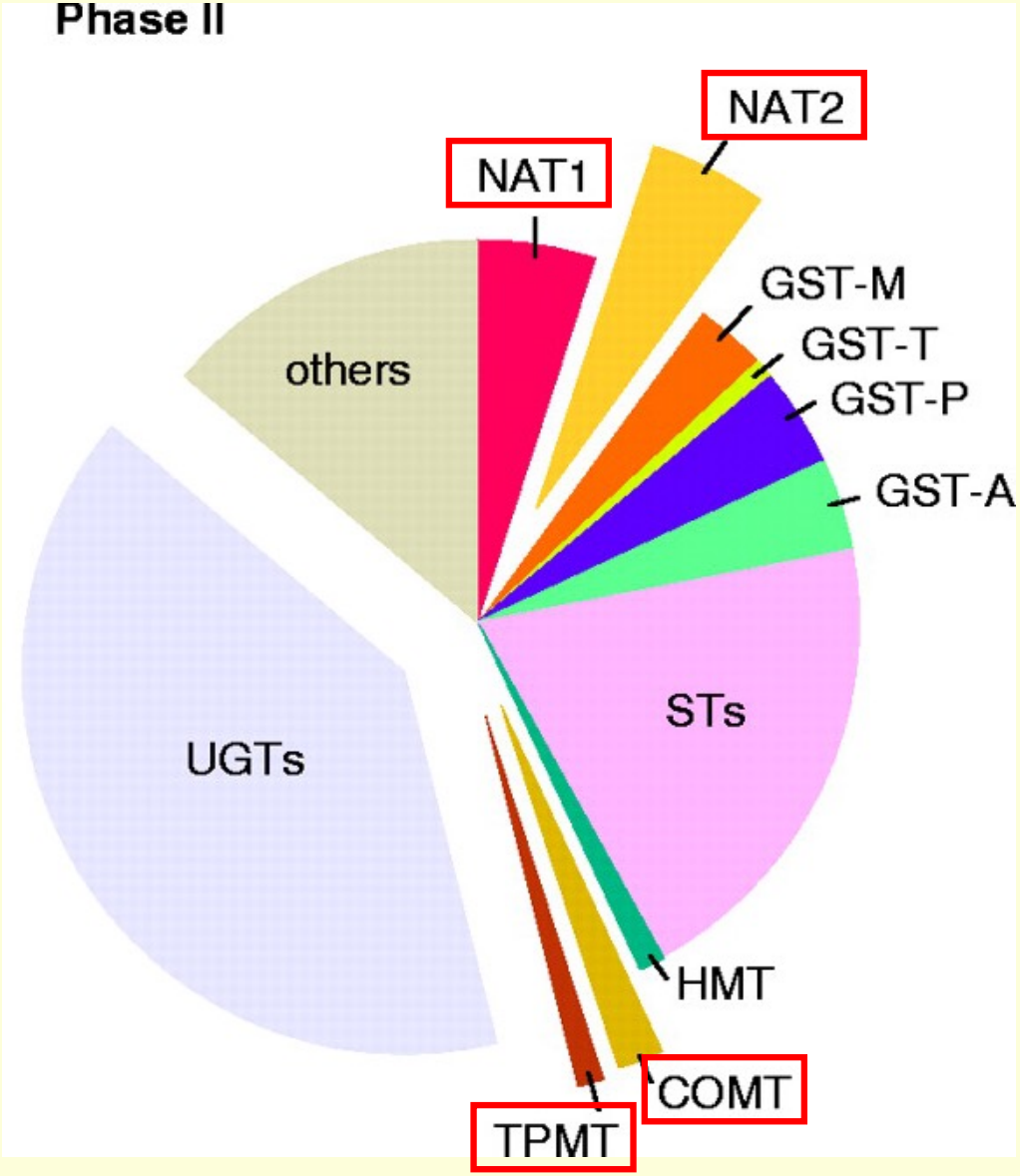


Phase I and II reactions lead to formation of **more polar** than original drug conjugated metabolites, that are **easily excreted.**

Phase II reactions:

- glutathione-S-transferases (GST)
- UDP-glucuronosyltransferases (UGT)
- N-acetyltransferases (NAT)
- Amino acid N-acetyl transferases
- Sulfotransferases (SULT)
- Methyltransferases

Relative contribution of type II enzymes for drug metabolism



Evans and Relling, 1999, Science

-Enzymes with functional polymorphisms

- NAT2 (N-acetyltransferase)
- COMT (Catechol-O-methyltransfertase)
- TMPT (thiopurine methyltransferase

Example: N-acetylation

NAT1 & NAT2 gene on chromosome 8 are responsible for N-acetylation (deactivation) and O-acetylation (activation) of aromatic and heterocyclic amines.

NAT1: 19 different polymorphisms are known

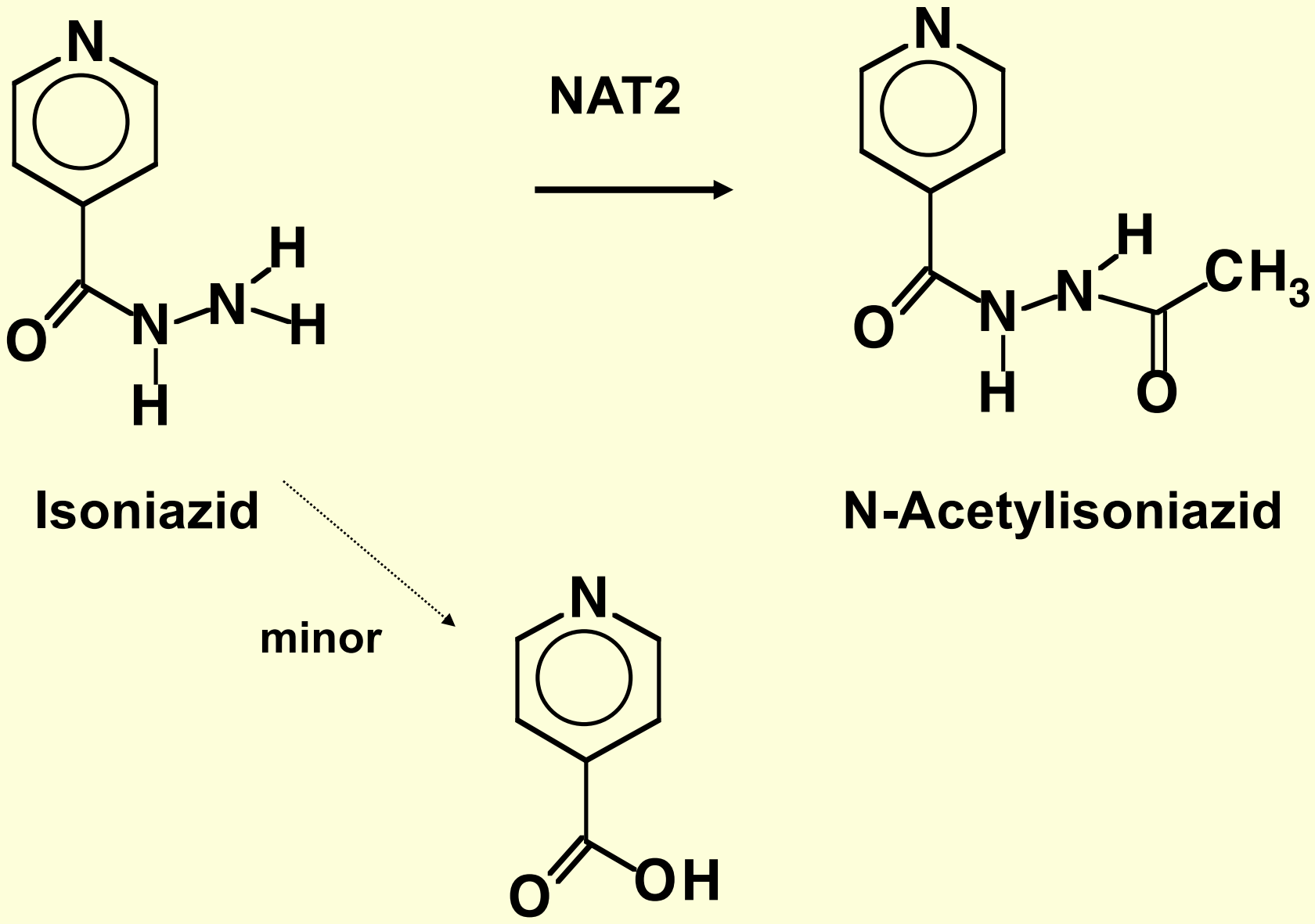
NAT2: 24 different polymorphisms are known

