Pharmacogenetics

You’re at MD at urgent care…

Both need painkillers. You decide on codeine

Codeine is a very common painkiller and is on the list of the World Health Organization's Essential Medicines.

How much do you prescribe each of them?

Based on your codeine dose…

Italian grandma is still in pain

Lebron is asleep, constipated, and wakes up only to vomit.

What do you do now?

Decreased dose for Lebron

Now, he’s getting way less than what you prescribed for a 5year old yesterday, but:

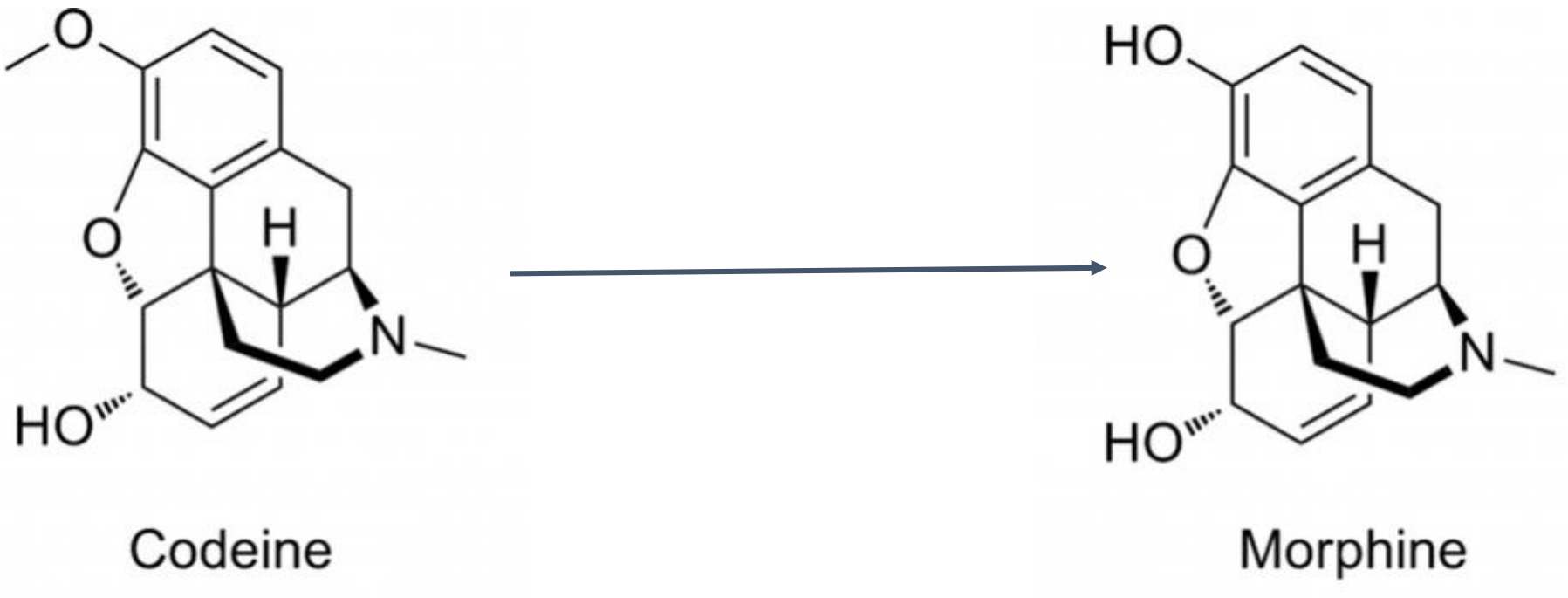
Increased the dose for grandma…

Still in pain?

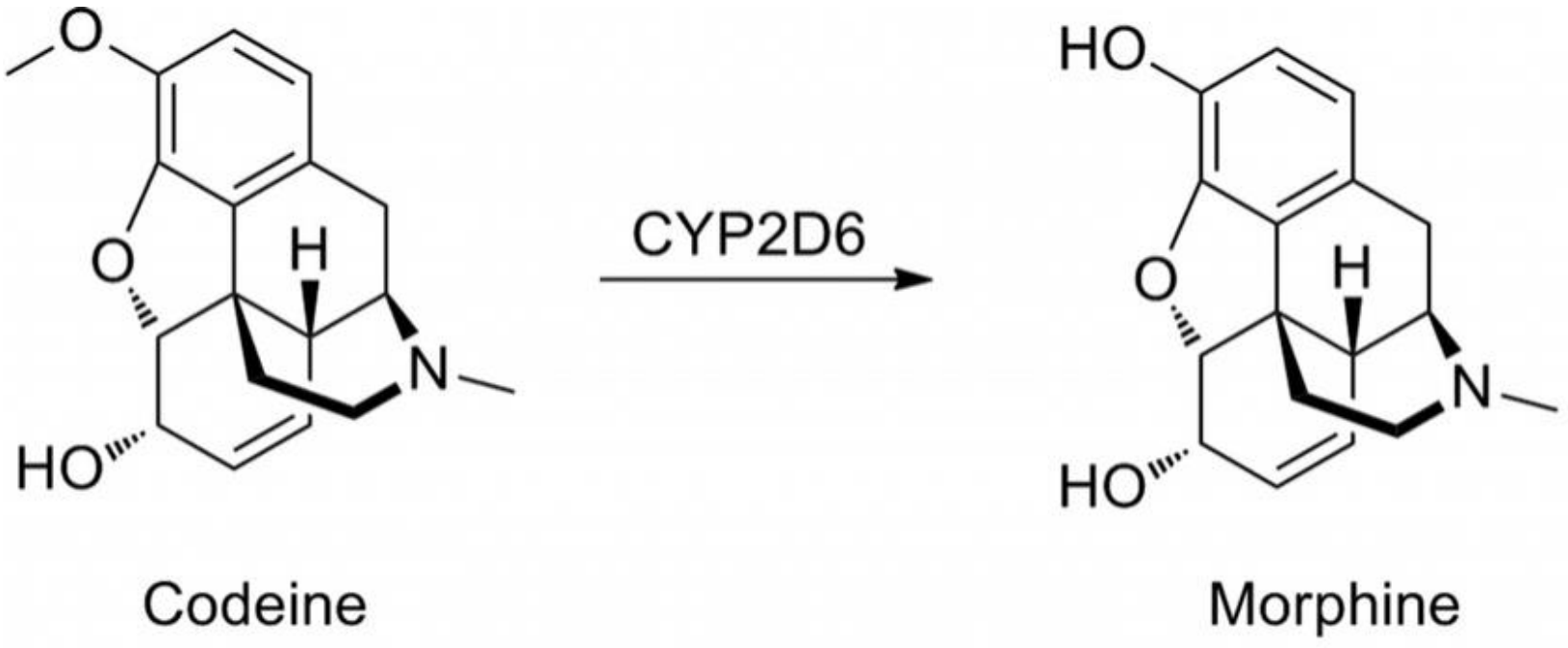
Drug seeking behavior??

