Friday	8:30-9:15	**Sara/Alie**	Journal Club	Benonisdottir, S et al. "Epigenetic and genetic components of height regulation"
	9:15-10:00	**Alie**	Bioethics and Implementation	PPV, NPV, sensitivity, specificity, principles of bioethics
	10:30-12:00	**Sara**	Gene-Environment Interactions	Definitions, methods, practical issues
	1:30-2:15	**Alie**	Pharmacogenetics	Pathways and analysis
		Sara	Mendelian Randomization	Concept, methods
	2:15-3:00			
	3:30-4:30	**Sara**	Risk prediction	Methods, applications
	4:30-5:00	**Alie/Sara**	Wrap-up	

Pharmacogenetics

Section 12

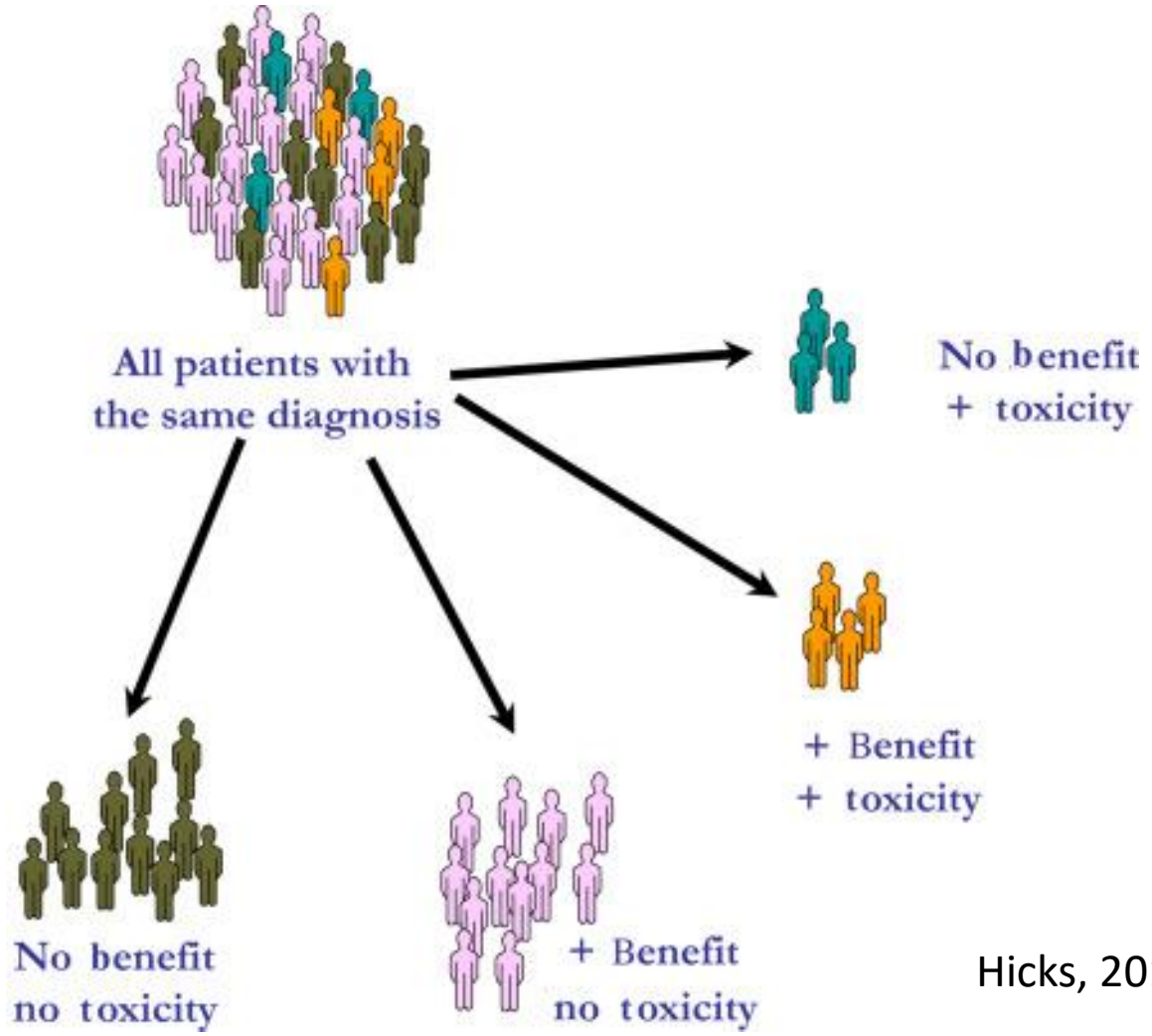
(45 minutes)

Learning objectives

- Describe the ways genetic variation can affect drug response.
- Place odds ratios in the context of population impact.
- Interpret genotyping results to make a pharmacogenetic recommendation.

What is pharmacogenetics?

- How genetic variation affects drug and xenobiotic response, including therapeutic effect and adverse events (side effects).
- GlaxoSmithKline executive, “90% of drugs only work in 30-50% of people”
- Cornerstone of precision medicine. “Right drug, right dose, right time”.

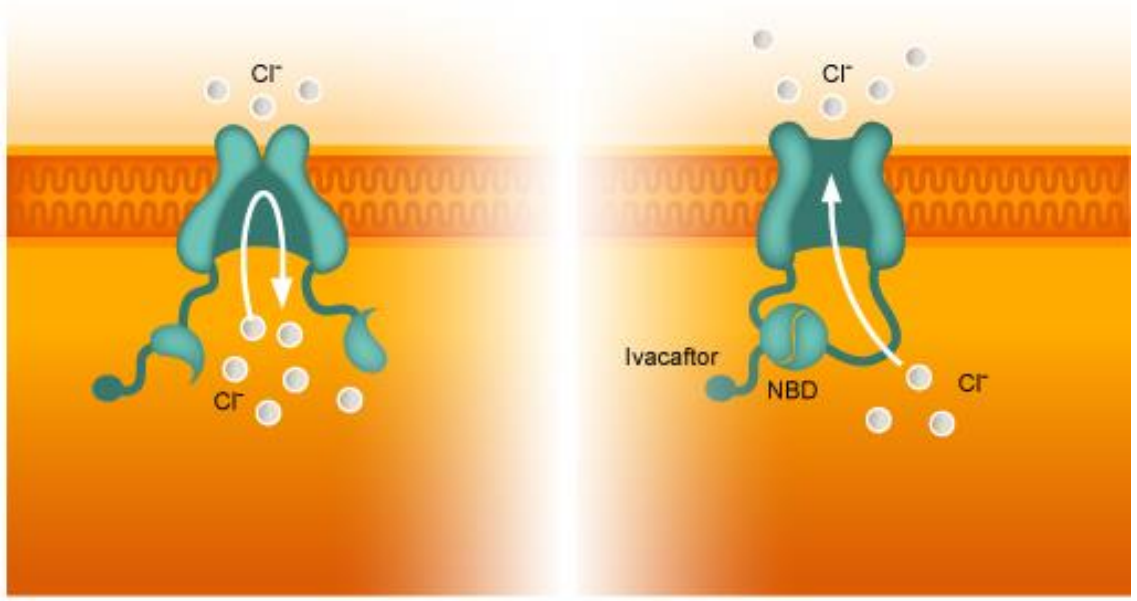


Hicks, 2017

Classes of pharmacogenetics

- Drug target

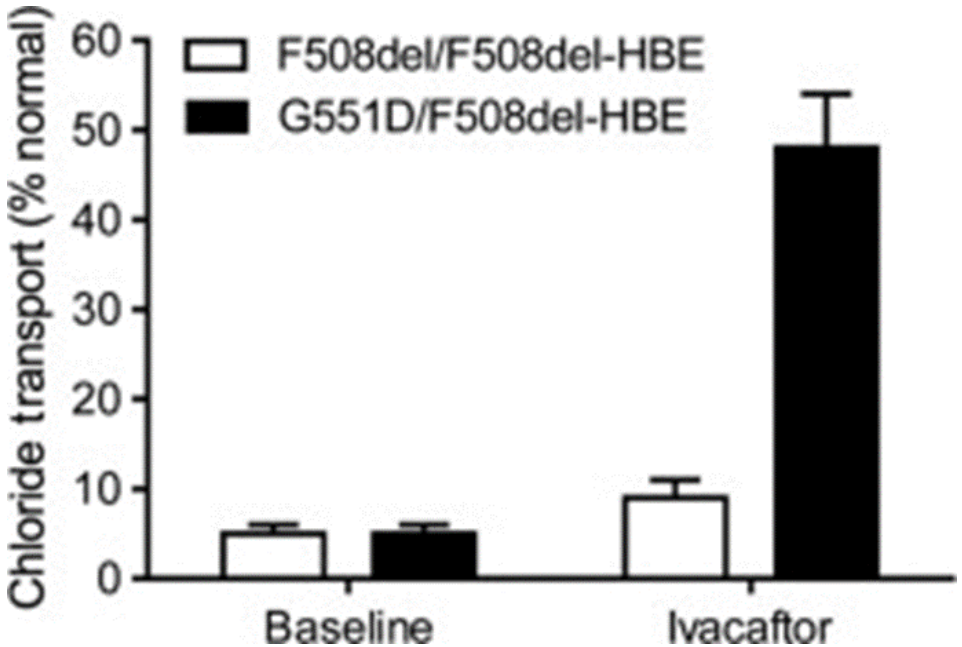
Example – Ivacaftor (Kalydeco)