Functional consequences:

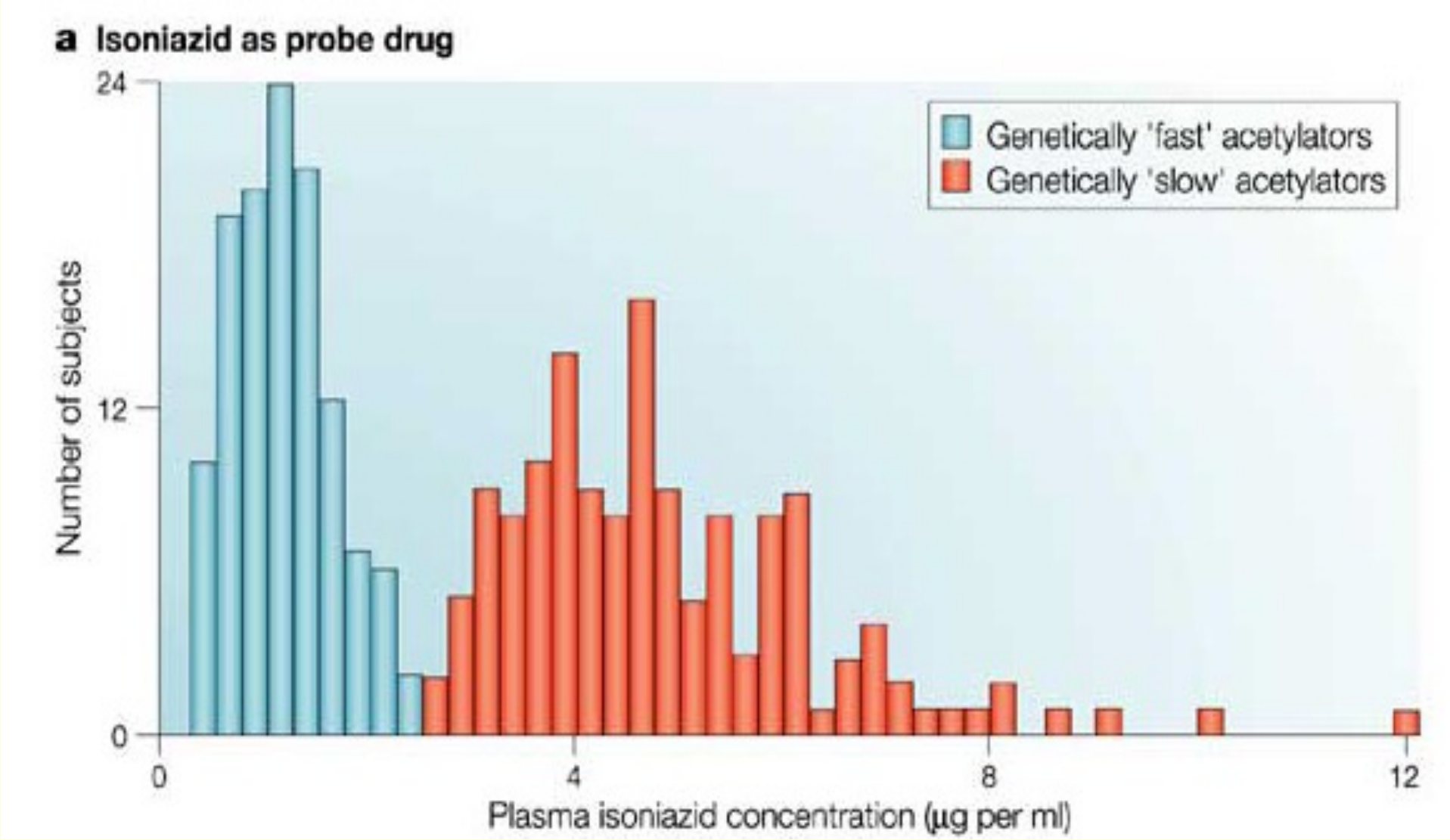
- reduced catalytic activity
- less stable protein
- protein with no activity

} **slow acetylators**

Example of NAT2 reaction: isoniazid (antituberculosis drug)



Polymorphism in NAT2 and variations in plasma isoniazid concentration



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.

Candidate genes for variable drug response

PHARMACOKINETICS:

- plasma drug carrier proteins (Distribution)
- drug transporters (Absorption,Distribution,Excretion)
- metabolizing enzymes (Metabolism)
- ...

PHARMACODYNAMICS

- receptors
- ion channels, transporters
- enzymes
- immune molecules….

Drug transporters responsible for drug uptake/excretion

SLC (solute carrier) family:

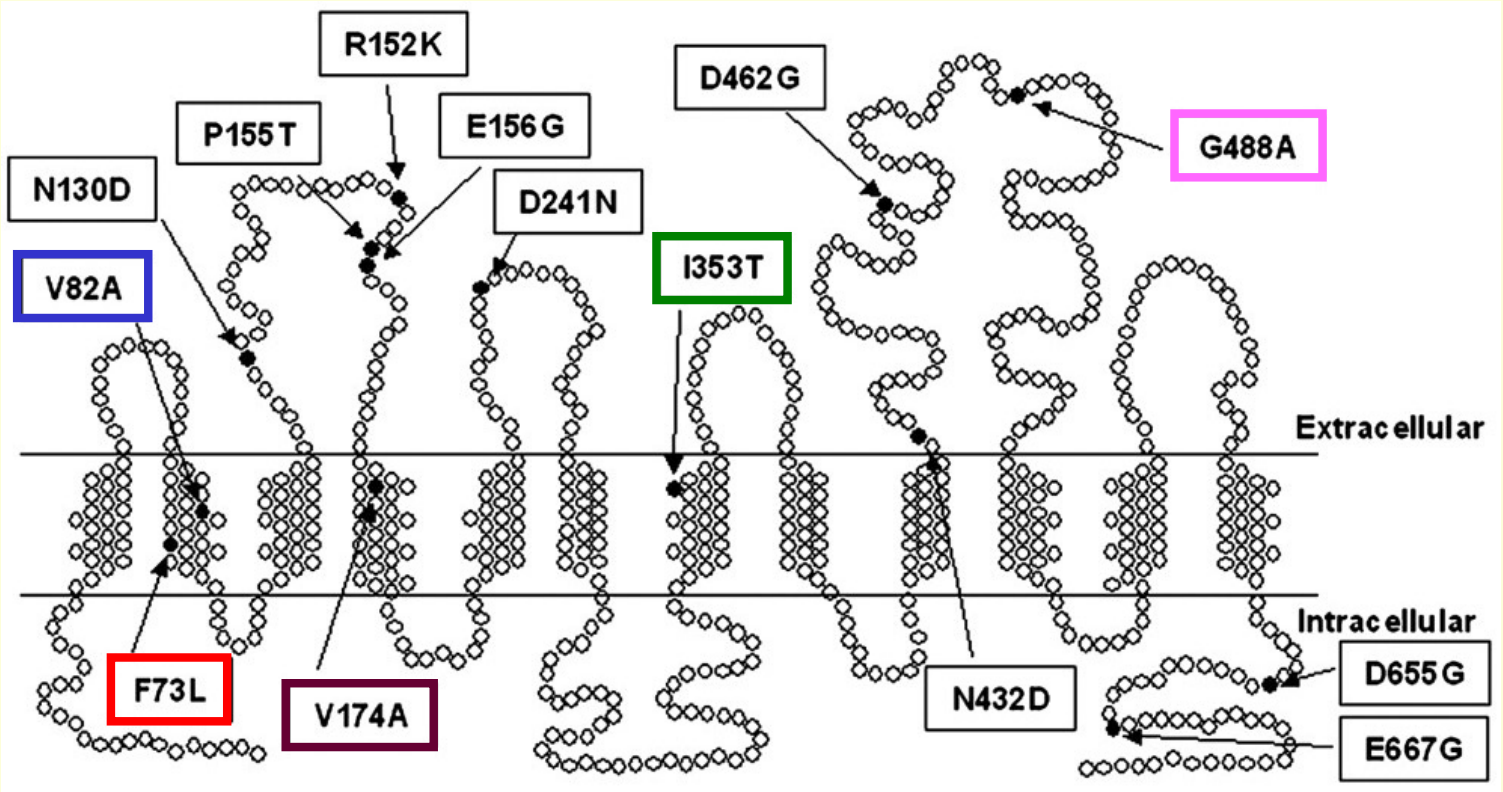
- Organic Anion Transporters (OAT)
- Organic Anion Transporting Polypeptides (OATP)
- Na+/Taurocholate Cotransporting Polypeptides (NTCP)
- Organic Cation Transporters (OCT)
- Peptide Transporters (PEPT)

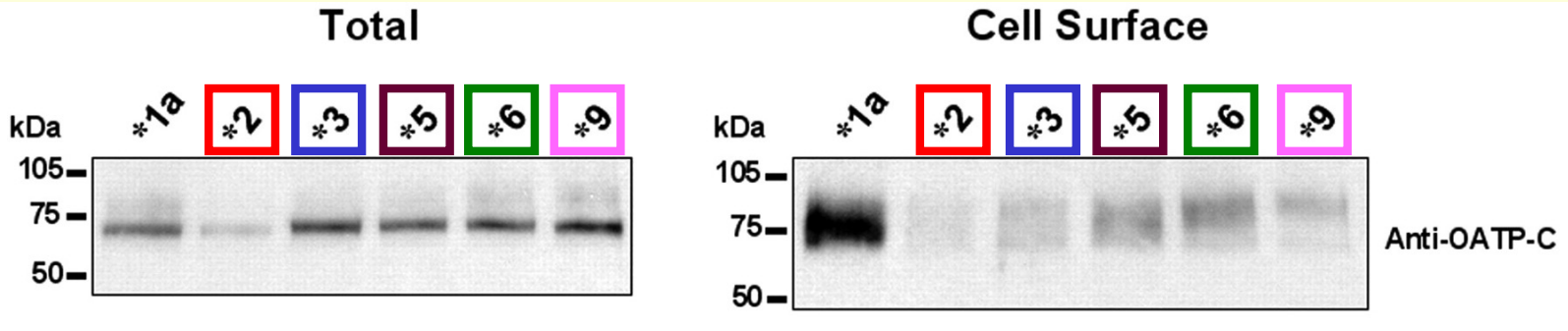
ABC (ATP binding cassette) family:

- Bile Salt Excreting Protein (BSEP)
- P-glycoprotein (Pgp = MDR1)
- Multidrug Resistance Associated Proteins (MRP)
- Breast Cancer Resistance Protein (BCRP)

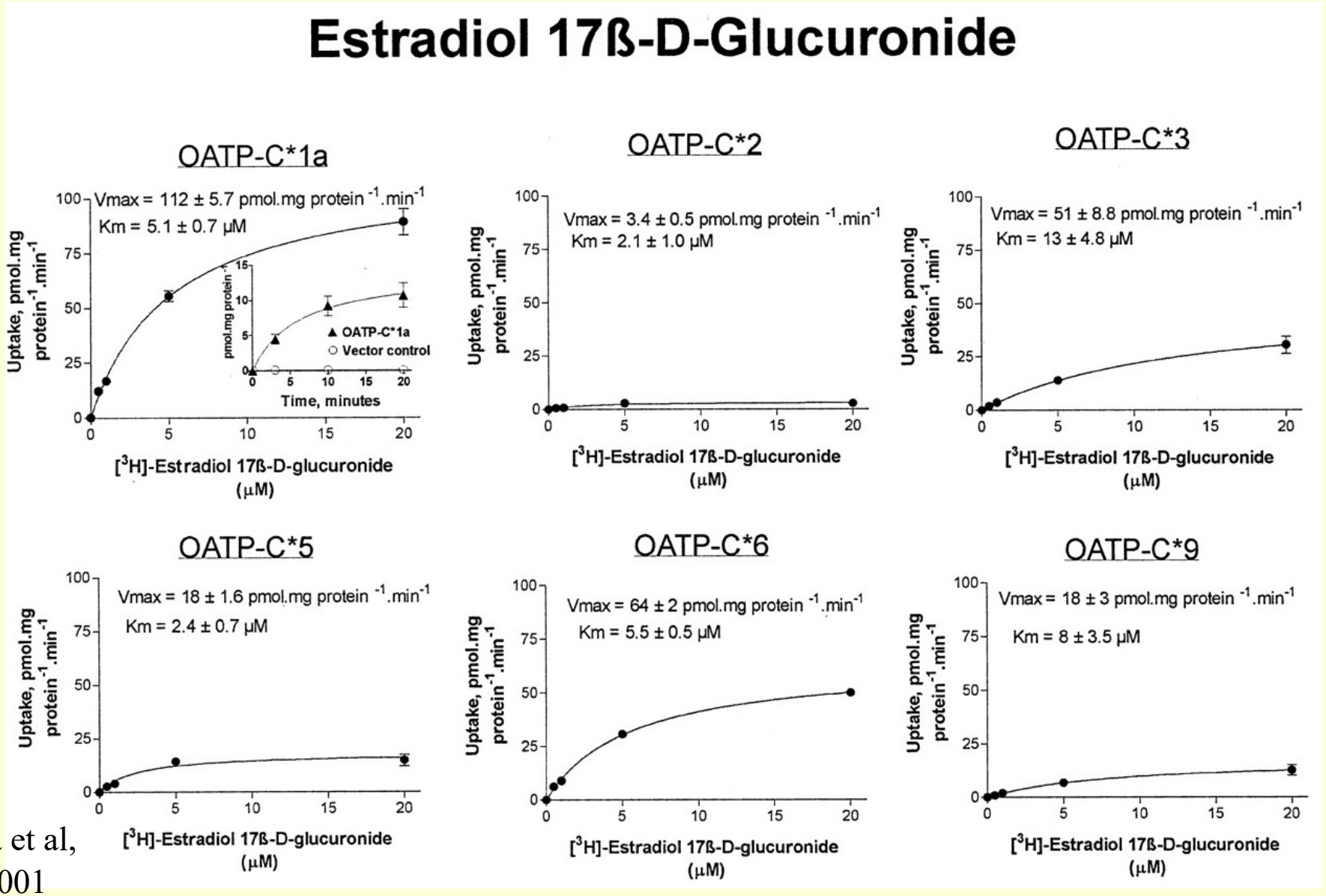
OATP-C polymorphisms affecting surface expression