Give grandma a very small dose of morphine

Codeine is a prodrug



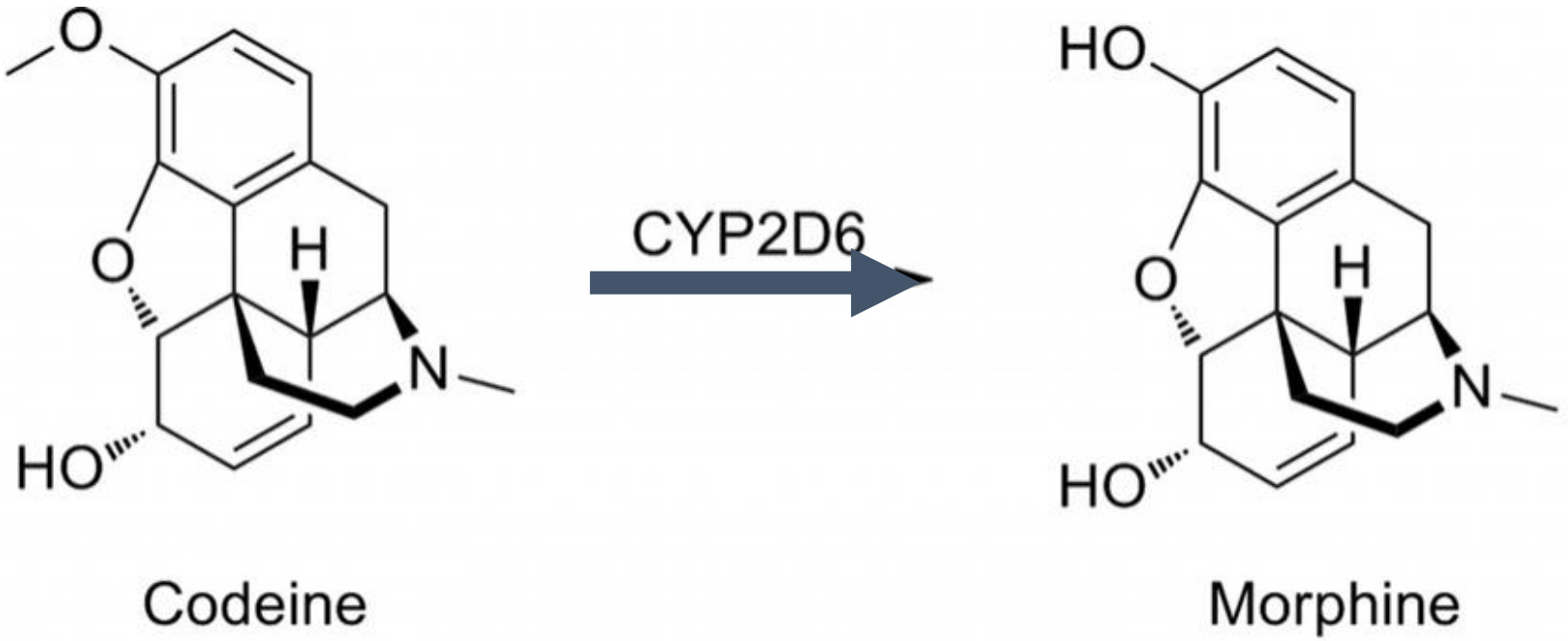
Bioactivation by CYP2D6



Codeine

Morphine

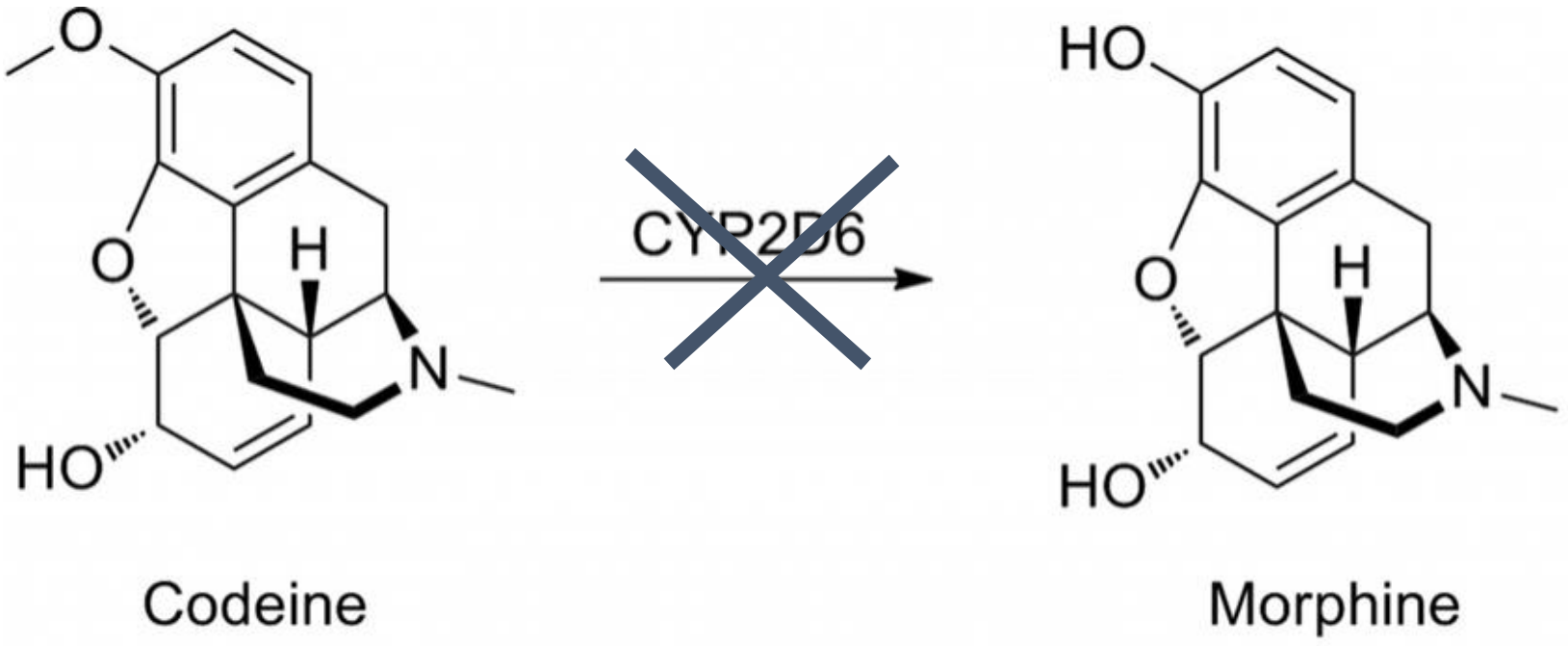
Bioactivation by CYP2D6



Codeine

Morphine

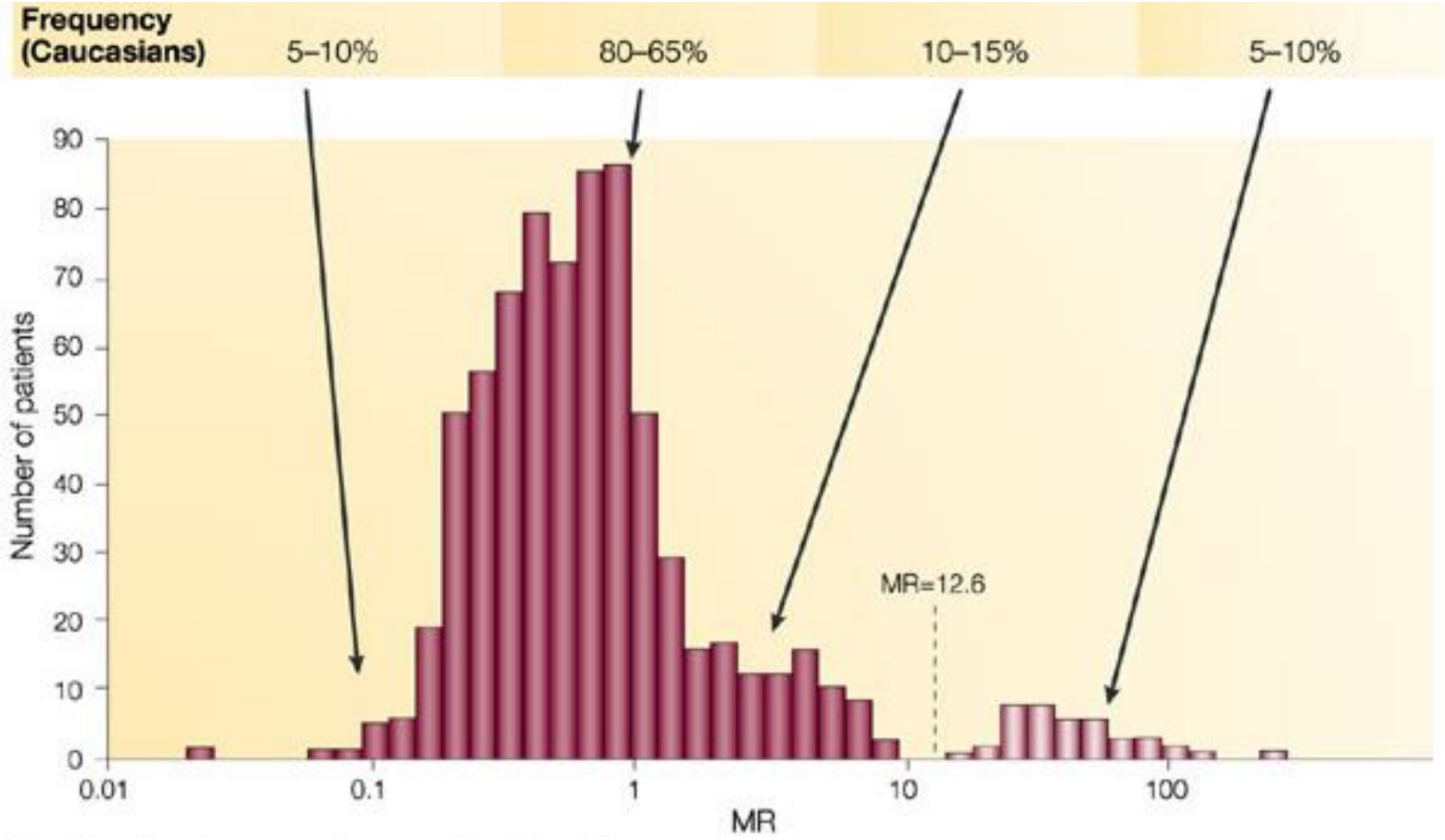
Bioactivation by CYP2D6



Codeine

Morphine

Variation in CYP2D6 activity

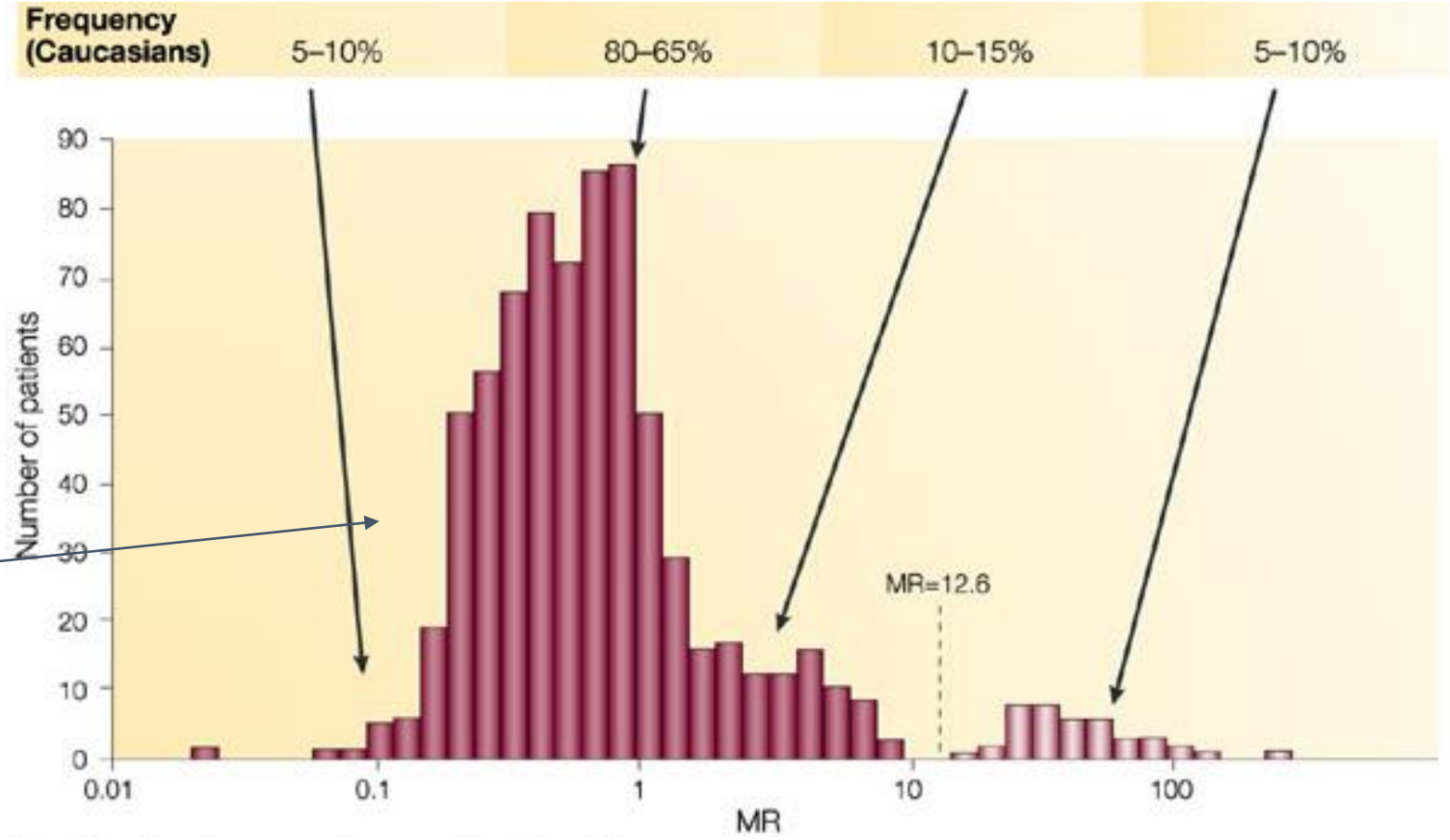


1/Efficiency of metabolizing codeine

Nature Reviews | Genetics

Variation in CYP2D6 activity

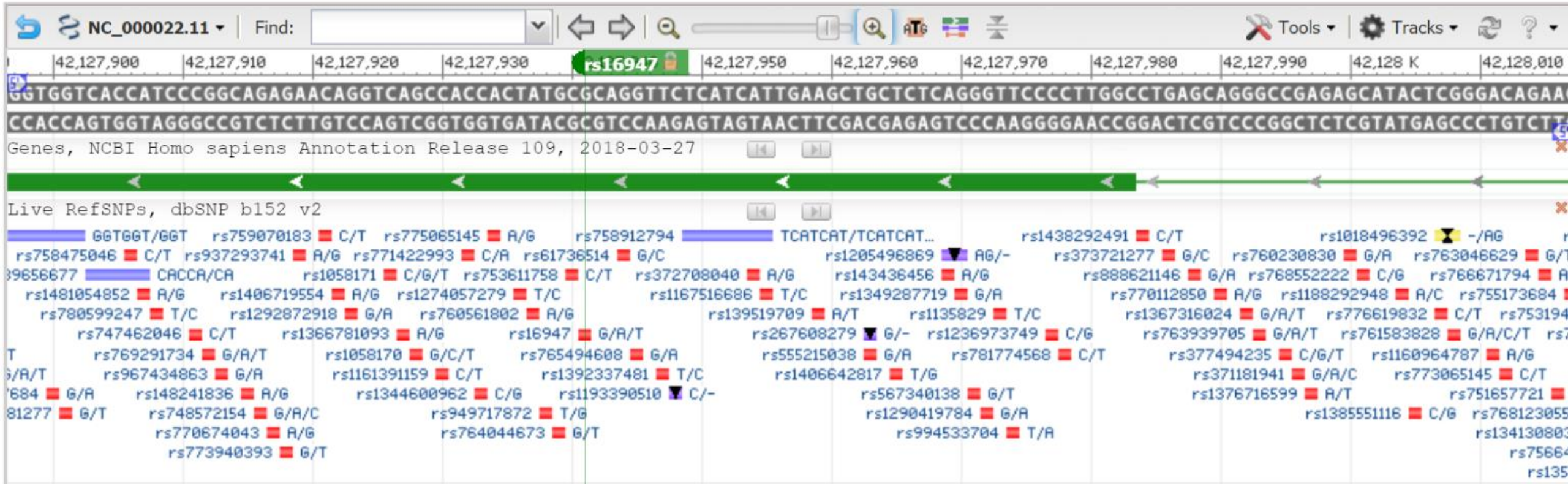
Why don't we have 3 distinct buckets?



