Optimizing Pharmacotherapy with Pharmacogenomics

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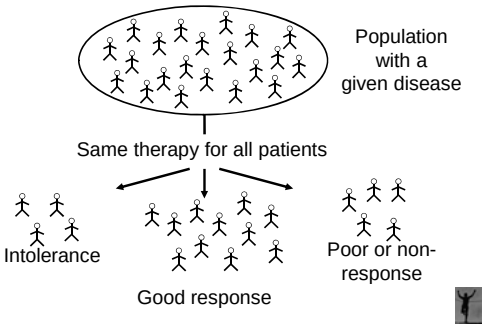
Dr. Cavallari has no conflicts of interest to disclose.

Objectives

- Describe basic pharmacogenomic concepts.
- Identify genetic variations influencing pharmacokinetic and pharmacodynamic properties.
- Recognize examples of genetic information in drug labeling.
- Explain how pharmacogenomic principles affect drug therapy decisions.

Current Pharmacotherapy Approach



Factors Influencing Drug Response

- Age
- Race/ ethnicity
- Pharmacokinetics
- Concomitant diseases
- Concomitant medications

Inter-Patient Variability in Warfarin Response

Patient #1
- African American male
- 55 yo
- BMI 28 kg/m^2
- No interacting drugs
- Normal liver function
- Low vitamin K intake
- Taking warfarin 3.2 mg/day to maintain INR of 2-3.

Patient #2
- African American male
- 53 yo
- BMI 29 kg/m^2
- No interacting drugs
- Normal liver function
- Low vitamin K intake
- Taking warfarin 10 mg/day to maintain INR of 2-3.

Factors Influencing Drug Response

- Age
- Race/ ethnicity
- Pharmacokinetics
- Concomitant diseases
- Concomitant medications
- GENOTYPE

Incorporating the Personal Genome in Clinical Assessment

Ashley EA et al. *Lancet* 2010;375:1525-35.

- Analyzed complete genome sequence of a 40-yo man with a family h/o vascular disease and sudden cardiac death.
  - Analysis of 2.6 million variants showed an increased risk for MI, type 2 DM, and some cancers.
  - Had 3 rare mutations associated with SCD.
  - Had *CYP2C19*, *HMGCR*, *SLCO1B1*, and *VKORC1* variants suggesting possible clopidogrel resistance, good response to statins, and need for lower warfarin dose requirements.

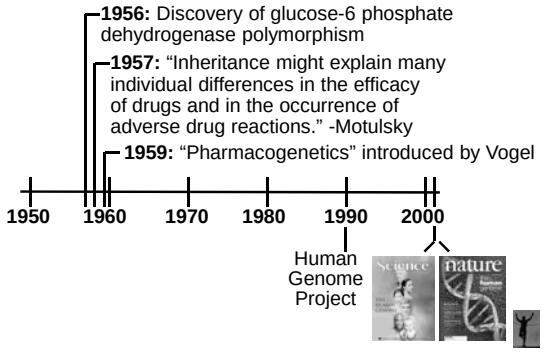
Pharmacogenetics

- Hereditary basis for inter-individual differences in drug response.
- Goal: optimize drug therapy and limit drug toxicity based on a person's DNA.

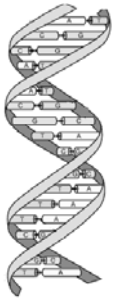
PharmacogenETics vs. PharmacogenOMics

- Pharmacogenetics: a single gene that influences drug response.
- Pharmacogenomics: multiple genes that influence drug response.

History of Pharmacogenomics

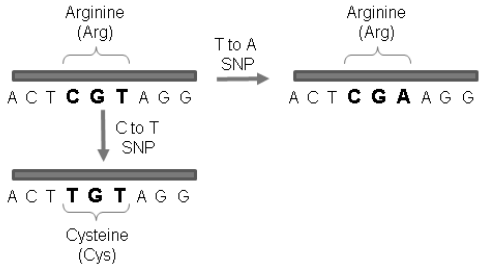


Human Genome



- Composed of 4 nucleotides
  - Adenine
  - Thymidine
  - Cytosine
  - Guanine
- Central dogma: one strand transcribed into RNA and translated to proteins

Single Nucleotide Polymorphism (SNP)



Other Types of Genetic Variants

- Insertion/deletion polymorphism – addition or removal of a strand of nucleotides
- Tandem repeat polymorphism – series of nucleotides that may be repeated in the genome a variable number of times (e.g. CAA repeat in GGCX)

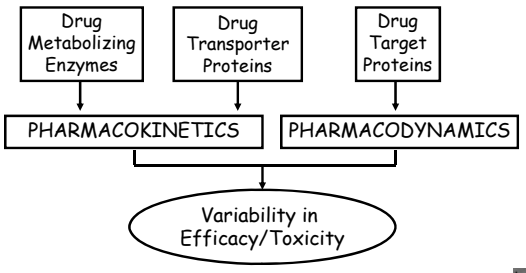
What is the most common type of genetic variation?