Tirona et al,
JBC 2001



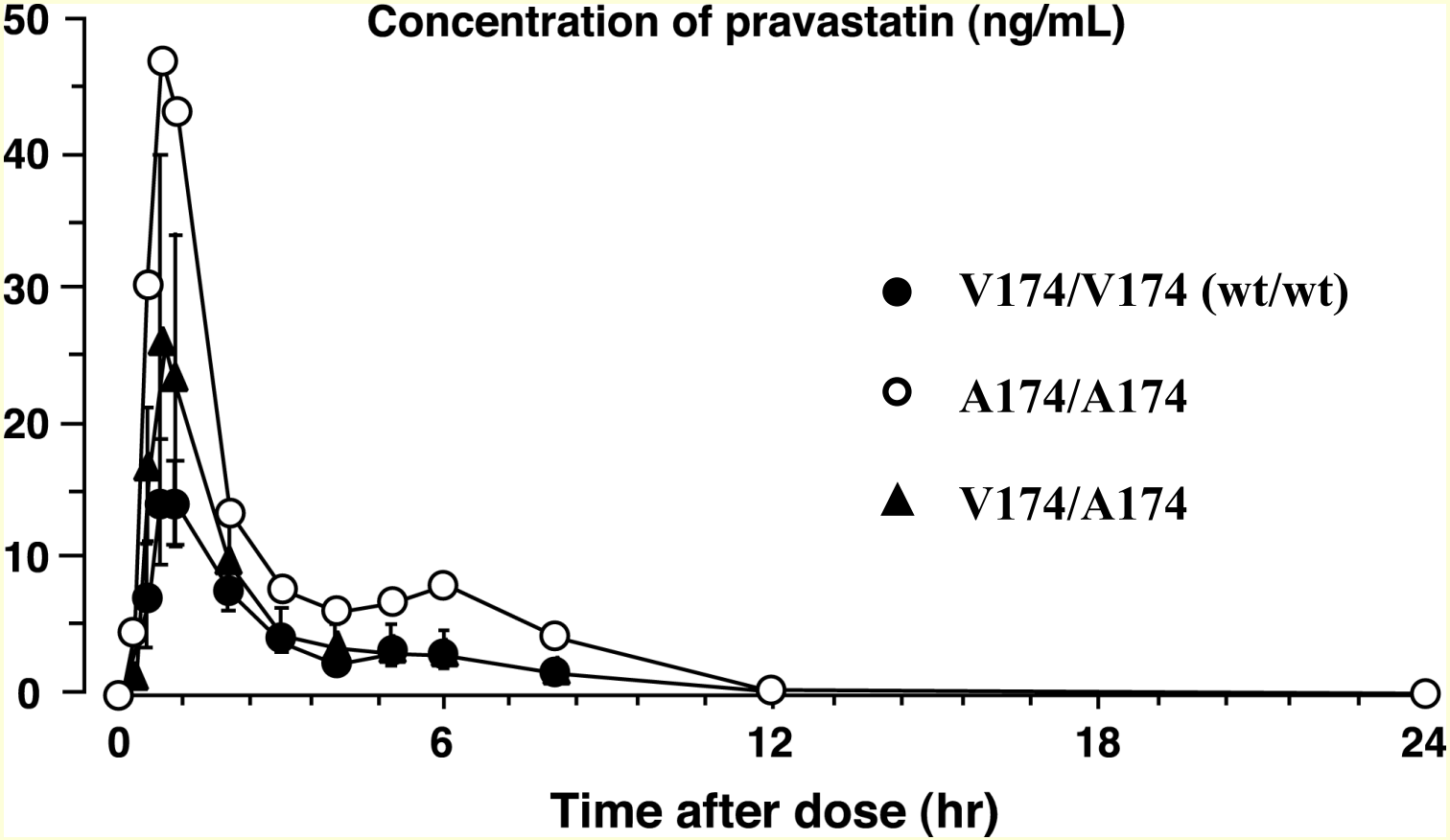


OATP-C polymorphisms affect drugs uptake in transfected HEK cells



Tirona et al, JBC 2001

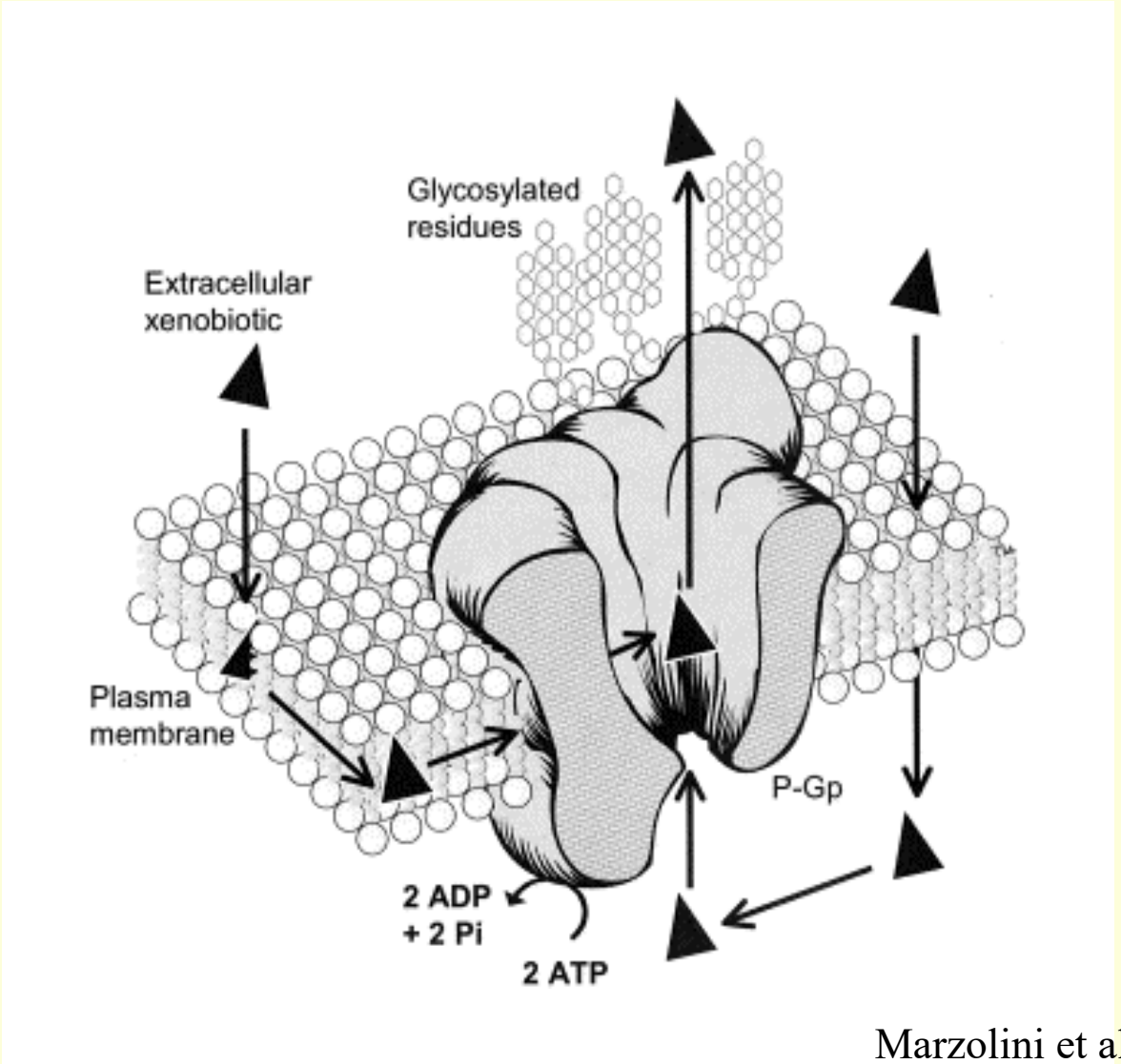
Example in humans: effect of V174A polymorphism on pravastatin elimination time