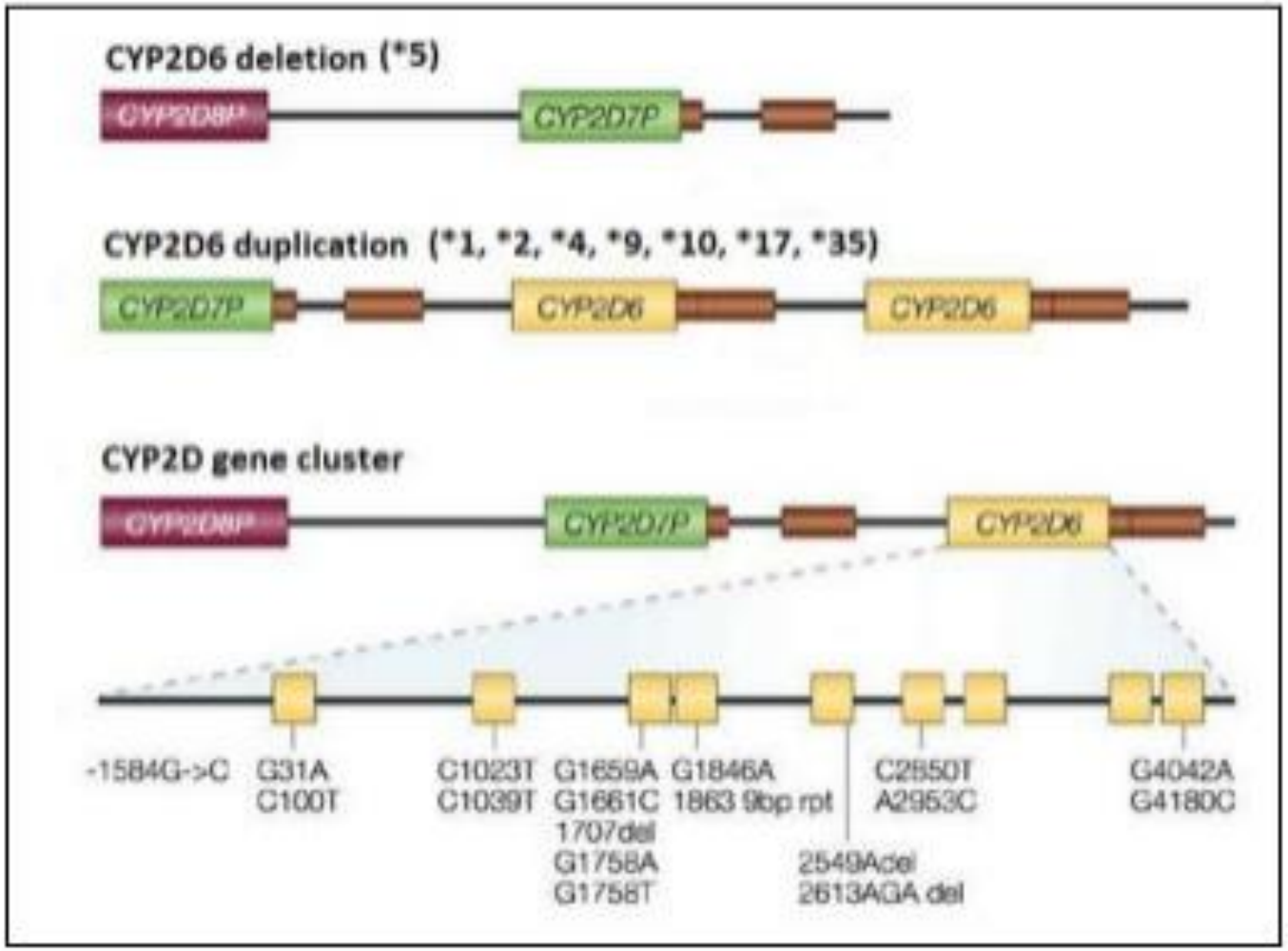
1/Efficiency of metabolizing codeine

Nature Reviews | Genetics

dbSNP showing CYP2D6 region

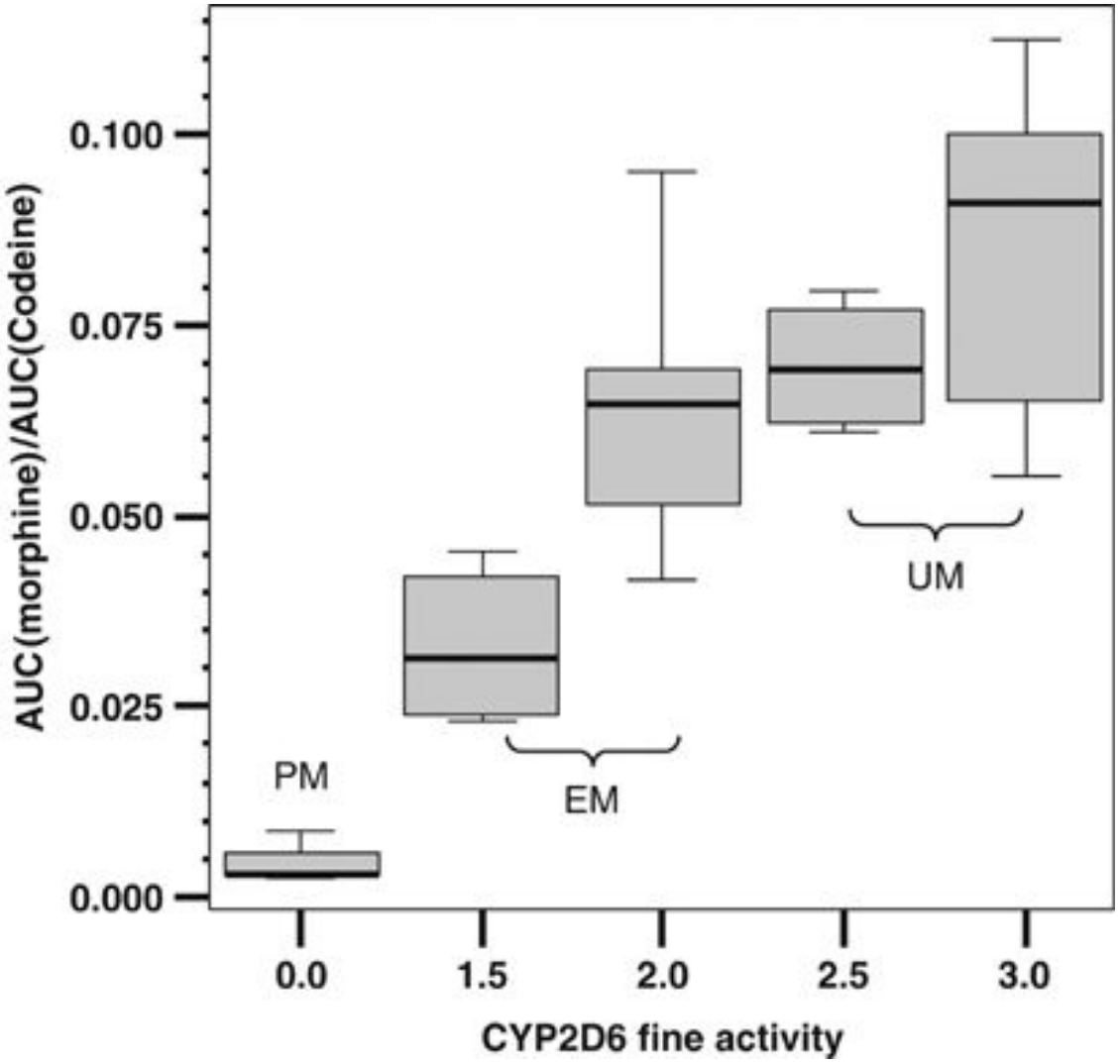


- > 80 known CYP2D6 polymorphisms within coding and regulatory regions
  - includes SNPs, InDels, CNVs, and gene conversion events
- > 100 characterized CYP2D6 'star' alleles that can contain multiple polymorphisms
- Genotype analysis requires both SNP genoptyping and CNV analysis



life technologies

CYP2D6 and codeine

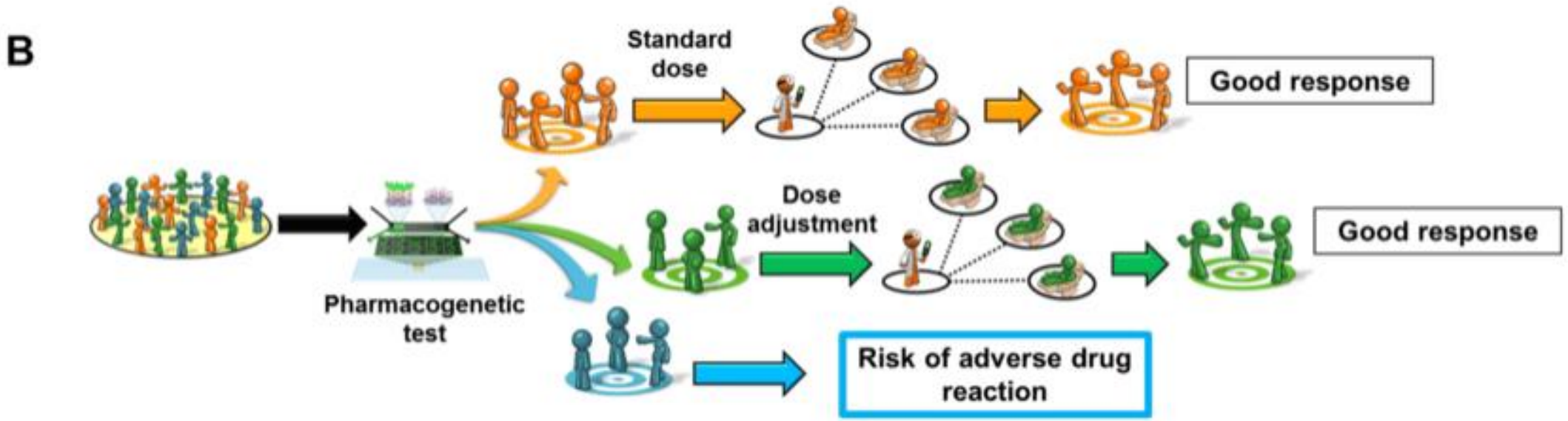


Death of 3 children in 2012

Ultrametabolizers who take codeine may end up with 50% more morphine in their bodies than the average person taking the same dose

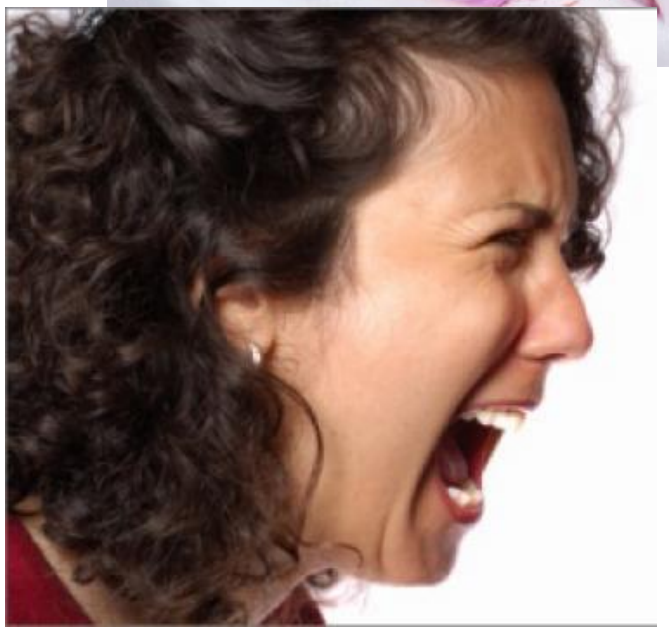
Kirchheiner 2007

Pharmacogenetic dream



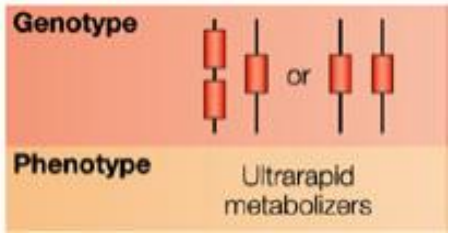
You just performed a cesarean section…

24 hours later…



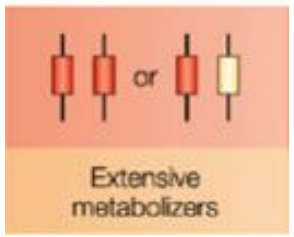
What may have happened?