G551D Mutation - Class III gating defect

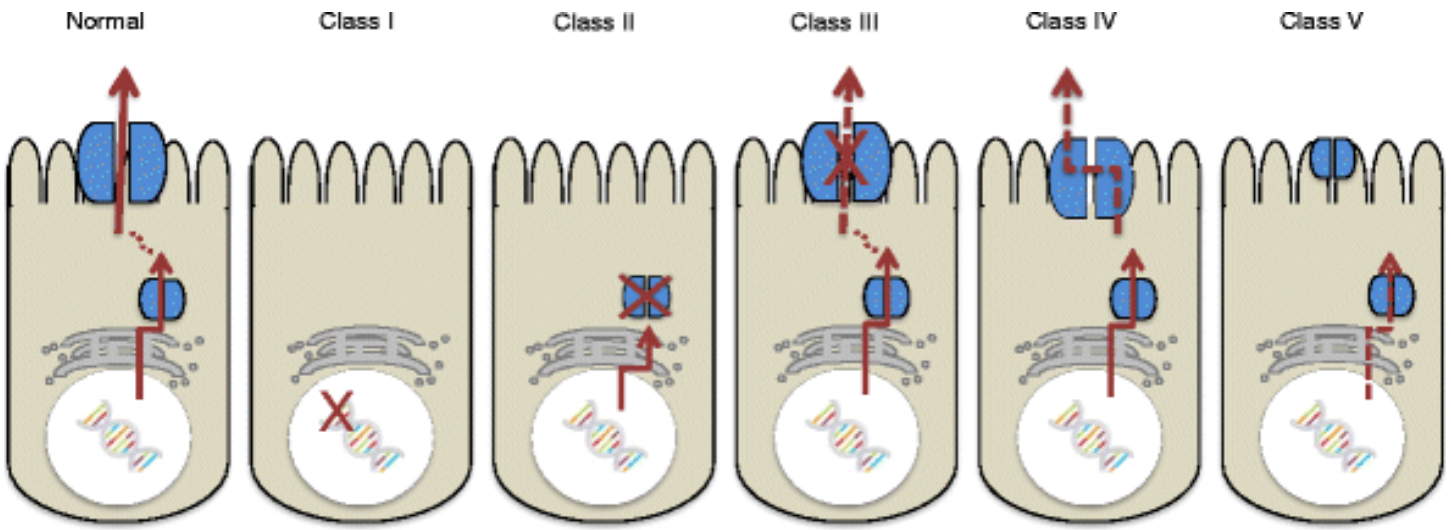
G551D mutation defect reversed with ivacaftor

- Ivacaftor “potentiates” CFTR protein on the cell surface that cannot activate to transport chloride ions
- Ivacaftor only works in people who specific CFTR variants (5% of total cystic fibrosis).



Example – Ivacaftor (Kalydeco)

- FDA approved ivacaftor only for specific variants (class III and class IV).
- First FDA approval process to allow molecular data to expand approval.



Phenotype	No synthesis	Reduced trafficking	Reduced gating	Decreased conductance	Reduced synthesis
Mutation	Nonsense, frame-shift or splicing mutations prevent CFTR biosynthesis	CFTR is mis-processed in the ER, leading to an absence of functional protein at the cell membrane	CFTR protein reaches the cell membrane, but once there is unstable	CFTR protein reaches the cell membrane but abnormal conformation of the pore leads to disrupted ion flow	Reduced amount of CFTR protein at the cell surface due to reduced protein synthesis
Genotype	G542X	F508del	G551D	R117H	A455E