A174 allele exhibits lower uptake of pravastatin by hepatocytes, thus lower metabolism, thus higher blood concentration.

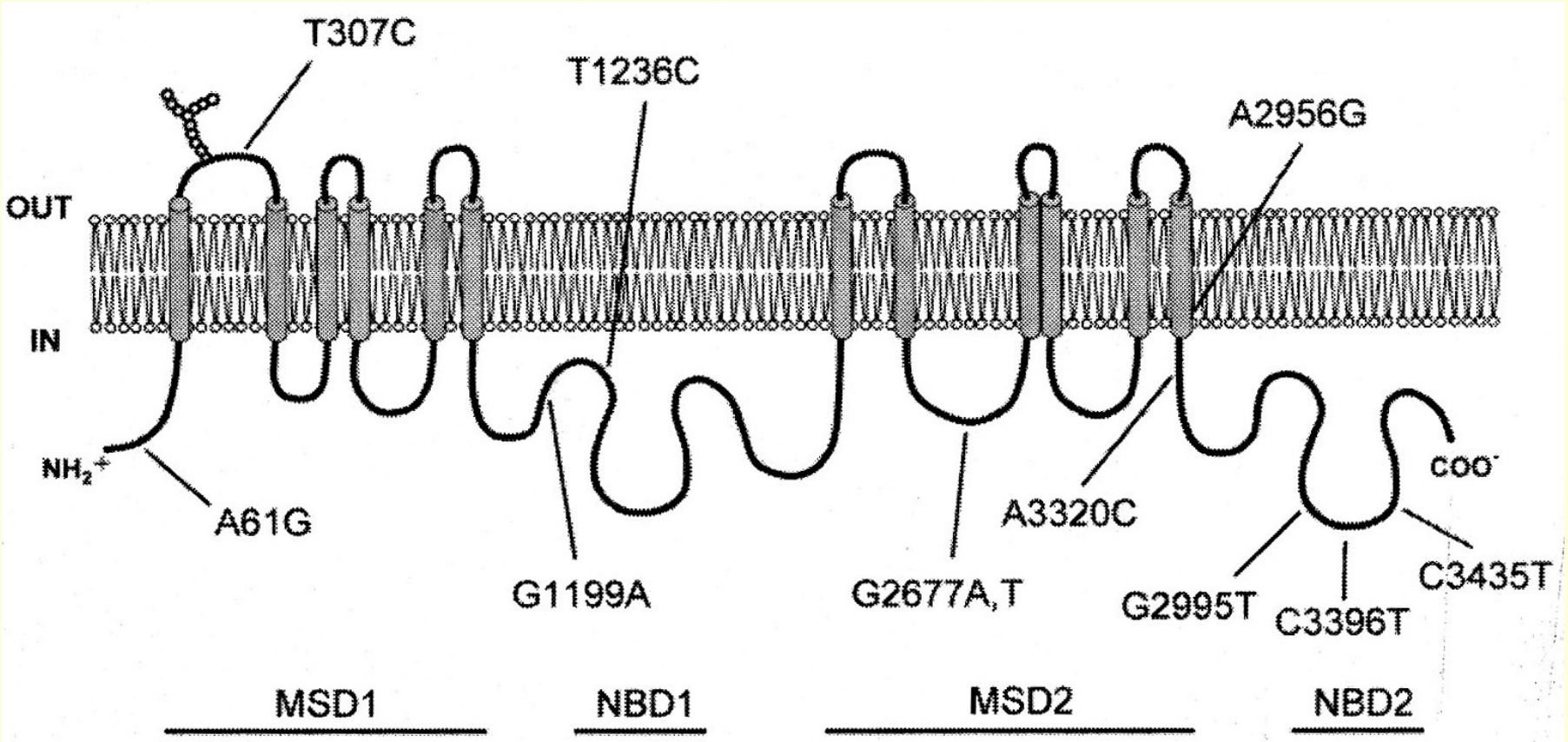
Ito et al, 2005, Pharm Res

ABC transporters: example of MDR1 polymorphism



Marzolini et al, 2004, Clin Pharm Ther

MDR1 gene bears numerous mutations affecting its function



Sakaeda, 2005 Drug Metab Pharmacokinet

Example: C3435T polymorphism

- a silent polymorphism resulting in two-fold decrease in MDR1 protein expression in duodenum
- this mutation correlates with higher intestinal absorption of digoxin and other drugs
- lower frequency of C3435T allele in Africans correlates with lower frequency of renal carcinoma?

MDR1 C3435T polymorphism in different populations

	N	Allele		Genotype		
		C	T	CC	CT	TT
Caucasian in UK	190	0.48	0.52	0.24	0.48	0.28
Caucasian in Germany	188	0.52	0.48	0.28	0.48	0.24
Caucasian in Germany	461	0.46	0.54	0.21	0.50	0.29
Caucasian in Poland	122	0.62	0.38	0.42	0.41	0.17
Itarian	106	0.54	0.46	0.26	0.55	0.19
Portuguese	100	0.43	0.57	0.22	0.42	0.36
Portuguese in Southern Portugal	100	0.36	0.65	0.12	0.47	0.41
Russian	290	0.46	0.54	0.21	0.49	0.30
Spanish	408	0.52	0.48	0.26	0.52	0.22
African American	88	0.84	0.16	0.68	0.31	0.01
African in KwaZulu-Natal, South Africa	110	0.86	0.14	0.75	0.21	0.04
Ghanaian	206	0.83	0.17	0.67	0.34	0.00
Kenyan	80	0.83	0.17	0.70	0.26	0.04
Sudanese	51	0.73	0.27	0.52	0.43	0.06
Chinese	132	0.53	0.47	0.32	0.42	0.26
Chinese	98	0.46	0.54	0.24	0.44	0.32
Filipino	60	0.59	0.41	0.38	0.42	0.20
Indian in KwaZulu-Natal, South Africa	103	0.42	0.58	0.17	0.50	0.33
Indians	93	0.38	0.62	0.18	0.39	0.43
Japanese	114	0.61	0.39	0.35	0.53	0.12
Jewish in Israel, Ashkenazi	100	0.65	0.35	0.42	0.46	0.12
Malays	99	0.48	0.52	0.25	0.46	0.28
Saudi	96	0.55	0.45	0.37	0.38	0.26
South-west Asians	89	0.34	0.66	0.15	0.38	0.47