24 hours later…



codeine → **morphine**

At least one baby has died from this in real life.



codeine → morphine

Clinical Pharmacogenetics Implementation Consortium

Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (*CYP2D6*) diplotypes

Likely phenotype[a]	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (~77–92% of patients)	1.0–2.0[b]	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	**1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10*
Intermediate metabolizer (~2–11% of patients)	0.5[b]	An individual carrying one reduced-function and one nonfunctional allele	**4/*10, *5/*41*
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*

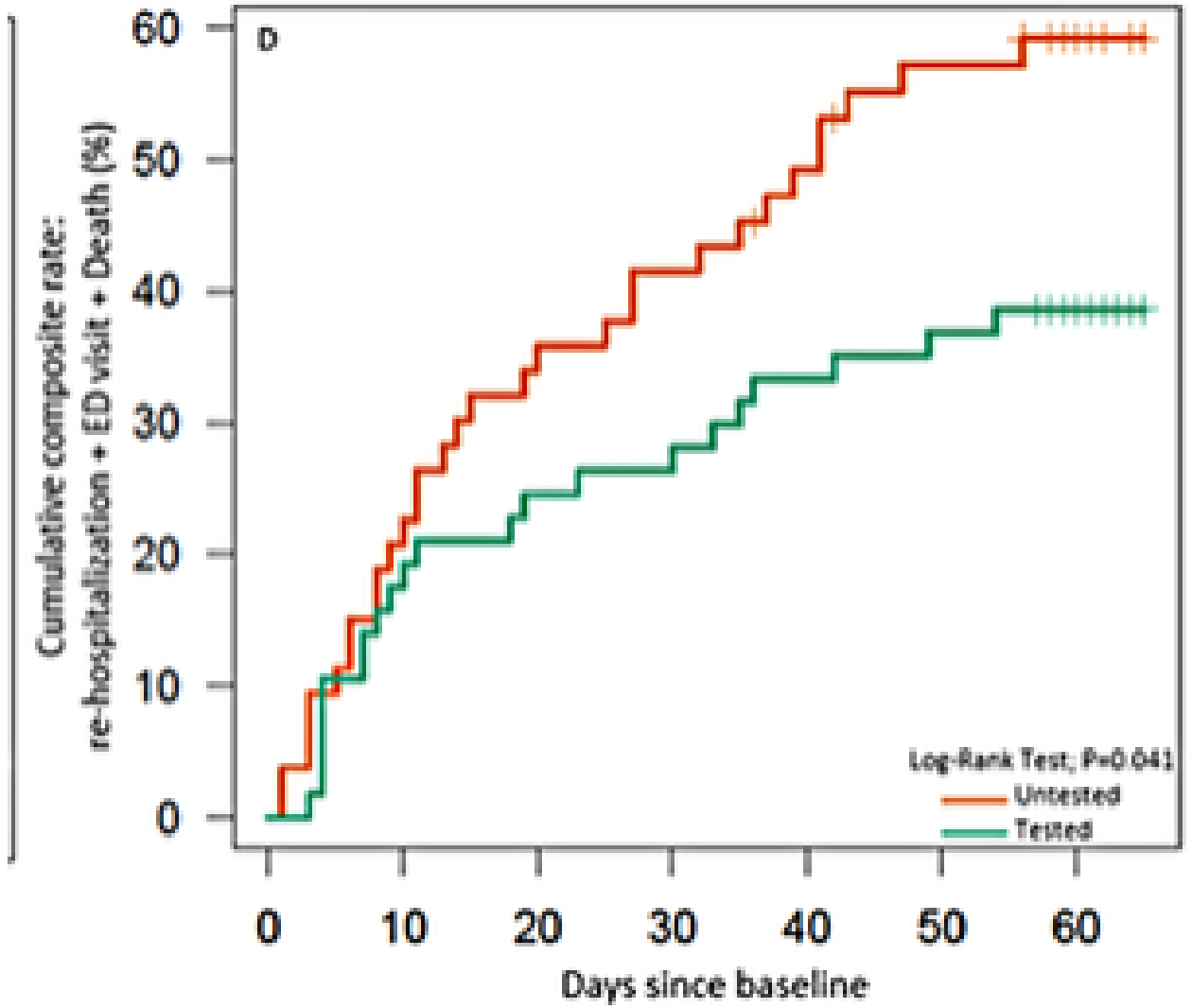
[a]The frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See **Supplementary Data** online for estimates of phenotype frequencies among different ethnic/geographic groups. [b]Note that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and those with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.[12]

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0170905

Pharmacogenetic testing is safer



CPIC

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

CPIC®
Clinical Pharmacogenetics Implementation Consortium

CPIC

HOW not WHETHER

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Cytochrome P450 family

Common theme: **Detoxification** of endogenous and environmental compounds. (hormones, drugs, carcinogenic compounds in food, plant chemicals).

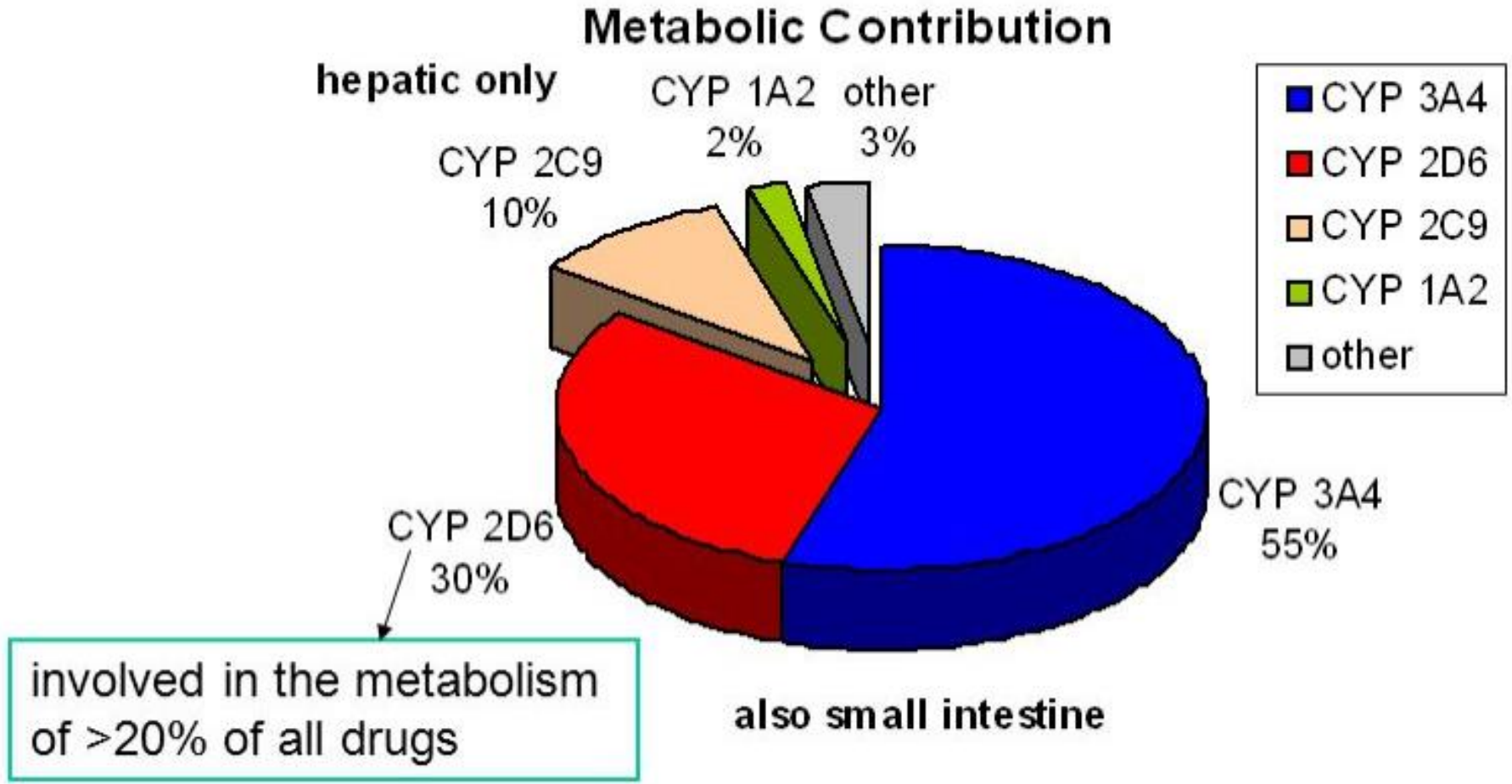
One original cytochrome P450 from 2 billion years ago that has duplicated and divided into 14 families.

The recent 'burst' in new P450 genes appears to be the result of animal-plant warfare.

Induction of expression by environmental exposures.

Cytochrome P450 Enzymes (IV)

The metabolism of endogenous substances (xenobiotics) is carried out predominately by CYP 3A4, CYP 2D6, and CYP 2C9.