1. SNP
2. Tandem repeat
3. Insertion/deletion

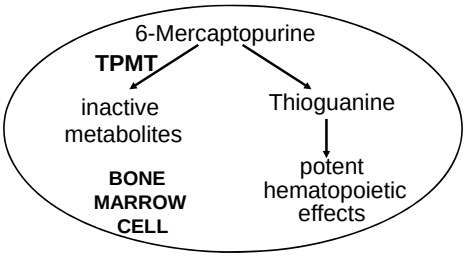
What is a SNP?

1. Addition or removal of a strand of nucleotides
2. Substitution of one nucleotide base by another
3. Series of nucleotide repeated a variable number of times

Pharmacogenomics



Thiopurine S-Methyltransferase (TPMT)



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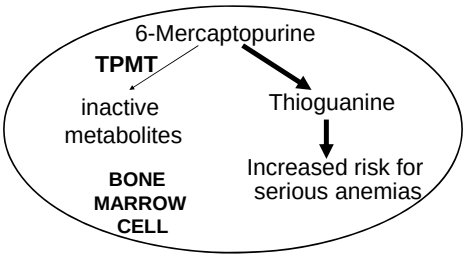


10% of population carries a variant *TPMT* allele.

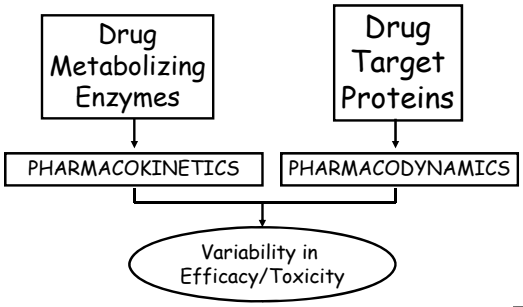
Clinical Implications of *TPMT* Polymorphisms

- Genetic testing for *TPMT* is available for clinical use.
- 6-mercaptopurine dose reduction required for patients with a dysfunctional *TPMT* allele:
  - Moderate dose reduction required in heterozygotes.
  - 90%-95% reduction required in homozygotes.

Warfarin

- Anticoagulant drug used for the prevention of thromboembolic disorders.
- Challenges with warfarin therapy:
  - Narrow therapeutic index.
  - Substantial inter-patient variability in warfarin dose requirements.
- S-isomer metabolized by CYP2C9.

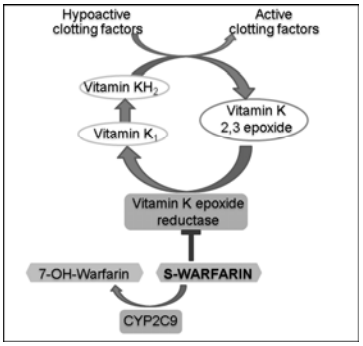
Pharmacogenomics of Warfarin



What are the primary genes affecting warfarin dose requirements?

1. CYP2C19 and Prothrombin
2. CYP4F2 and Factor X
3. CYP2C9 and vitamin K epoxide reductase
4. CYP3A4 and calumenin

Warfarin Pharmacodynamics: Vitamin K Recycling

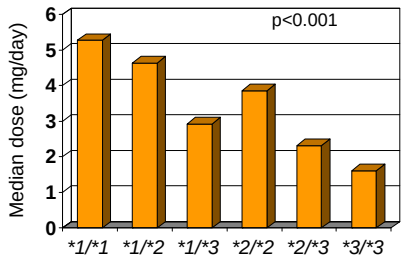


CYP2C9 Gene Alleles

Allele	Amino acid change	Prevalence		
		Caucasians	African Americans	Asians
*2	144Arg/Cys	20%	4%	<1%
*3	359Ile/Leu	12%	2%	6-8%
*8	150Arg/His	<1%	12%	<1%

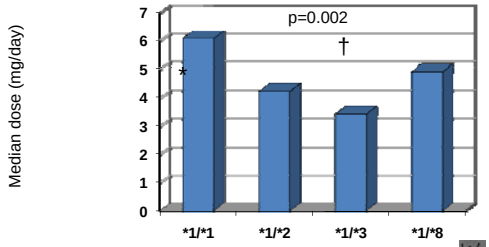
CYP2C9 and Warfarin Dose Requirements in Caucasians

Higashi et al. *JAMA* 2002;287:1690-8.