Sakaeda, 2005 Drug Metab Pharmacokinet

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- metabolizing enzymes (Metabolism)
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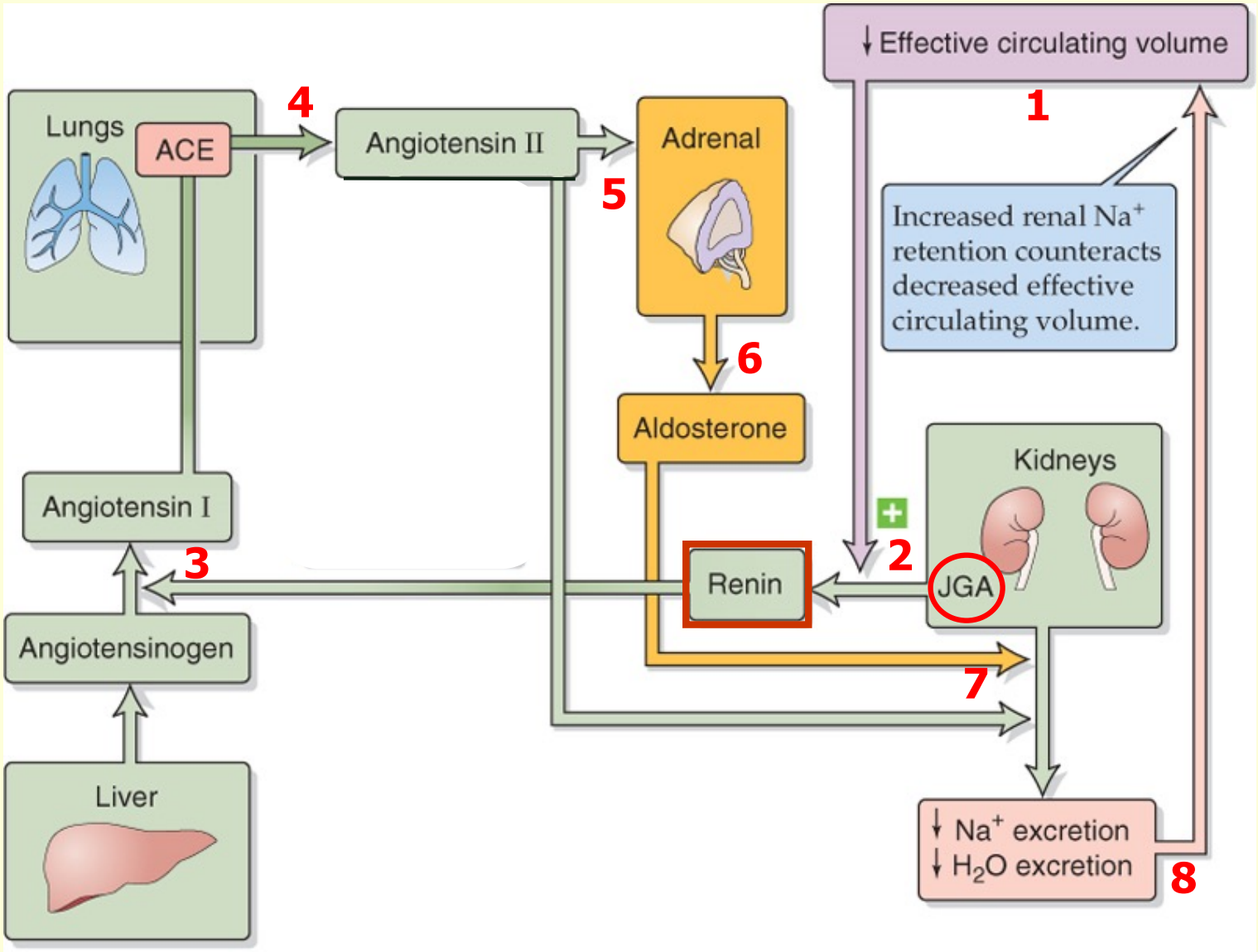
PHARMACODYNAMICS

- receptors
- ion channels, transporters
- enzymes
- immune molecules….

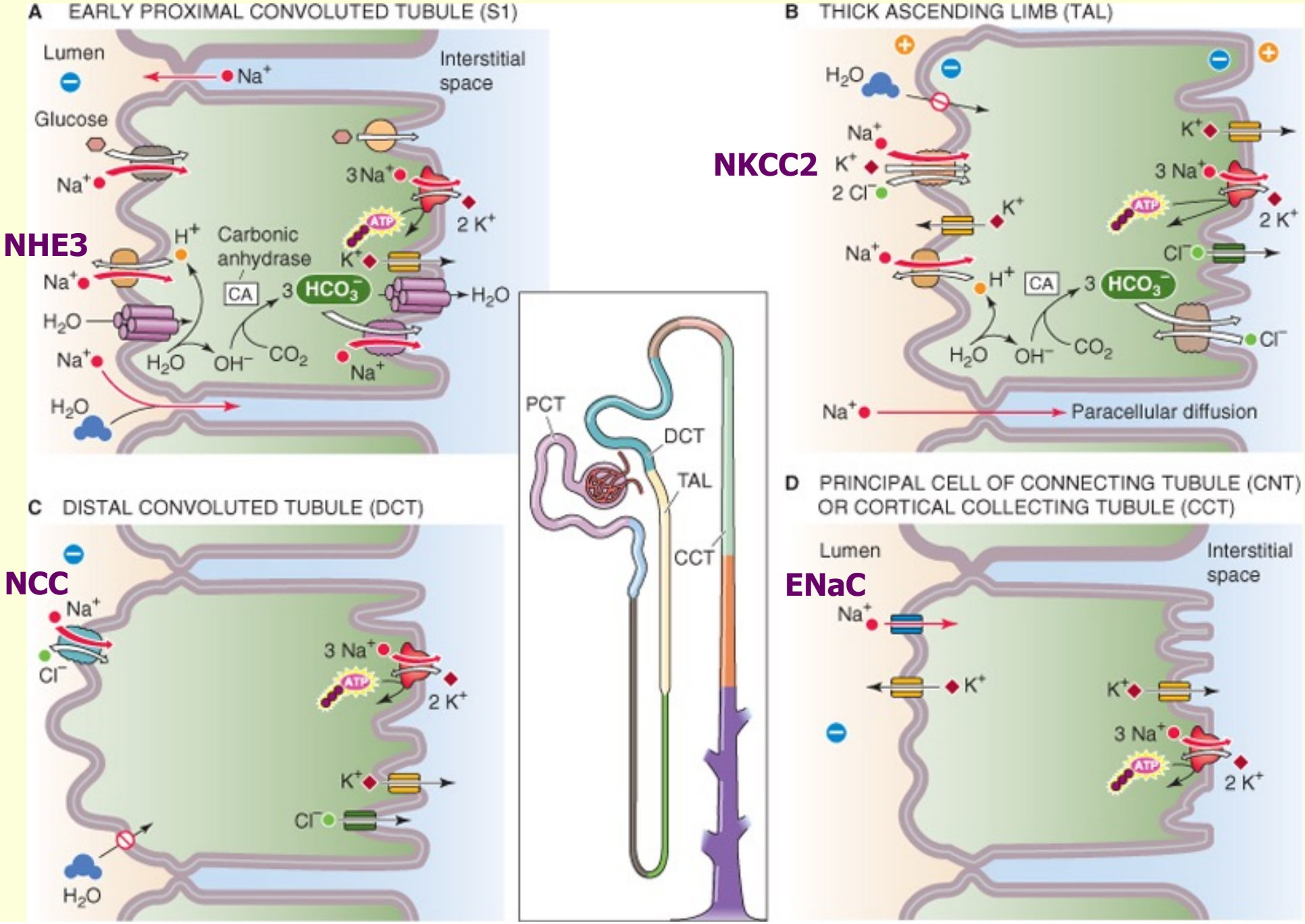
Example: Mutation in Mineralocorticoid Receptor (MR) – dysregulation of blood pressure control