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Annotated Drugs

657

Curated Pathways

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Clinical Guideline Annotations

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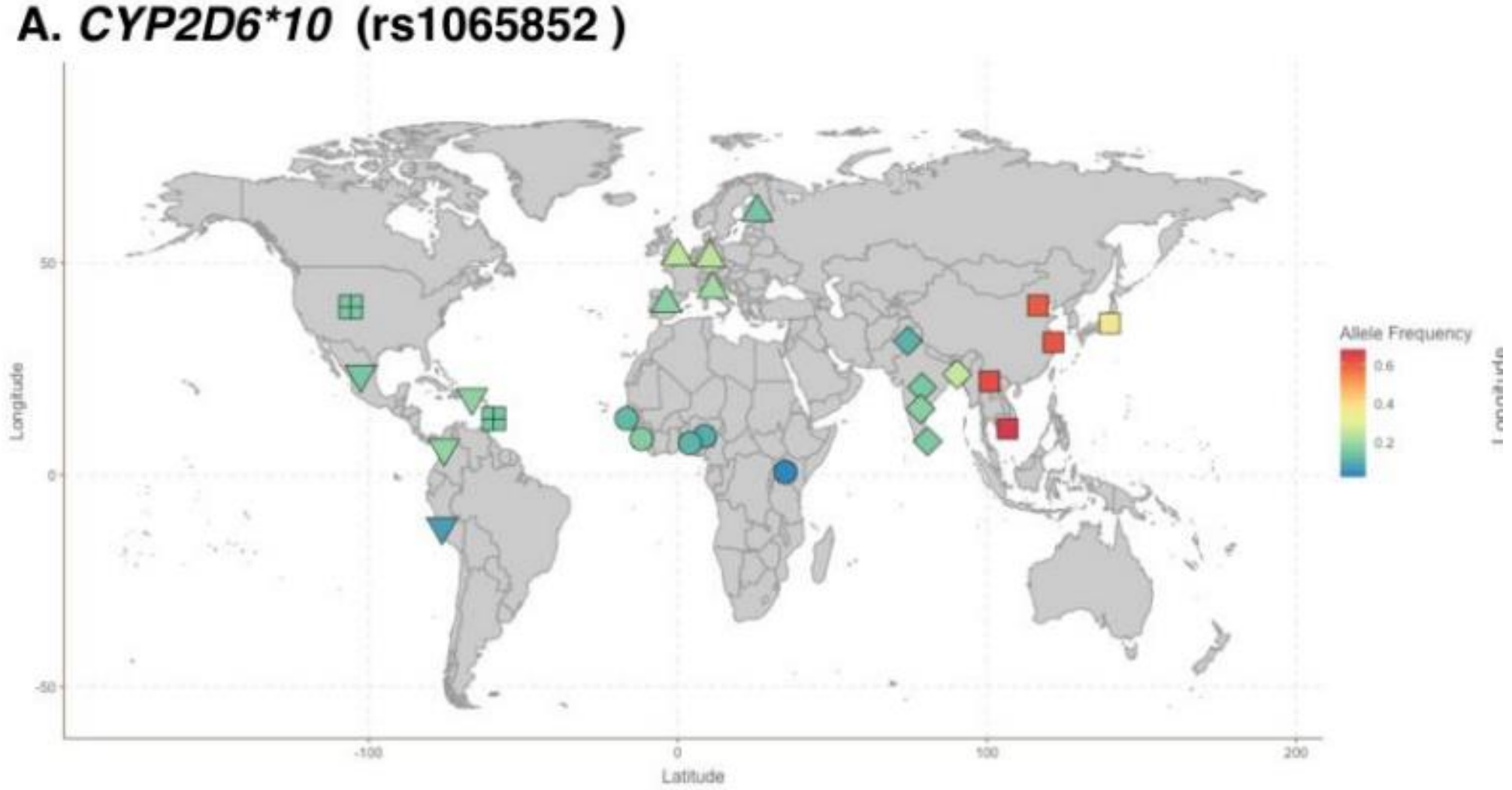
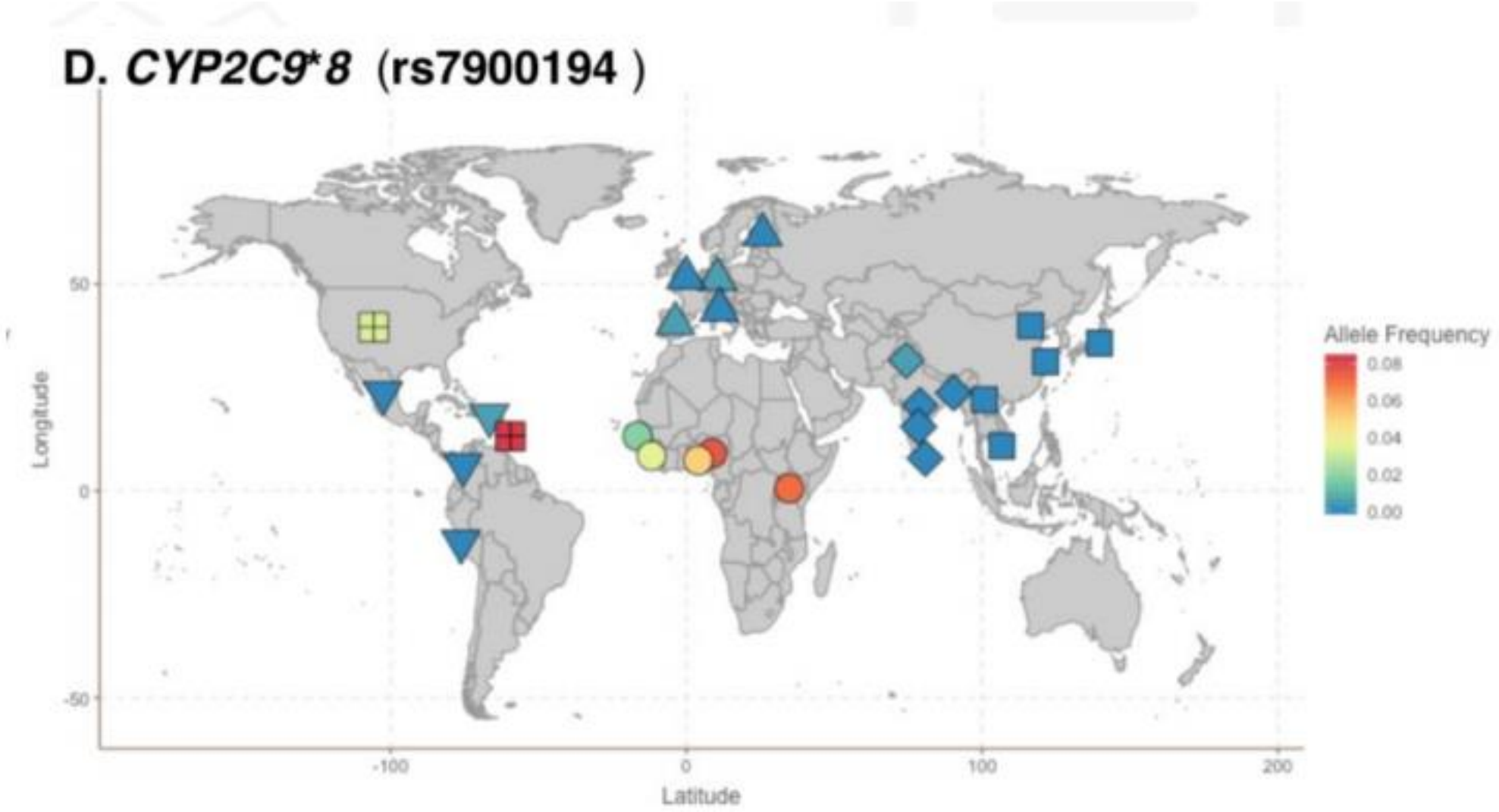
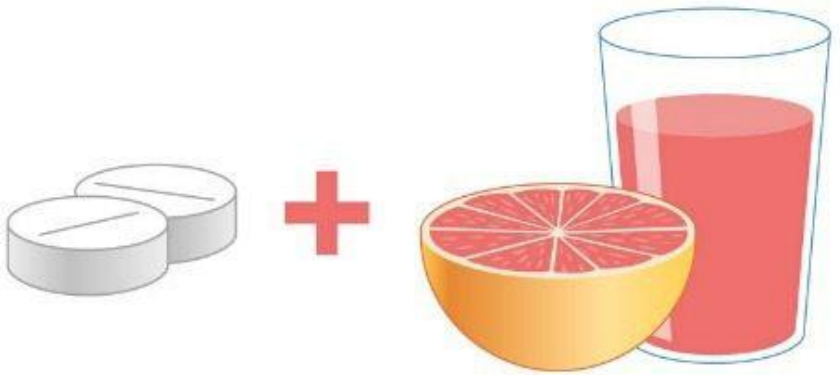
Cytochrome P450s and genetic variation

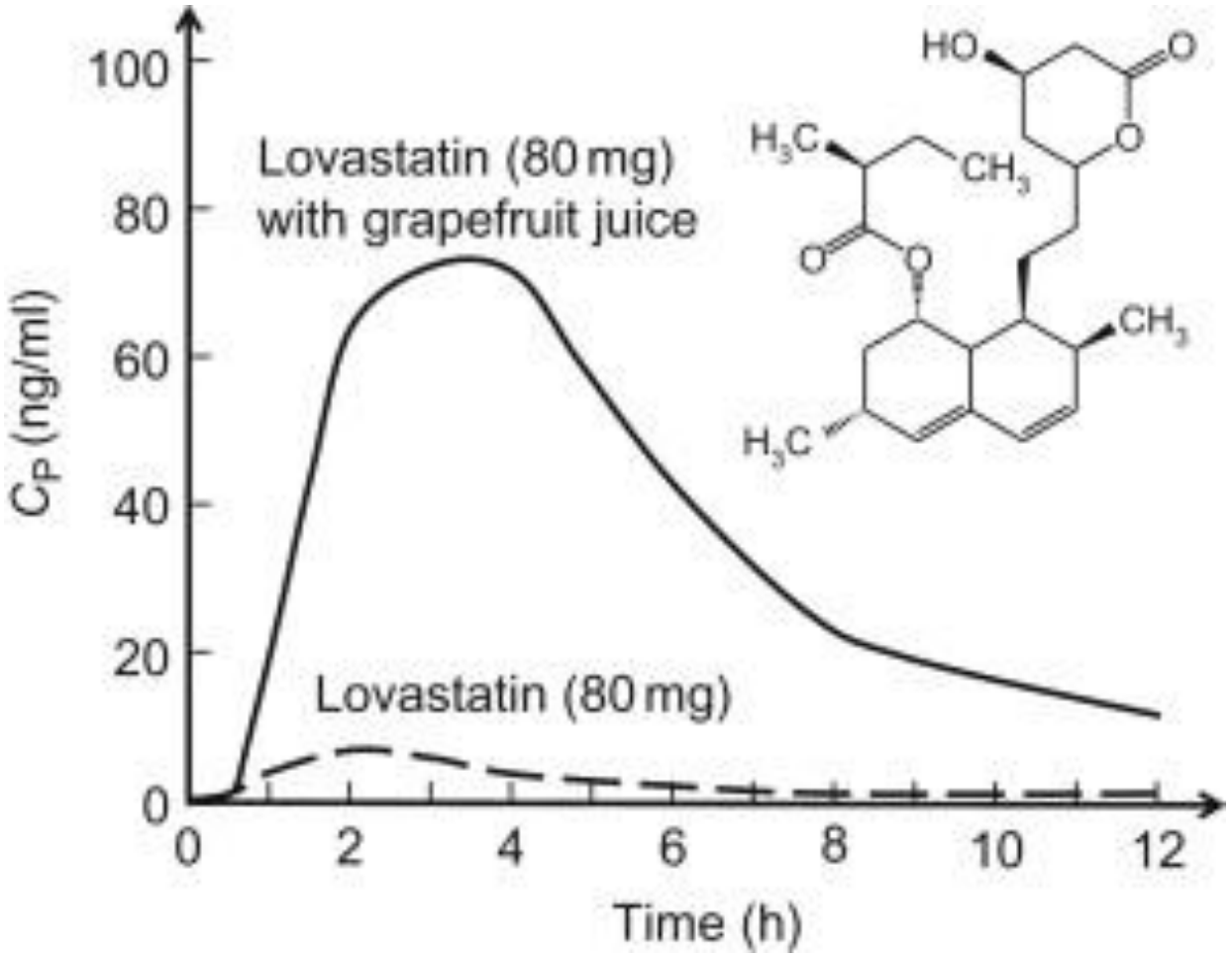


Cytochrome P450s and genetic variation



Grapefruit and CYP3A4 inhibition





What type of pharmacogenetic metabolizer group does this mimic?