Koivula 2016

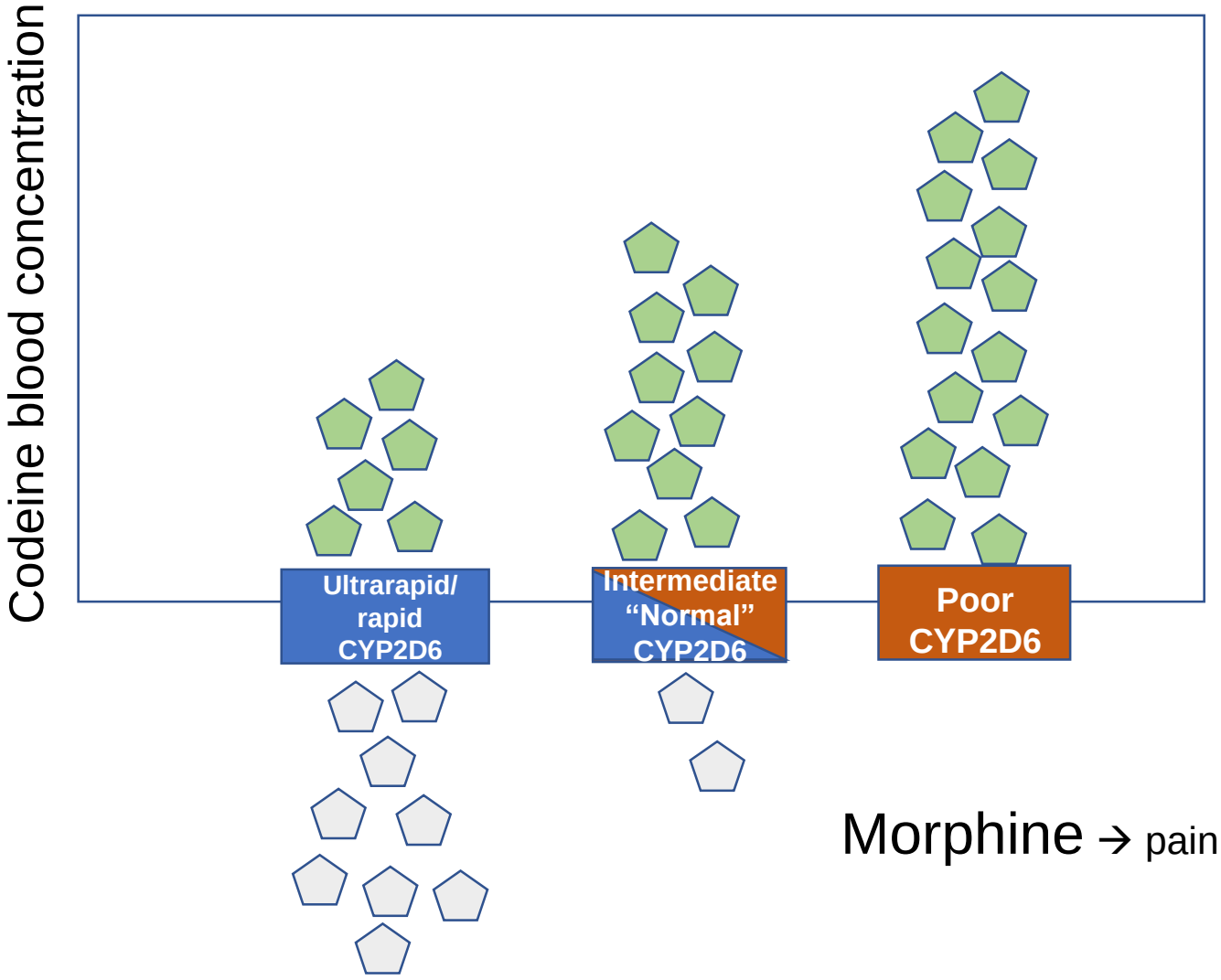
Classes of pharmacogenetics

- Drug target
- Drug metabolism

Pharmacogenetic nomenclature

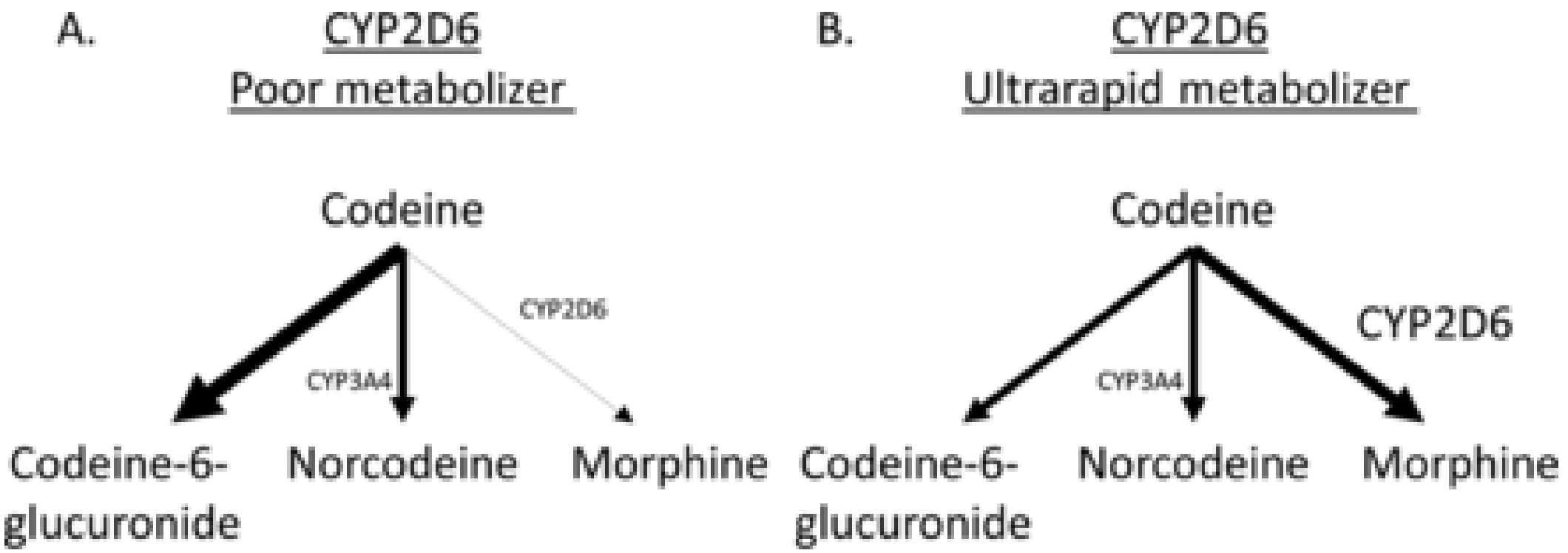
Haplotype	Variants (variant = variants with dbSNP rsID)	Impact	Function	References
CYP2D6*56B	-1426C>T, -1235A>G, -1000G>A, 100C>T, 310G>T, 842T>G, 1038C>T, 1662G>C, 2098A>G, 3202C>T, 3583A>G, 4181G>C	P34S, R344X	no function	Gaedigk et al, 2007
CYP2D6*57	100C>T, 310G>T, 842T>G, 886C>T, 1038C>T, 1662G>C, 3583A>G, 4125G>C, 4129C>G, 4132A>G, 4134T>C, 4156C>T, 4157A>C, 4159G>C, 4165T>G, 4167T>C, 4168G>A, 4169C>G, 4170T>C, 4173C>T, 4181G>C	P34S, R62W, P469A, T470A, H478S, H478S, G479R, F481V, A482S, S486T	no function	Sakuyama et al, 2008 Soyama et al, 2006
CYP2D6*58	-1426C>T, -1235A>G, -740C>T, 214G>C, 221C>A, 223C>G, 227T>C, 232G>C, 233A>C, 245A>G, 310G>T, 842T>G, 1022C>T, 1662G>C, 1864_1865insTTTCGCCCC, 2851C>T, 3385A>C, 3585G>A, 3791C>T, 4181G>C	T107I, 174_175insFRP, R296C, S486T	unknown function	Gaedigk et al(unpublished) Koch et al
CYP2D6*59	1662G>C, 2292G>A, 2851C>T, 2940G>A, 4181G>C	R296C, S486T	decreased function	Marez et al, 1997 Toskano et al, 2006
CYP2D6*60	1888_1889insTA, 2304C>T	S183X	unknown function	Lee et al, 2009
CYP2D6*61	CYP2D6-CYP2D7 hybrid gene; see ReadMe		unknown function	Kramer et al, 2009
CYP2D6*62	4045C>T	R441C	no function	Klein et al, 2007
CYP2D6*63	CYP2D6-CYP2D7 hybrid gene; see ReadMe		unknown function	Kramer et al, 2009
CYP2D6*64	-1426C>T, -1235A>G, -1000G>A, 100C>T, 310G>T, 842T>G, 1022C>T, 1662G>C, 2098A>G, 3583A>G, 4181G>C, 4402C>T	P34S, T107I, S486T	unknown function	Gaedigk et al, 2008