JGA - juxtaglomerular apparatus - Macula densa

ACE - angiotensin converting enzyme

Nephron: main apical Na^+ transporters



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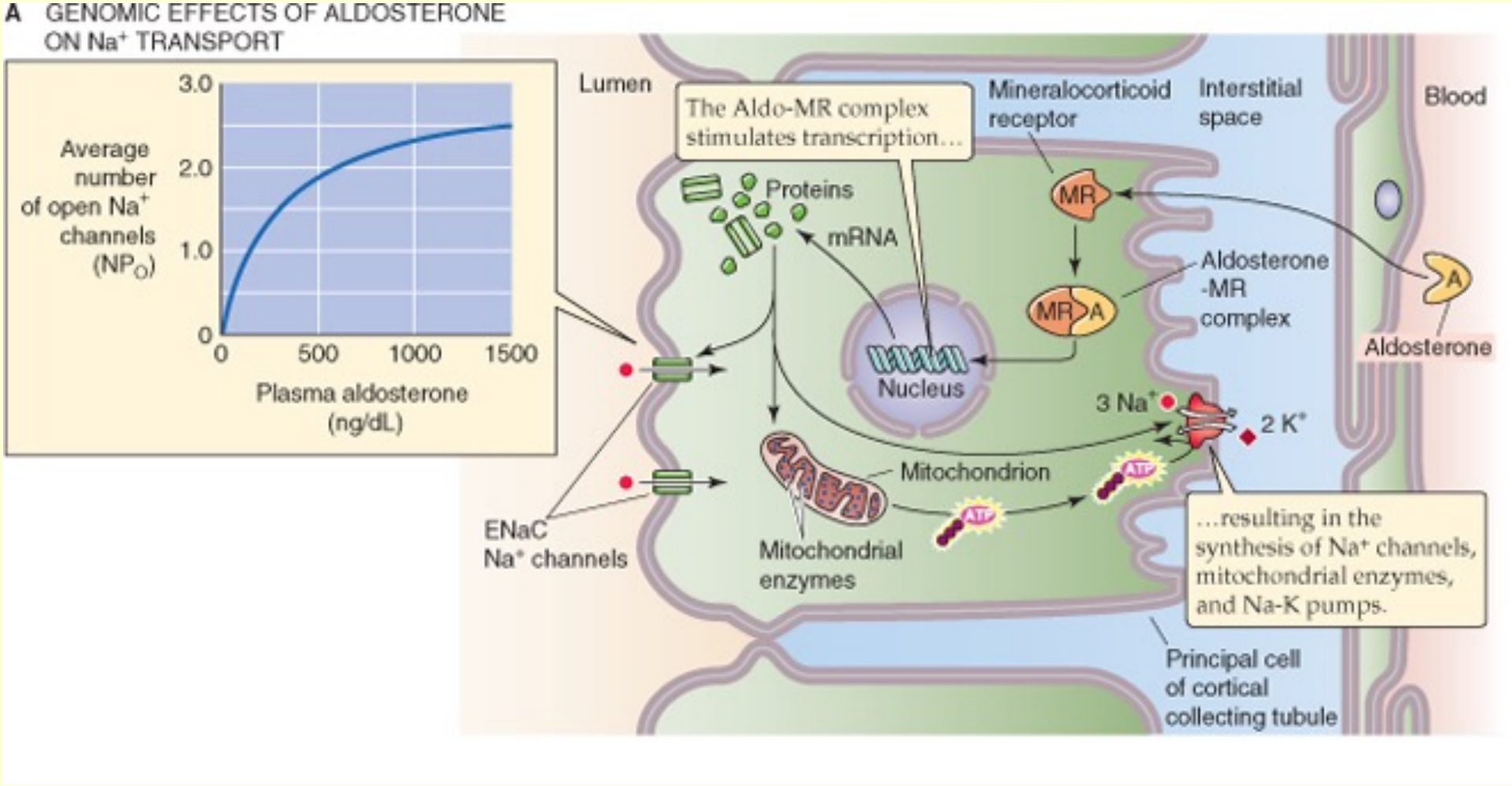
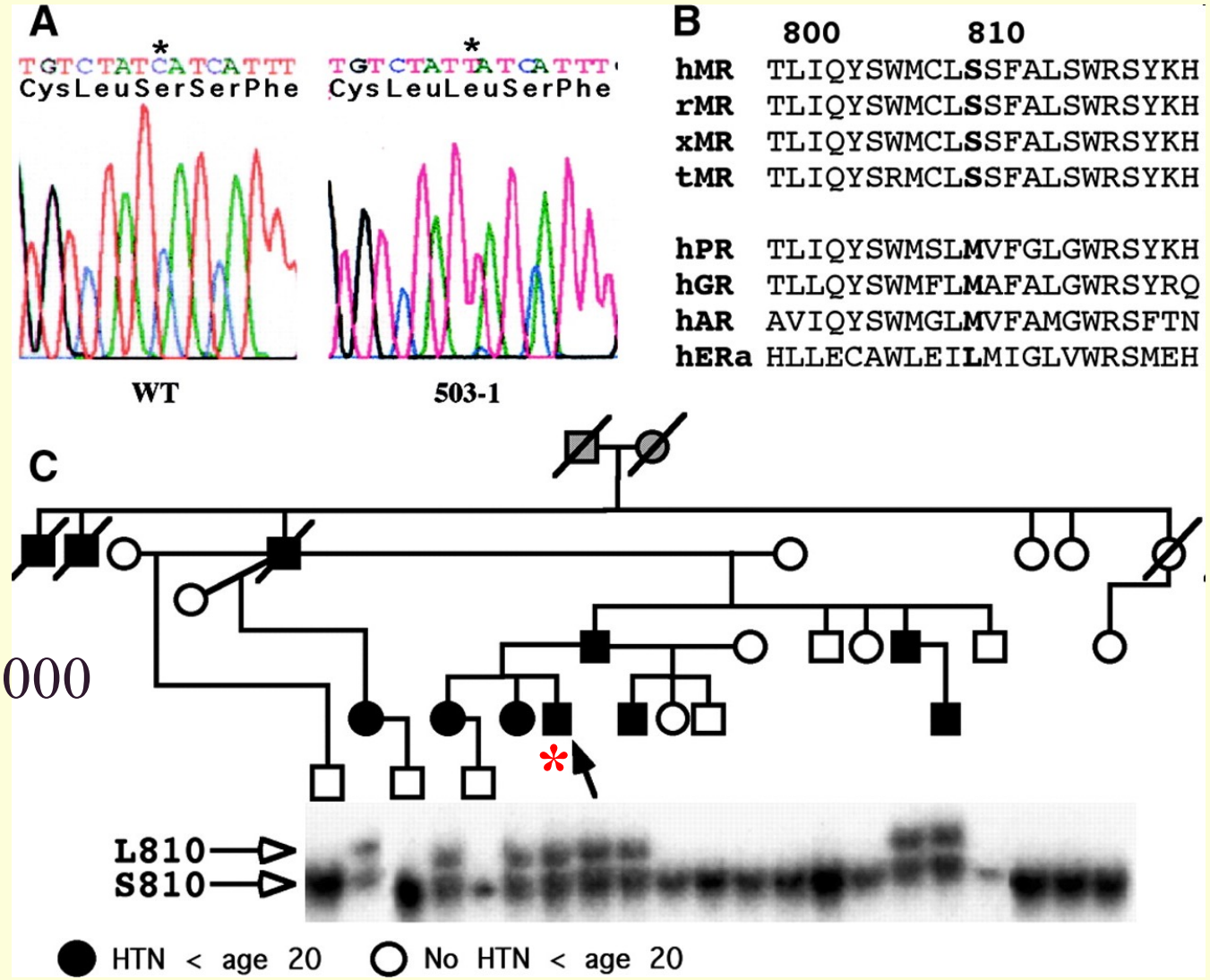