Types of pharmacogenetic variation

Metabolizer enzymes (like the Cytochrome P450s)

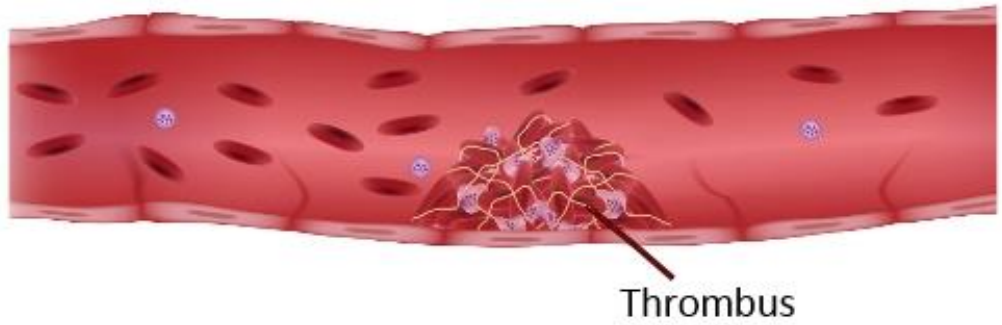
Transporter proteins (control flow of molecules through membranes)

Allergic reactions (like abacavir and HLA-B*15:02 hypersensitivty)

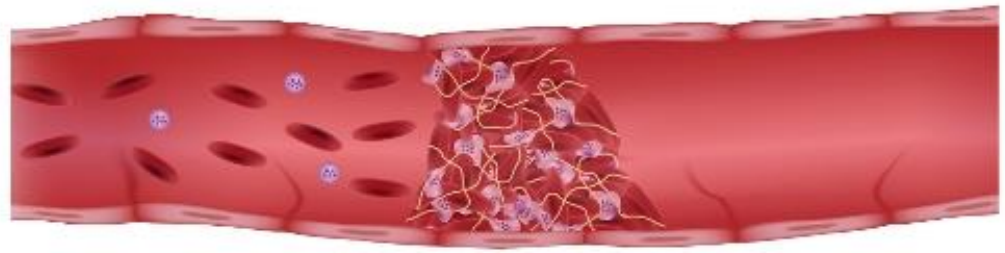
Pharmacodynamic effects (the mechanism of action like ivacaftor in cystic fibrosis)