Example – CYP2D6 and Codeine



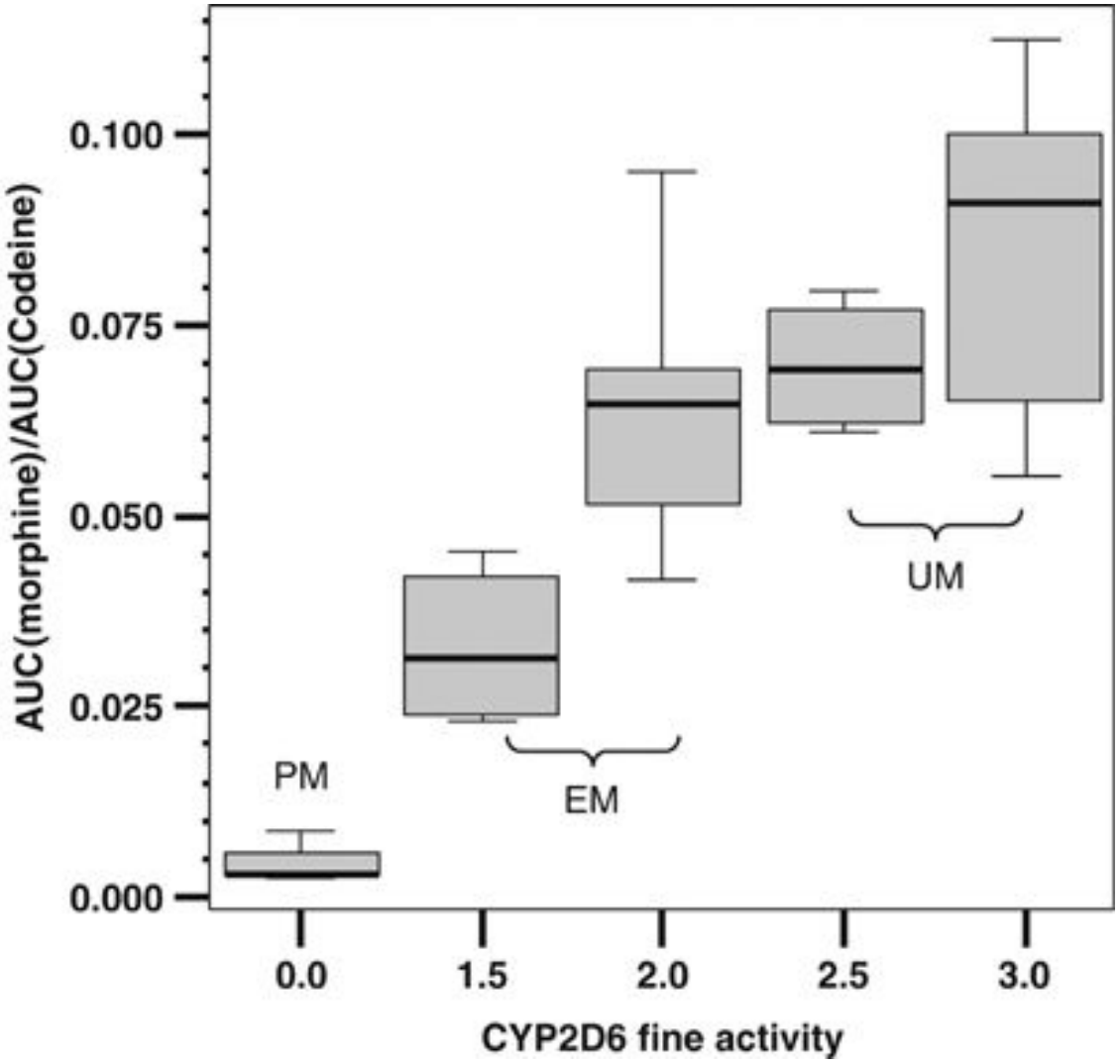
Morphine → pain killing effects

Example – CYP2D6 and codeine



Nerenz, 2017

Example – CYP2D6 and codeine



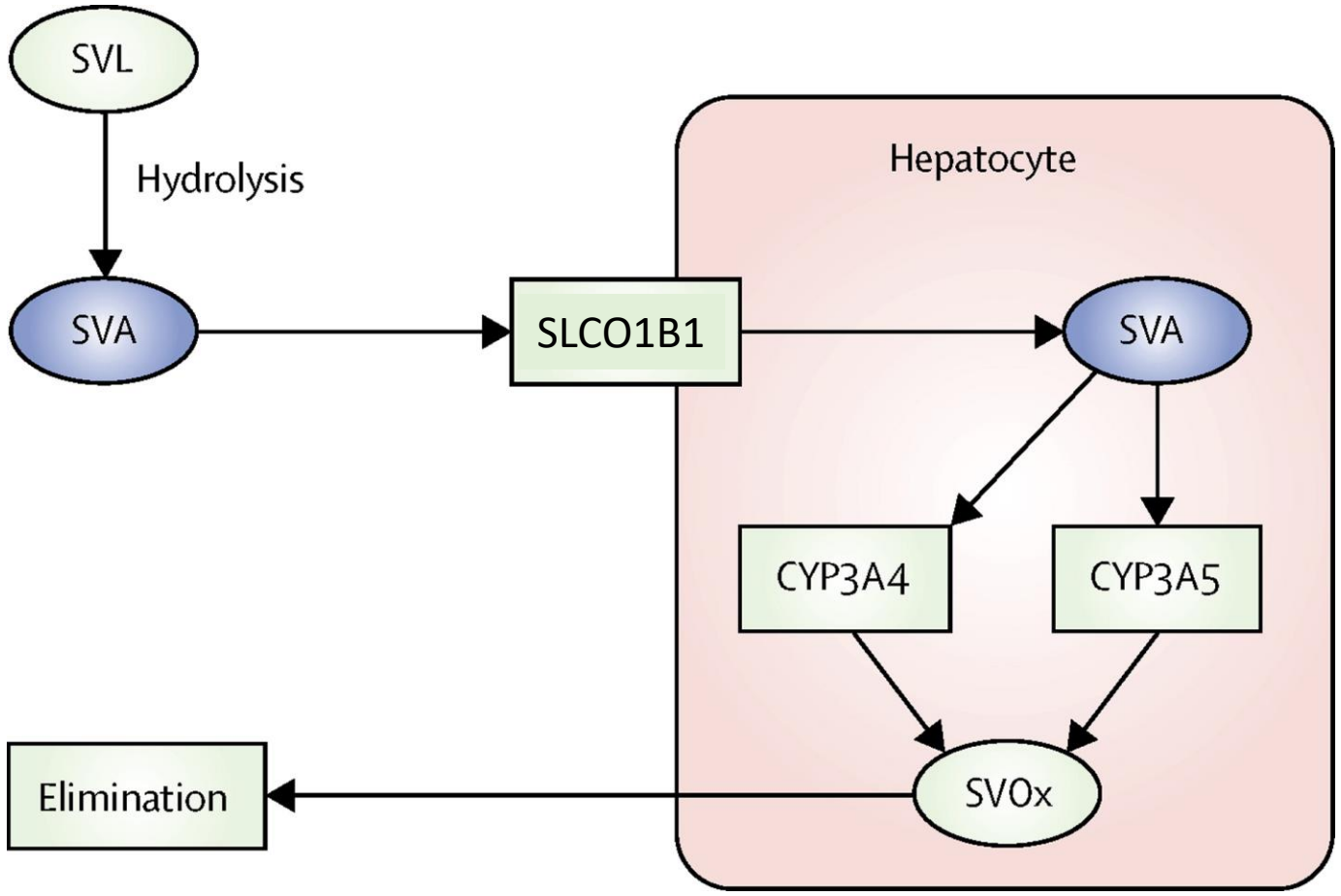
Death of 3 children in 2012

Kirchheiner 2007

Classes of pharmacogenetics

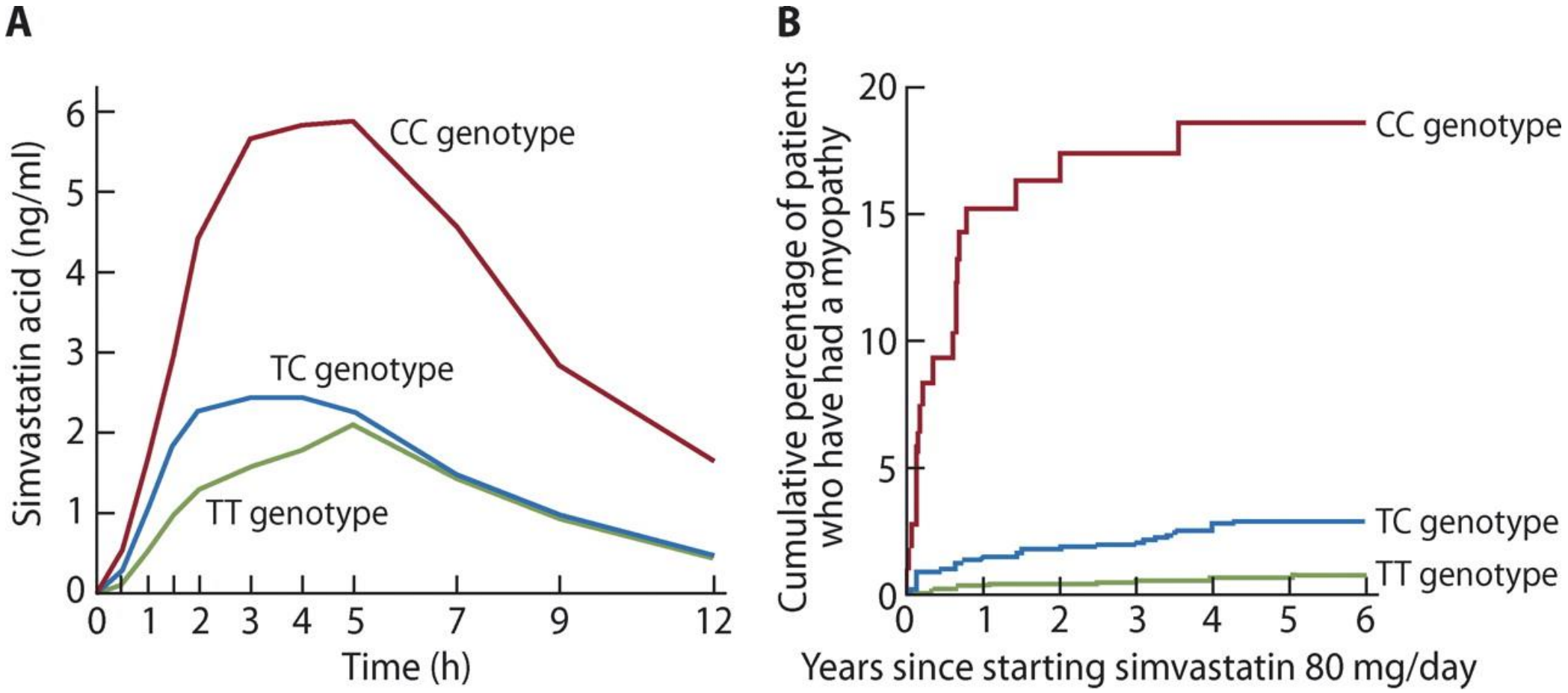
- Drug target
- Drug metabolism
- Drug transport