Clinical case: severe hypertension, suppressed renin, low aldosterone



Geller et al, 2000
Science

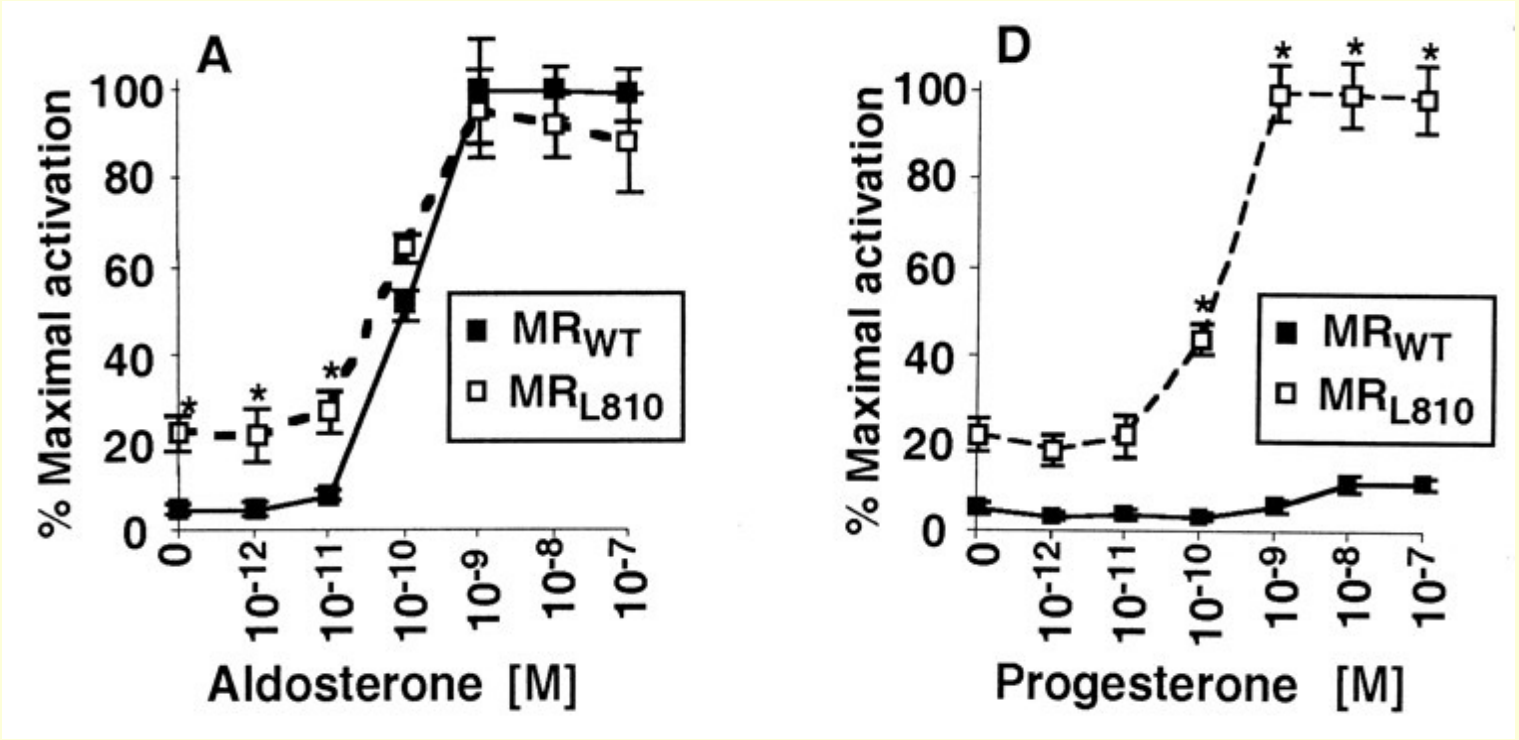
genetic screen identified MR_{S810L} mutation

Clinical features of MR_{L810} carriers (+) and noncarriers (-) in 503-1 family

Clinical parameter	MR_{L810}^{+} (n = 8)	MR_{L810}^{-} (n = 11)	P
Age	29.1 ± 6.3	32.9 ± 8.1	0.88
HTN < age 20	100%	0%	<0.0001
Anti-HTN medication	1.5 ± 0.27	0.2 ± 0.12	0.001
SBP (mmHg)	167 ± 11	126 ± 10	0.014
DBP (mmHg)	110 ± 6	78 ± 6	0.002
Serum K^+ (mM)	3.91 ± 0.18	4.36 ± 0.11	0.08
Serum HCO_3 (mM)	27.1 ± 0.87	26.4 ± 0.83	0.59
Serum aldosterone (ng/dl)	2.48 ± 0.68	12.1 ± 2.96	0.008
Urinary aldosterone (µg/24 hours)	<2	7.75 ± 1.55	0.03

- Clinical features: severe hypertension despite anti-hypertensive medication

MR_{WT} and MR_{L810} – response to aldosterone and progesterone



- activities of MR_{WT} and MR_{L810} in response to aldosterone are indistinguishable
- but, MRL810 exhibits a significantly higher basal activity
- MRL810 is strongly activated by progesterone

MR_{L810} mutation in pregnancy

- Progesterone levels increase 100-fold in pregnancy
- Two MRL810 carriers have undergone five pregnancies
  - all have been complicated by marked exacerbation of hypertension
  - low serum potassium levels, undetectable aldosterone
- Patients were advised to avoid further pregnancy

Spironolactone, a clinical antagonist of MR_{WT} acts as an agonist at MR_{L810}