Warfarin (Coumadin) - anticoagulant

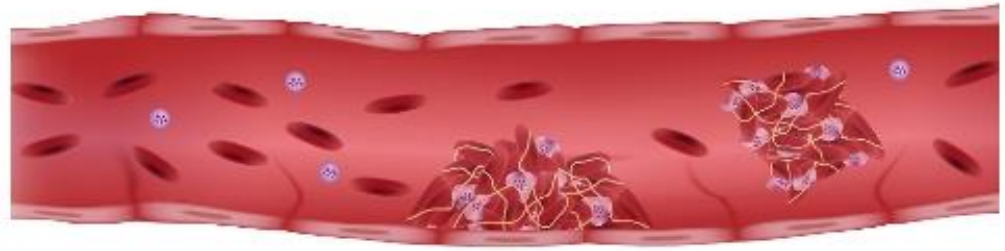
Thrombus causing partial obstruction



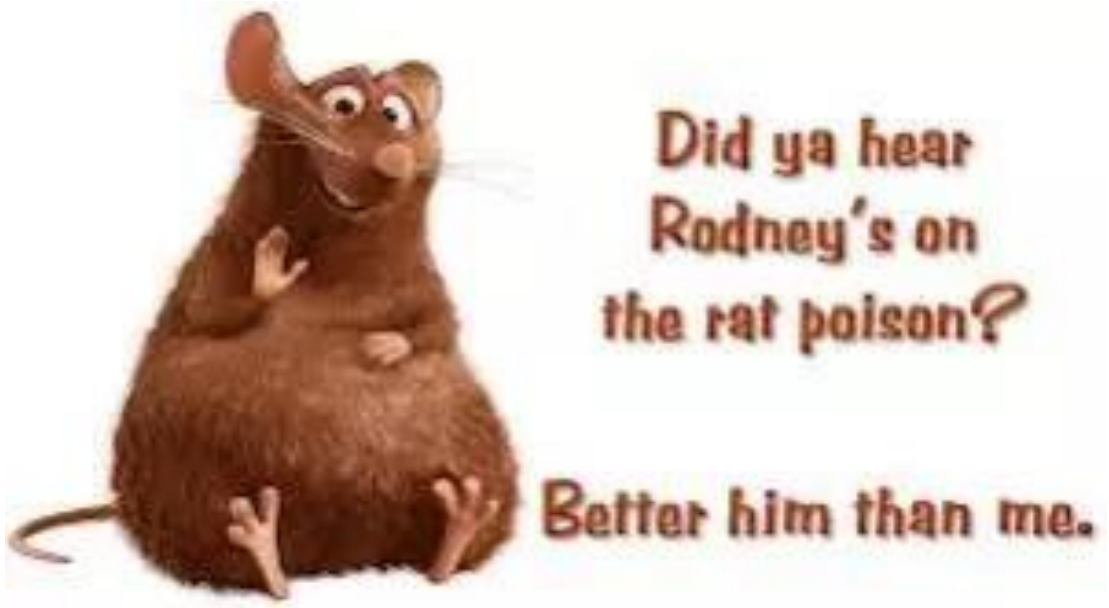
Thrombus causing total obstruction



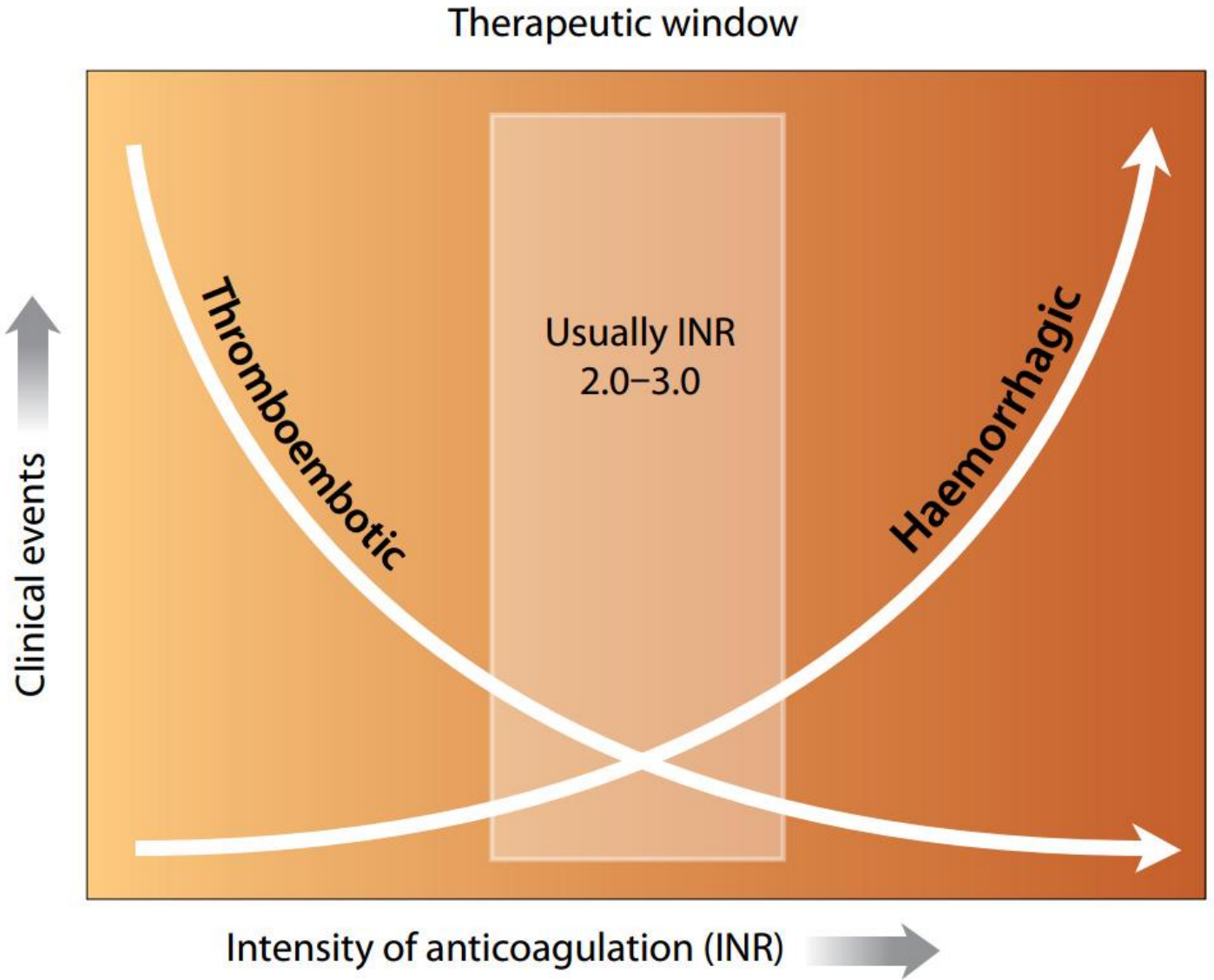
Thrombus travels, embolus

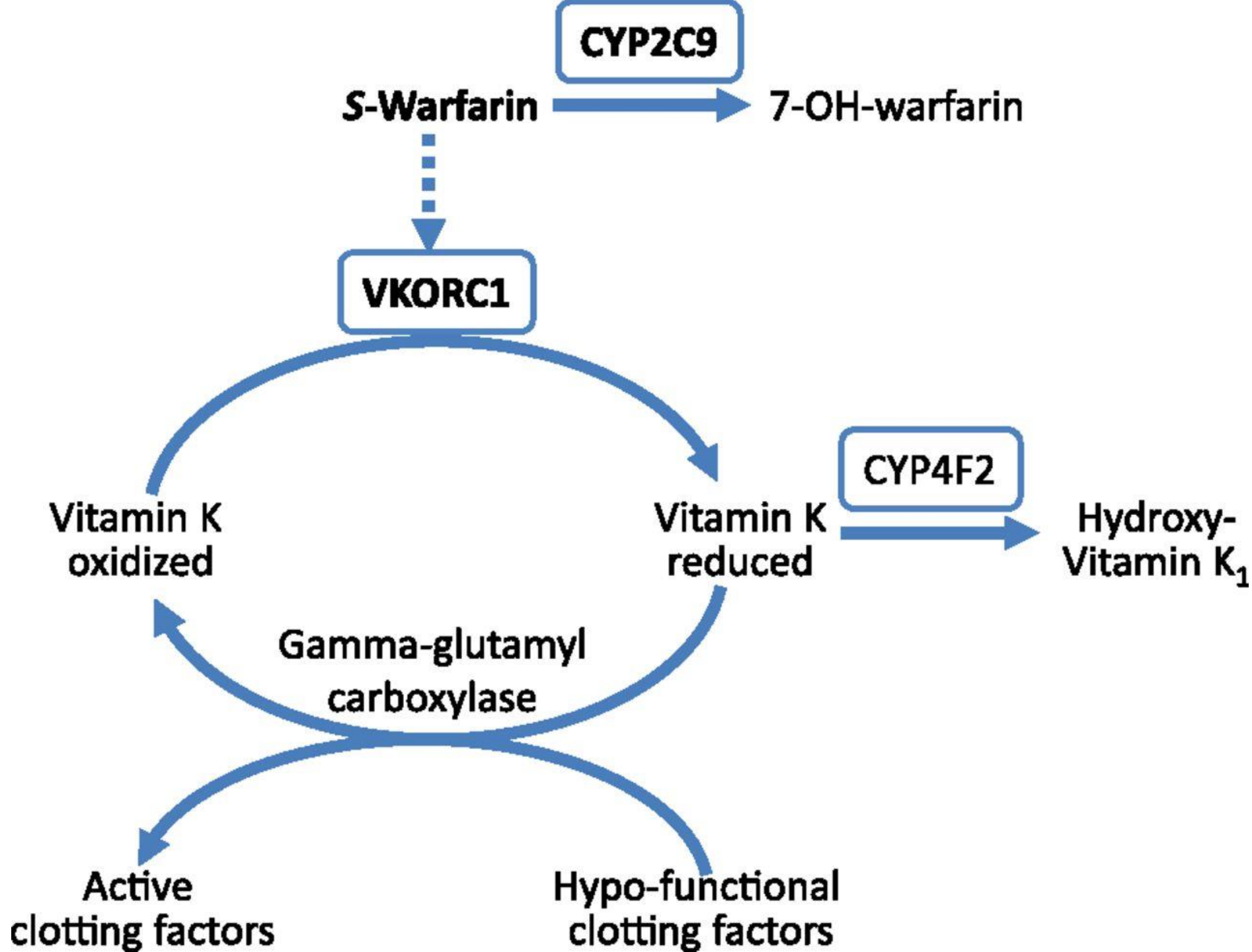


Warfarin (Coumadin) - anticoagulant

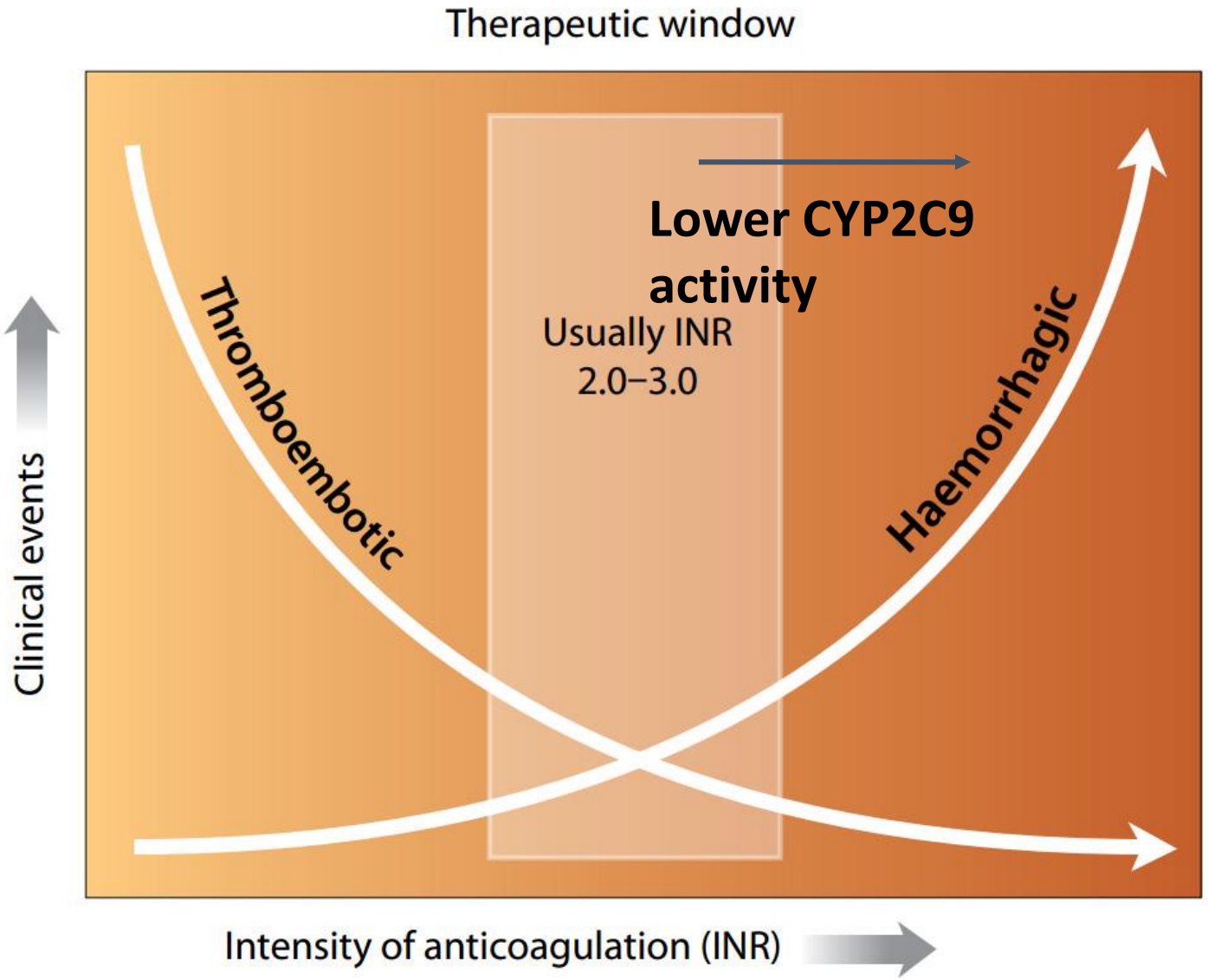


Narrow therapeutic window




CYP2C9
S-Warfarin
7-OH-warfarin
VKORC1
Vitamin K
oxidized
Vitamin K
reduced
CYP4F2
Hydroxy-
Vitamin K1
Gamma-glutamyl
carboxylase
Active
clotting factors
Hypo-functional
clotting factors

Narrow therapeutic window



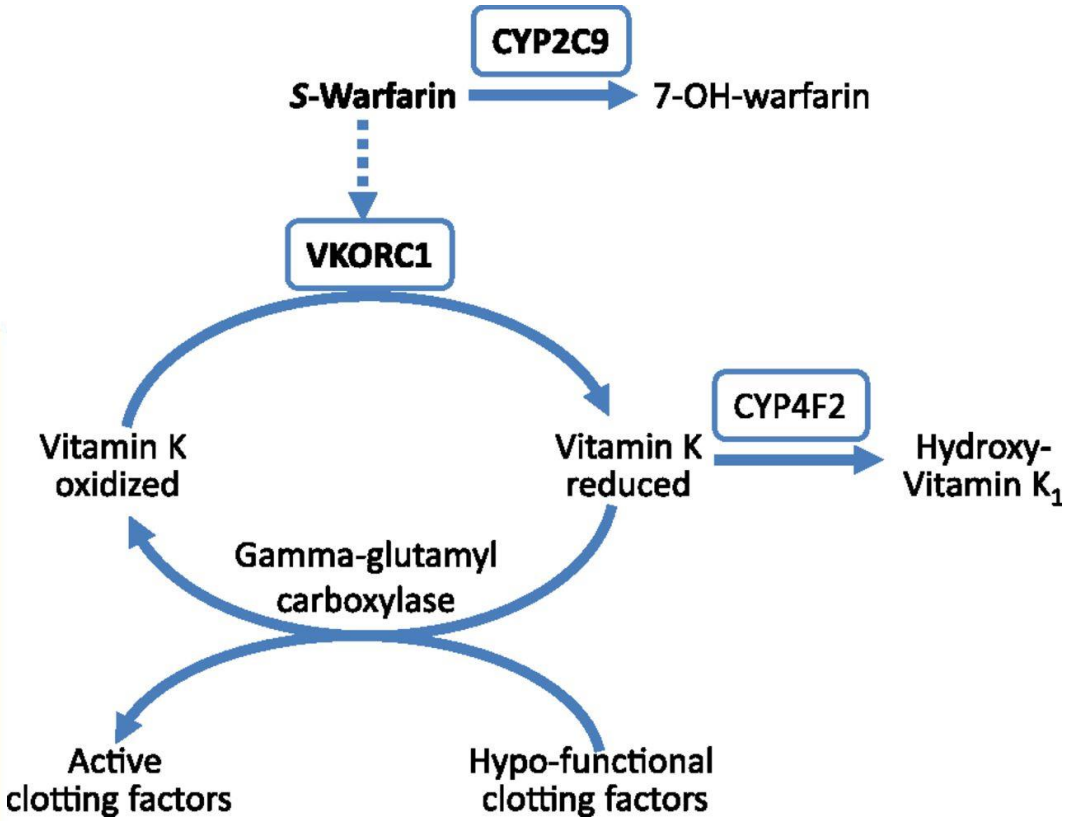
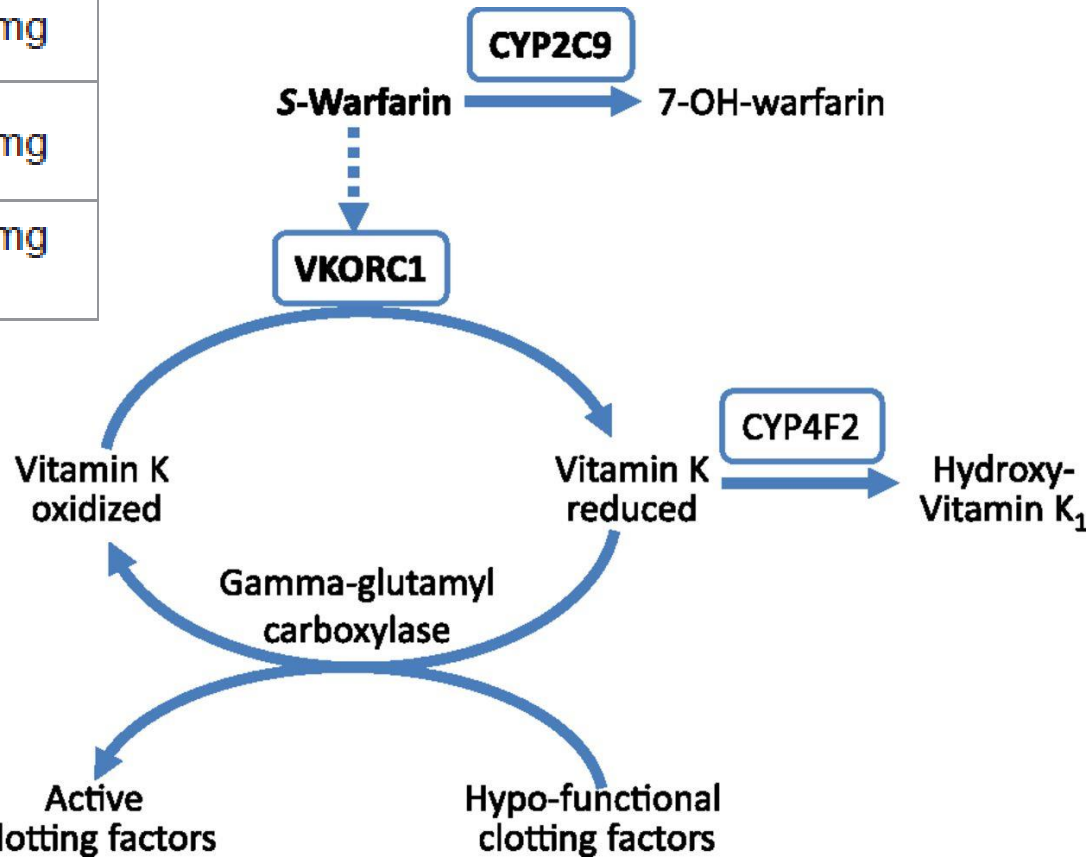


Table vs Algorithm. Genetics and warfarin dose

	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
VKORC1						
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
GA	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg



Genetic variation and warfarin dose in Caucasians

The CYP2C9*2 and CYP2C9*3 alleles explain **12%** of dose variability.

Two SNPs in VKORC1 explain **30%** of dose variability.