Example – SLCO1B1 and simvastatin



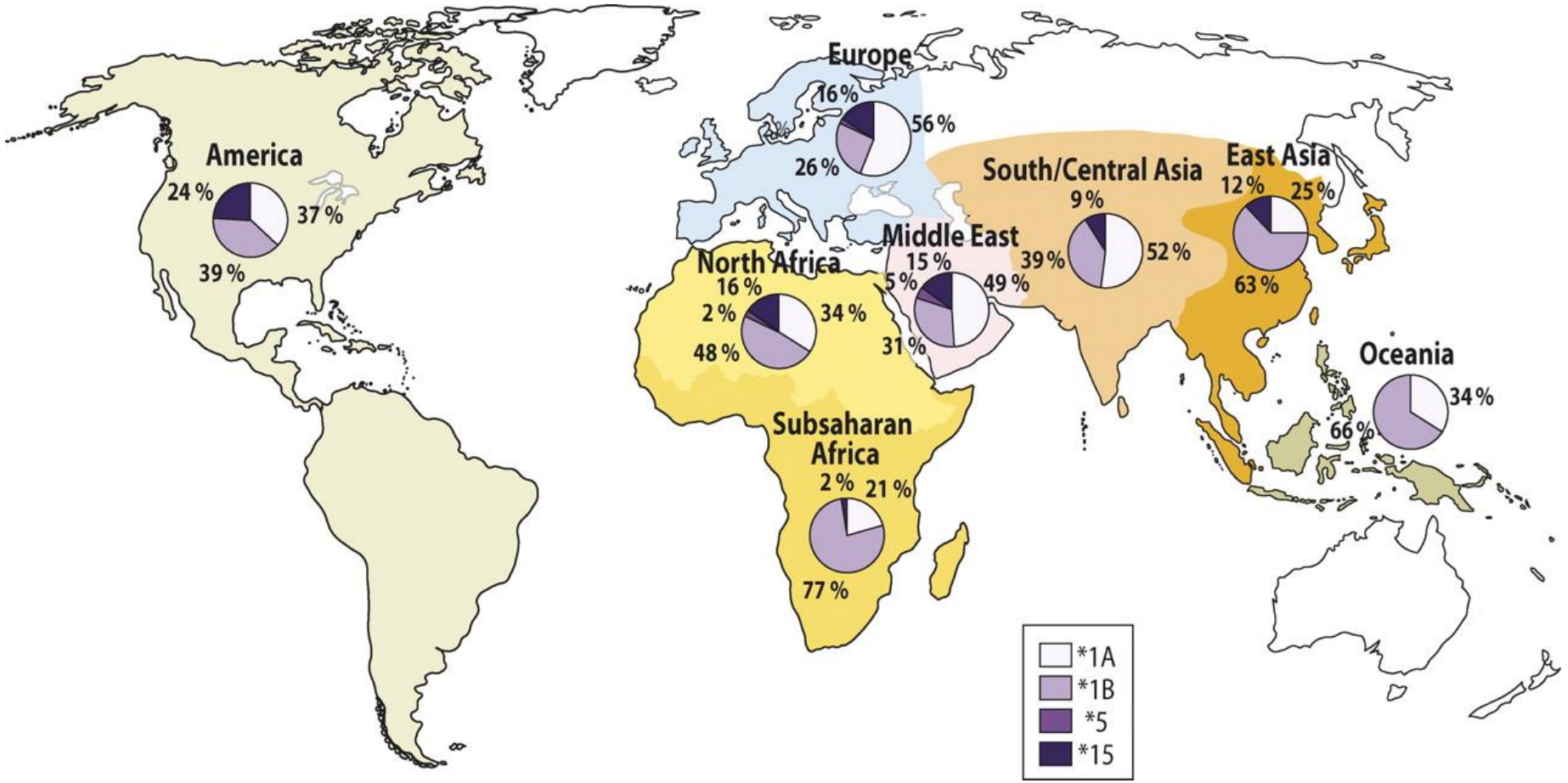
Sadee 2013

Example – SLCO1B1 and simvastatin



Nieme 2011

Global variant frequencies – *SLCO1B1*



Nieme 2011

Compare myopathy in global populations

- OR=4.5 for TC compared to TT at rs4149056
- OR = 16.1 for CC compared to TT at rs4149056
- C allele frequency in African populations: 3%
- C allele frequency in European populations: 15%
- C allele in South/Central American: 20%

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- C allele in South/Central American: 20%

1) Use Hardy Weinberg to calculate expected genotypes in the 3 populations ($p+q = 1$; $p^2 +2pq+q^2 =1$)

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- C allele frequency in African populations: 3%
  - 0.1% CC, 6% TC, 94.1% TT
- C allele frequency in European populations: 15%
  - 2% CC, 26% TC, 72% TT
- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

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2) 2% of TT patients will experience muscle pain. How many people out of 1000 taking simvastatin in each of these populations you would expect to have muscle pain.

Compare myopathy in global populations

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- OR=4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056
- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

	Disease status		
	Muscle pain	No muscle pain	Total
CC	10	30	40
TT	13	627	640
total	23	657	960

640*0.02 = 12.8

$$\text{OR} = \frac{ad}{bc} \qquad 40 = a + b;\ 40 - b = a$$

$$16.1 = \frac{a * 627}{b * 13}$$

$$16.1 = \frac{627(40 - b)}{b * 13} = \frac{25080 - 627b}{b * 13}$$

$$209.3b = 25080 - 627b$$

$836.3b = 25080$

$b = 25080/836.3 = 30$

Compare myopathy in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 taking simvastatin in each of these populations you would expect to have muscle pain.

- OR = 4.5 for TC at rs4149056
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- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

In the South/Central American population,
10 (CC) + 27 (TC) + 13 (TT) = 50 out of 1000
on simvastatin will experience muscle pain.

Compare myopathy in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 in each of these populations you would expect to have muscle pain.

- OR=4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056
- C allele frequency in African populations: 3%
  - 0.1% CC, 6% TC, 94.1% TT

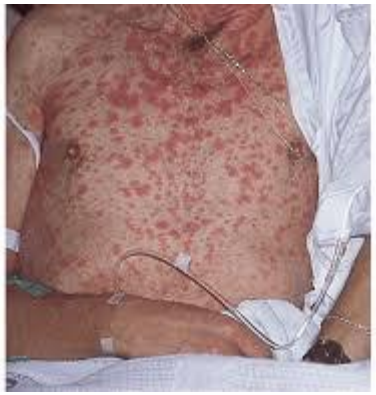
In African populations,
1 (CC) + 5 (TC) + 19 (TT)
25 out of every 1000 patients will experience muscle pain

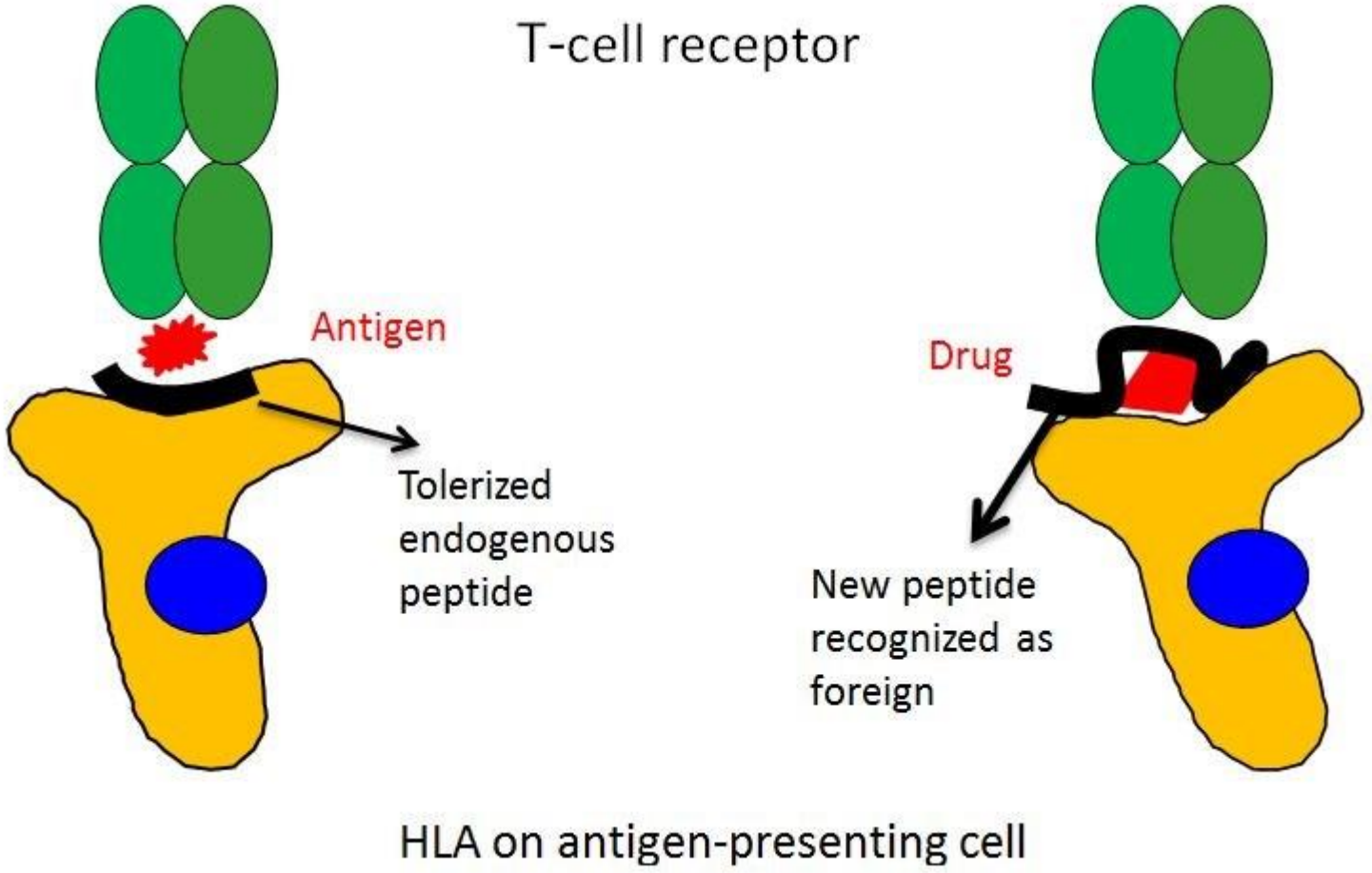
*screening in different populations
*who actually develops muscle pain
*compared to in population not taking simvastatin and impact on study size, implementation

Classes of pharmacogenetics

- Drug target
- Drug metabolism
- Drug transport
- Hypersensitivity/allergy

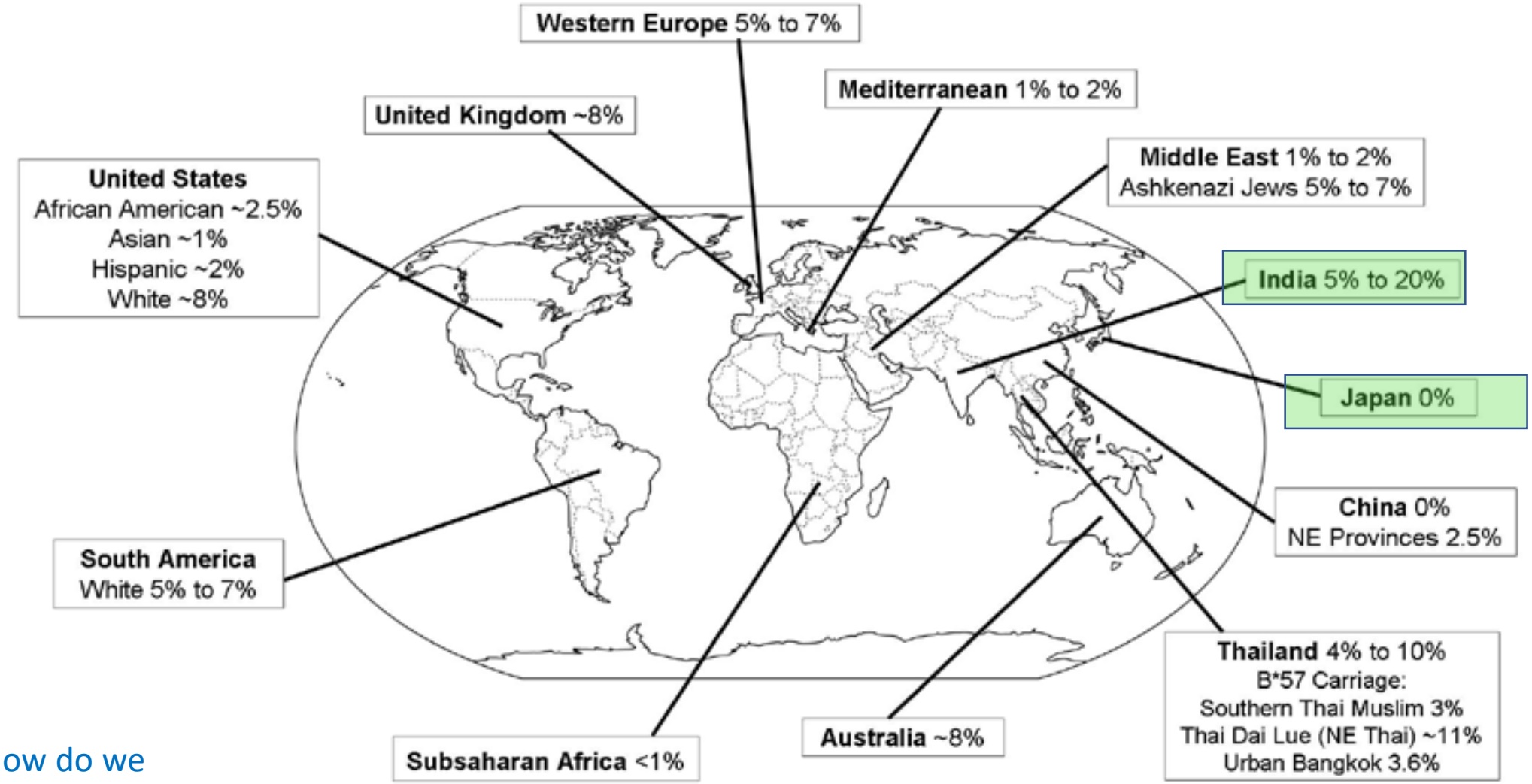
Example – HLA-B and abacavir





Roujeau 2014

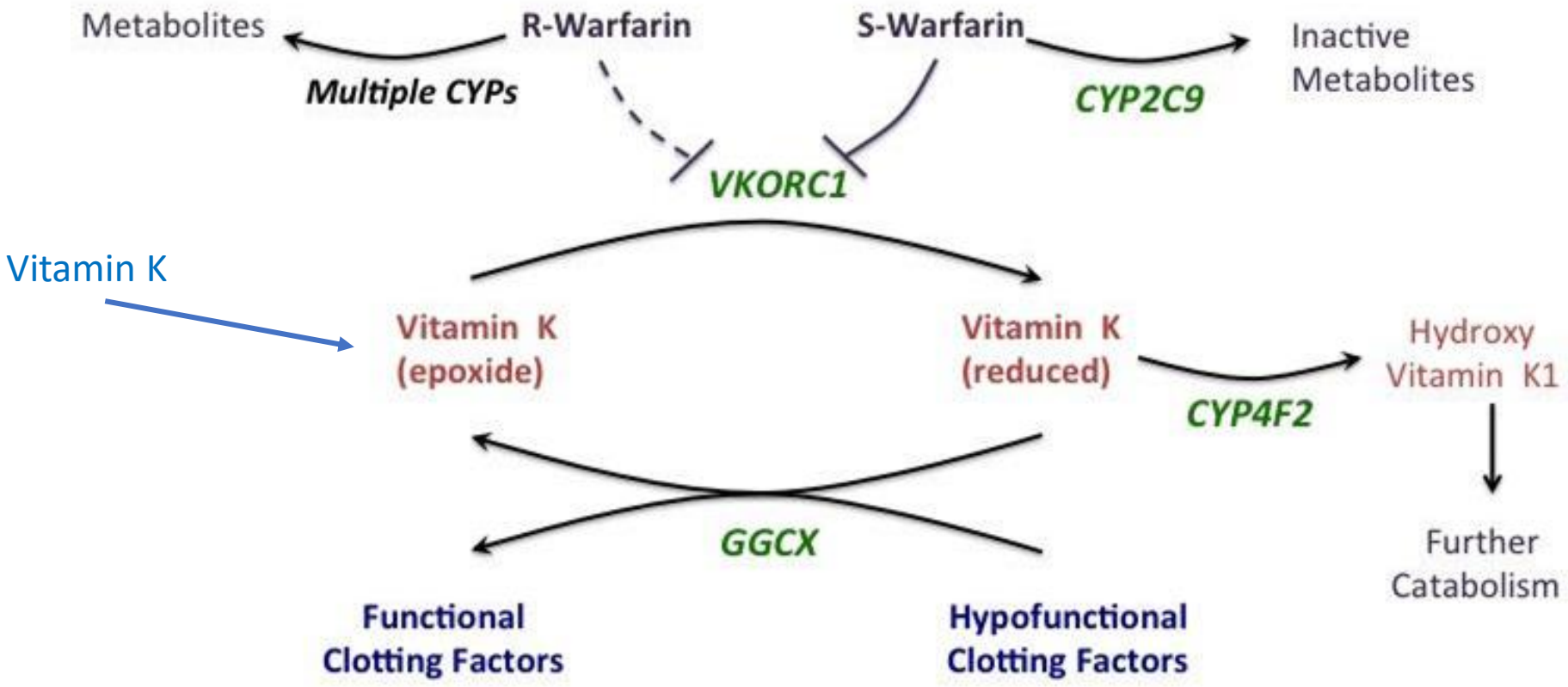
Global Frequency of HLA-B*5701



How do we ethically, effectively target?