How we can get these values of proportions explained?

http://www.bloodjournal.org/content/113/4/784?sso-checked=true

Warfarin daily dose algorithm (Caucasian only)

Coefficients	Estimate	Standard error	*P*
Intercept	9.468	0.118	$< 2 \times 10^{-16}$
VKORC1 rs9923231 A/G	−0.901	0.049	$< 2 \times 10^{-16}$
rs9923231 A/A	−2.018	0.067	$< 2 \times 10^{-16}$
CYP2C9 *1/*1 (no *2 or *3 variant)	0		
*1/*2	−0.508	0.058	$< 2 \times 10^{-16}$
*1/*3	−0.975	0.070	$< 2 \times 10^{-16}$
*2/*2	−1.102	0.197	3.0×10^{-8}
*2/*3	−1.747	0.203	$< 2 \times 10^{-16}$
*3/*3	−3.400	0.330	$< 2 \times 10^{-16}$
Age, y	−0.036	0.001	$< 2 \times 10^{-16}$
sexF	−0.276	0.046	4.2×10^{-9}
Interaction × number of drugs that increase INR†	−0.069	0.018	.001

Warfarin daily dose algorithm (Caucasian only)

Variants don't all do the same thing!

Coefficients	Estimate	Standard error	*P*
Intercept	9.468	0.118	$< 2 \times 10^{-16}$
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*2/*2	−1.102	0.197	3.0×10^{-8}
*2/*3	−1.747	0.203	$< 2 \times 10^{-16}$
*3/*3	−3.400	0.330	$< 2 \times 10^{-16}$
Age, y	−0.036	0.001	$< 2 \times 10^{-16}$
sexF	−0.276	0.046	4.2×10^{-9}
Interaction × number of drugs that increase INR†	−0.069	0.018	.001

CYP2C9 variation globally

Frequencies[a] of *CYP2C9* alleles in major race/ethnic groups[b]

CYP2C9 allele[c]	African Allele Frequency	African American Allele Frequency	Caucasian (European + North American) Allele Frequency	Middle Eastern Allele Frequency	East Asian Allele Frequency	South/Central Asian Allele Frequency	Americas Allele Frequency	Oceanian Allele Frequency
*1[d]	86.420	86.700	80.010	76.910	96.570	78.900	88.920	96.620
*2	2.356	2.304	12.602	13.211	0.064	10.738	6.625	0.882
*3	1.033	1.170	7.083	9.312	3.365	10.165	3.254	2.502
*5	1.231	1.284	0.000	0.067	0.000	0.000	0.500	n/a
*6	0.960	0.772	0.000	0.000	0.000	0.000	0.150	n/a
*8	5.020	6.662	0.143	0.500	0.000	0.100	0.338	n/a
*11	2.700	1.386	0.167	0.000	0.003	0.100	0.213	n/a

pharmGKB allele frequency tables

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Knowledge of variant function

CYP2C9*3		PV00539	42614A>C (I359L)		decreased function
CYP2C9*3.001	CYP2C9*3A	PV00058	-1911T>C, -1885C>G, -1537G>A, -981G>A, 42614A>C (I359L), 50298A>T	Lim	Kidd et al. 1999 Shintani et al. 2001 Romkes et al. 1991 Haining et al. 1996 Sullivan-Klose et al. 1996 Aithal et al. 1999 Takanashi et al. 2000 Blaisdell et al. 2004 King et al. 2004
CYP2C9*3.002	CYP2C9*3B	PV00057	-1911T>C, -1885C>G, -1537G>A, -1188T>C, -981G>A, 42614A>C (I359L), 50298A>T	Def	deposited by Gaedigk et al Shintani et al. 2001 Blaisdell et al. 2004 King et al. 2004
CYP2C9*4		PV00540	42615T>C (I359T)		possibly decreased
CYP2C9*4.001	CYP2C9*4	PV00024	42615T>C (I359T)	Lim	Imai et al. 2000
CYP2C9*5		PV00541	42619C>G (D360E)		possibly decreased
CYP2C9*5.001	CYP2C9*5	PV00025	-1188T>C, 42619C>G (D360E)	Def	deposited by Gaedigk et al Dickman et al., 2001 Allabi et al. 2004 Allabi et al. 2005
CYP2C9*6		PV00542	10601delA (273frameshift)		no function
CYP2C9*6.001	CYP2C9*6	PV00027	10601delA (273frameshift)	Lim	Kidd et al. 2001 Allabi et al. 2004 Allabi et al. 2005

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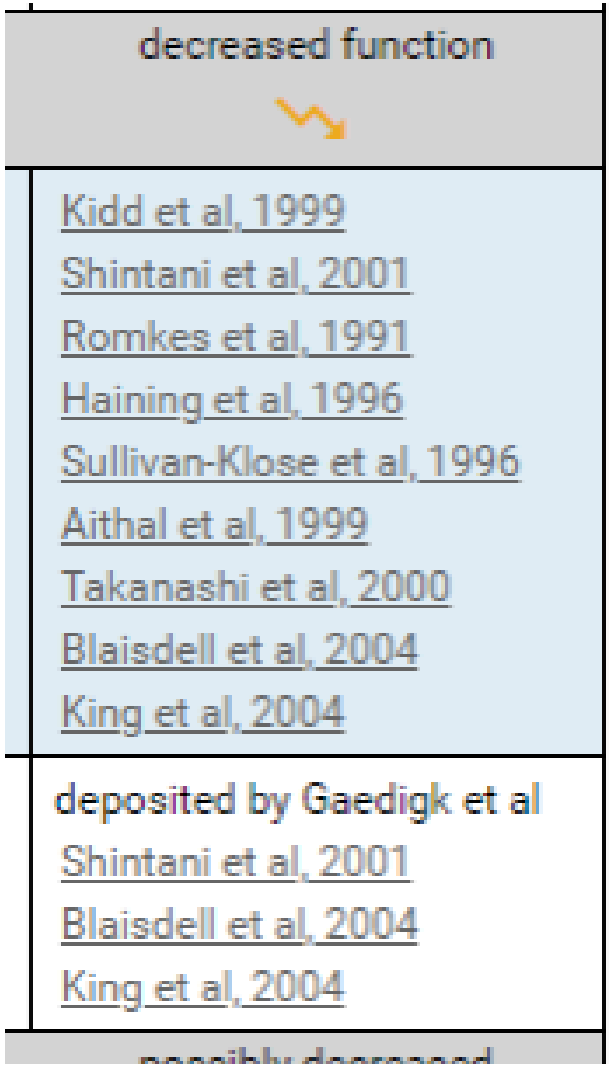
Knowledge of variant function

CYP2C9*3

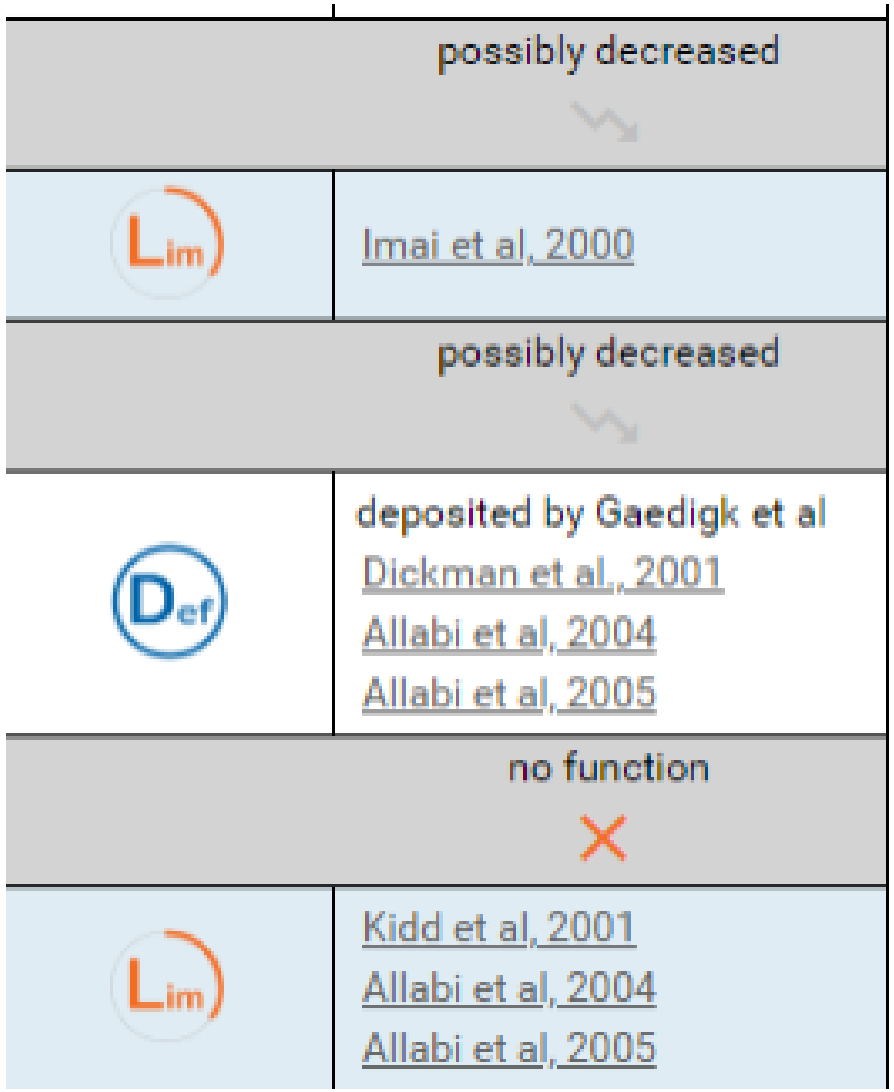


Knowledge of variant function

CYP2C9*4

CYP2C9*5

CYP2C9*6



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VKORC1 More SNPs, more precision?

rs2359612 explained 33.3% ($P = 5.78 \times 10^{-73}$) of dose variability

rs9923231 explained 32.8% ($P = 3.97 \times 10^{-72}$)

Included together, they explain 34% of variability.

Why?

Let’s look up our SNPs on LDpop

https://ldlink.nci.nih.gov/?tab=ldpop

rs9923231 and rs2359612
(use r^2)
Look at CEU, YRI, CHB and JPT.

rs9923231 rs2359612 LD | rs9923231 Allele Frequency | rs2359612 Allele Frequency

rs9923231 rs2359612 LD

Export LD Map

Let’s look up our SNPs on LDpop

https://ldlink.nci.nih.gov/?tab=ldpop

rs9923231 and rs2359612

CEU: 1.0

YRI: 0.13

CHB: 1.0

JPT: 1.0

Let’s look up our SNPs on LDpop

https://ldlink.nci.nih.gov/?tab=ldpop

rs9923231 and rs2359612

CEU: 1.0

YRI: 0.13

CHB: 1.0

JPT: 1.0

In African Americans, *VKORC1* genotype still matters, but results in ½ the effect size as in these other populations

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4513254/

African American as a variable

	β	% Dose change (95% CI)	*P*
Intercept	1.4564	—	—
African American	−0.0992	−9.44 (−13.57 to −5.11)	<.001
Age, y	−0.0068	−0.68 (−0.81 to −0.54)	<.001
BSA, per m^2	0.4219	52.48 (41.3 to 64.55)	<.001
Current smoker	−0.0022	−0.22 (−6.12 to 6.06)	.94
VTE	0.0512	5.26 (0.85 to 9.86)	.02
Amiodarone	−0.2245	−20.1 (−25.11 to −14.76)	<.001
***CYP2C9**2**‖	**−0.1929**	**−17.54 (−21.54 to −13.34)**	**<.001**
*CYP2C9*3*‖	−0.4183	−34.19 (−38.5 to −29.57)	<.001
VKORC1‖	**−0.3016**	**−26.03 (−28.45 to −23.54)**	**<.001**

Summary

- Genetics can change drug response by altering drug target, drug metabolism, and drug transport, and by triggering allergies. Using genetic information can improve toxicity and efficacy of drugs.
- These variants only matter when faced with an external substance.
- Frequencies of variants vary greatly across the world.
- Genetic tests can inform treatment but are based incomplete information (complex biological systems and limited understanding of functional effects of variants).