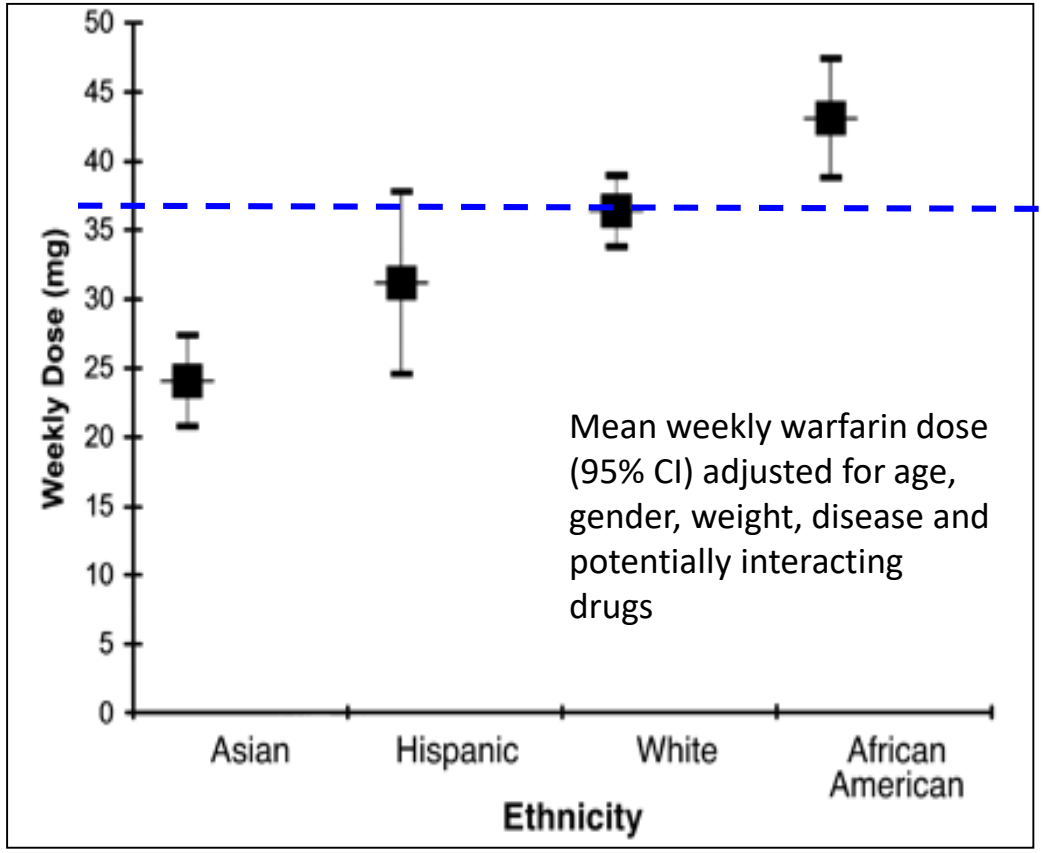
Adapted from David Nolan et al. J HIV Ther. 2003 May;8(2):36-41.

Warfarin response – target and metabolism



Adapted by Allan Rettie and Ken Thummel from Johnson, et al. 2011. “Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing” Clinical Pharmacology and Therapeutics

Ethnic Differences in Warfarin Dose



Average dose worldwide
= 36.4 mg/wk (unadjusted)

Dang et al., *Ann. Pharmacother.* (2005)

Warfarin dose algorithm

Variable†	Regression coefficient
Race (African Americans=1)	−0.08
Age	−0.01
VKORC1 1173 (CT=1)	−0.39
VKORC1 1173 (TT=1)	−0.82
CYP2C9 (any*2=1)	−0.16
CYP2C9 (any*3=1)	−0.30
BMI (less than 25=1)	−0.18
BMI (25 to 30=1)	−0.23
Number of interacting medications	−0.08

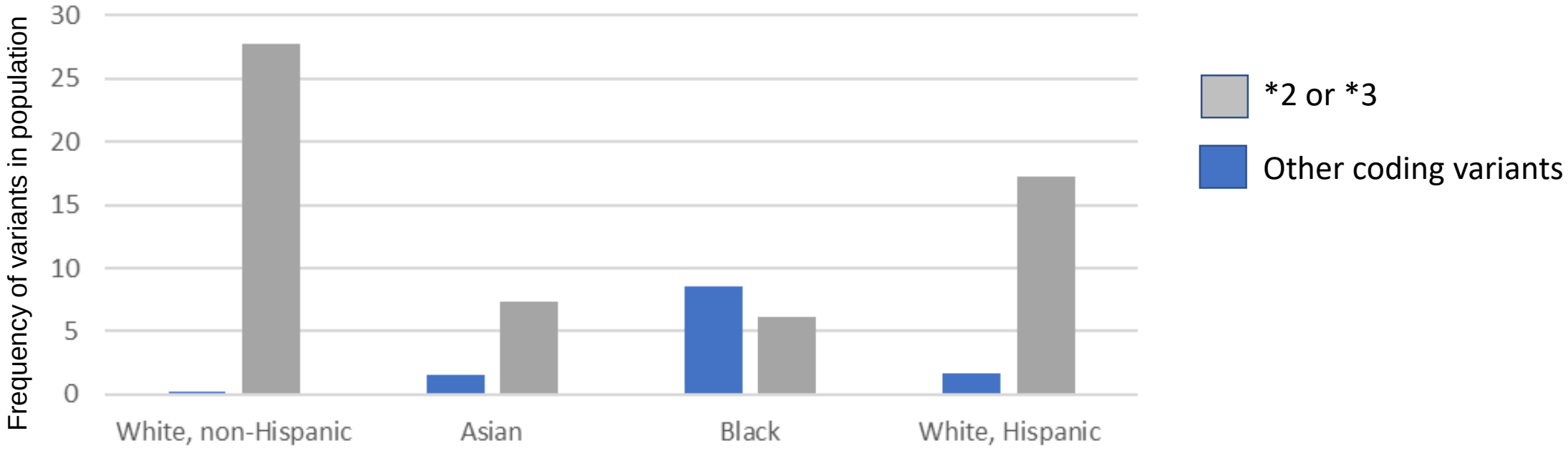
Schelleman. *Clinical pharmacology and therapeutics*. 2008

Warfarin pharmacogenetics clinical utility

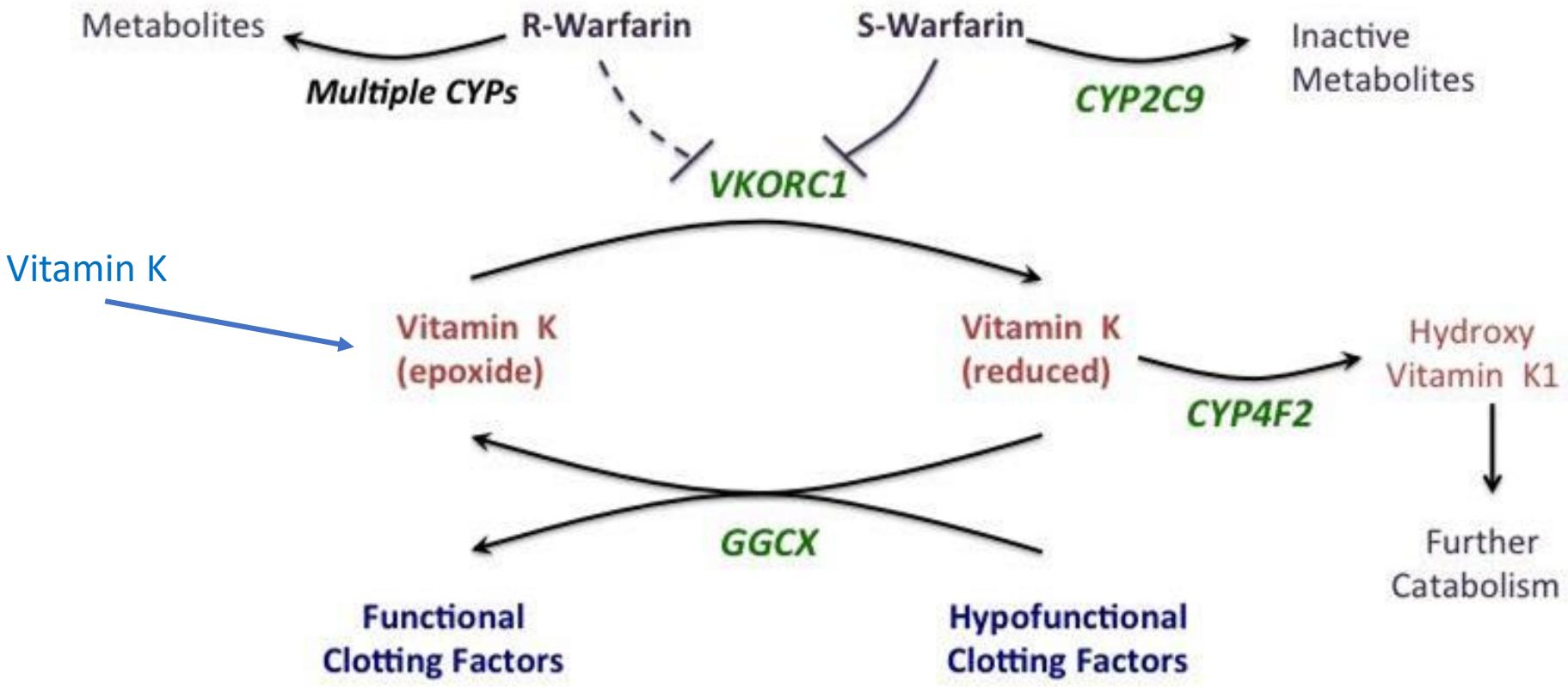
- Accounting for *CYP2C9* *2 and *3 and *VKORC1* rs9923231 explains ~40% of the variability in warfarin dose in whites, but only ~20% in people of African descent.
- EU-PACT study ~99% white patients, improved time in therapeutic range and time to therapeutic anticoagulation.
- COAG study 27% African ancestry found gene-based dosing actually performed worse than clinical dosing.

Warfarin pharmacogenetic variants

- VKORC1 rs9923231 does not seem to be functional and is likely linked to a causative locus in White populations but not African.
- Frequencies of CYP2C9 variants:



Warfarin response – target and metabolism



Adapted by Allan Rettie and Ken Thummel from Johnson, et al. 2011. “Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing” Clinical Pharmacology and Therapeutics

Summary

- Genetics can change drug response by altering drug target, drug metabolism, and drug transport, and by triggering allergies. It can also affect pathogen resistance.
- 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 on probabilities in a complex system.

Compare risk of muscle pain in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 in each of these populations you would expect to have muscle pain.

	Disease status		
	Muscle pain	No muscle pain	Total
TC	a	b	a+b
TT	c	d	c+d
total	a+c	b+d	

	Disease status		
	Muscle pain	No muscle pain	Total
CC	a	b	a+b
TT	c	d	c+d
total	a+c	b+d	

$$\text{OR} = \frac{ad}{bc}$$

Compare risk of muscle pain in global populations

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- OR=4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056
- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

	Disease status		
	Muscle pain	No muscle pain	Total
TC	a	b	320
TT	c	d	640
total	a+c	b+d	960

	Disease status		
	Muscle pain	No muscle pain	Total
CC	a	b	40
TT	c	d	640
total	a+c	b+d	680

Compare risk of muscle pain in global populations

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  - 4% CC, 32% TC, 64% TT

	Disease status		
	Muscle pain	No muscle pain	Total
TC	a	b	320
TT	13	627	640
total	a+c	b+d	960

$$\text{OR} = \frac{ad}{bc}$$

$$320 = a + b; 320 - b = a$$

$$4.5 = \frac{a * 627}{b * 13}$$

Compare risk of muscle pain in global populations

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- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

	Disease status		
	Muscle pain	No muscle pain	Total
TC	a	b	320
TT	13	627	640
total	a+c	b+d	960

$$\text{OR} = \frac{ad}{bc} \qquad 320 = a + b;\ 320 - b = a$$

$$4.5 = \frac{a * 627}{b * 13}$$

$$4.5 = \frac{627(320 - b)}{b * 13} = \frac{200640 - 627b}{b * 13}$$

$$58.5b = 200640 - 627b$$

$685.5b$ = 200640

b =200640/685.5 = 293

Compare risk of muscle pain in global populations

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- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

	Disease status		
	Muscle pain	No muscle pain	Total
TC	27	293	320
TT	13	627	640
total	a+c	b+d	960

$$\text{OR} = \frac{ad}{bc}$$

$$320 = a + b; 320 - b = a$$

$$4.5 = \frac{a * 627}{b * 13}$$

$$4.5 = \frac{627(320 - b)}{b * 13} = \frac{200640 - 627b}{b * 13}$$

$$58.5b = 200640 - 627b$$

$685.5b$ = 200640

b =200640/685.5 = 293

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	Disease status		
	Muscle pain	No muscle pain	Total
CC	a	b	40
TT	13	627	640
total	a+c	b+d	960

$$\text{OR} = \frac{ad}{bc}$$

$$16.1 = \frac{a * 627}{b * 13}$$

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- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

	Disease status		
	Muscle pain	No muscle pain	Total
CC	a	b	40
TT	13	627	640
total	a+c	b+d	960

$$\text{OR} = \frac{ad}{bc} \qquad 40 = a + b;\ 40 - b = a$$

$$16.1 = \frac{a * 627}{b * 13}$$

$$16.1 = \frac{627(40 - b)}{b * 13} = \frac{25080 - 627b}{b * 13}$$

$$209.3b = 25080 - 627b$$

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	Disease status		
	Muscle pain	No muscle pain	Total
CC	10	30	40
TT	13	627	640
total	23	657	960

$$\text{OR} = \frac{ad}{bc} \qquad 40 = a + b;\ 40 - b = a$$

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- OR=4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056
- C allele frequency in African populations: 3%
  - 0.1% CC, 5.8% TC, 94.1% TT

	Disease status		
	Muscle pain	No muscle pain	Total
TC	a	b	58
TT	19	922	941
total	a+c	b+d	999

	Disease status		
	Muscle pain	No muscle pain	Total
CC	a	b	1
TT	19	922	941
total	a+c	b+d	942

Compare risk of muscle pain in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 in each of these populations you would expect to have muscle pain.

- OR=4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056
- C allele frequency in African populations: 3%
  - 0.1% CC, 6% TC, 94.1% TT

	Disease status		
	Muscle pain	No muscle pain	Total
TC	5	53	58
TT	19	922	941
total	24	975	999

$$\text{OR} = \frac{ad}{bc}$$

$$58 = a + b \quad 580 - b = a$$

$$4.5 = \frac{a * 922}{b * 19}$$

$$4.5 = \frac{922(58 - b)}{b * 19} = \frac{53476 - 922b}{b * 19}$$

$$85.5b = 53476 - 922b$$

$1007.5b$ = 53476

b =53476/1007.5 = 53

Compare risk of muscle pain in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 in each of these populations you would expect to have muscle pain.

- OR=4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056
- C allele frequency in African populations: 3%
  - 0.1% CC, 6% TC, 94.1% TT

$$\text{OR} = \frac{ad}{bc} \qquad 1 = a + b; 1 - b = a$$

$$16.1 = \frac{a * 922}{b * 19}$$

$$16.1 = \frac{922(1-b)}{b * 19} = \frac{922 - 922b}{b * 19}$$

$$305.9b = 922 - 922b$$

$$1227.9b = 922$$

$$b = 922/1227.9 = 0.75$$

	Disease status		
	Muscle pain	No muscle pain	Total
CC	1	0	1
TT	19	922	941
total	20	922	942