CYP2C9 and Warfarin Dose Response in African Americans

Cavallari et al. *Clin Pharmacol Ther* 2010;87:459-64.



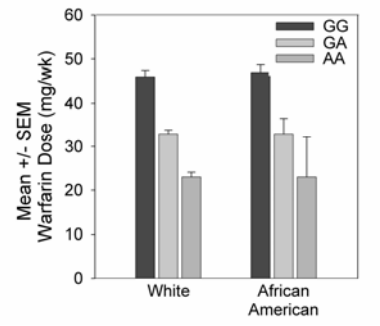
*p<0.01; †p=0.02 compared to *CYP2C9**1/*1

Vitamin K Epoxide Reductase (*VKORC1*) Gene and Warfarin

- *VKORC1* encodes the warfarin-sensitive component of vitamin K epoxide reductase.
- -1639G>A SNP in *VKORC1* promoter region
- 3 possible genotypes
  - GG – least sensitive
  - AG – intermediate sensitivity
  - AA – most sensitive

VKORC1 and Warfarin Dose Response

Wang et al. *Blood* 2008;112:1013-21.



FDA Revises Warfarin Label in 2010

VKORC1	**CYP2C9**					
	**1/*1*	**1/*2*	**1/*3*	**2/*2*	**2/*3*	**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

Warfarin product labeling. Rev 1/10.

Clinical Implications of *CYP2C9* and *VKORC1* Polymorphisms

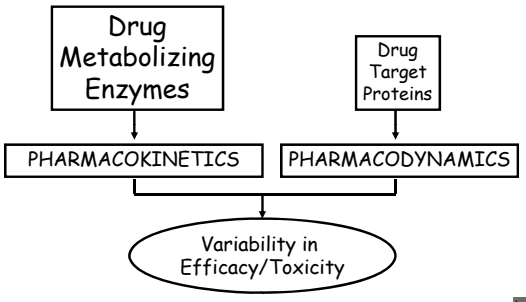
- Assist in choosing appropriate warfarin dosing for patients.
- May decrease the time to achieve optimal dosing.
- Reduce problems (bleeding) of high INRs during warfarin initiation.

Clopidogrel

- Thienopyridine that inhibits the P2Y12 receptor
- Reduces the risk for stent thrombosis
- Improves outcomes in:
  - Acute coronary syndromes
  - Percutaneous coronary intervention.
- Approximately 25% of patients are non-responders to clopidogrel.

Combescure C et al 2010 *J Thomb Haemost* 2010 [PMID 20156305]

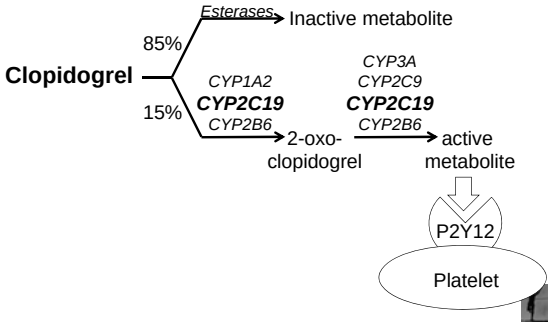
Pharmacogenomics of Clopidogrel



Which gene is associated with response to clopidogrel?

1. CYP2C19
2. CYP1A2
3. CYP2B6
4. CYP2C9

Clopidogrel Pharmacokinetics



Clopidogrel: *CYP2C19*

- Loss of function alleles: *2, *3, *4, *5
- Phenotype

***CYP2C19* alleles**	**Phenotype**
2 loss-of-function alleles	**PM** - Poor Metabolizer
1 loss-of-function allele	**IM** - Intermediate Metabolizer

- Population prevalence

Race	**PM**	**IM**
Caucasian	2%	25%
African American	4%	30%
Asian	14%	50%

Clopidogrel: *CYP2C19*

- Meta-analysis of 10 trials (9684 patients):

	Risk Ratio (95% CI)	
Outcome	**1 variant vs *1/*1**	**2 variants vs *1/*1**
Major adverse cardiac events	1.5 (1.1-2.1)	1.8 (1.2-2.7)
Stent thrombosis	2.5 (1.6-4.0)	4.8 (2.0-11.4)

Mega JL et al. *Circulation.* 2009;120:S598-S599

Clopidogrel Labeling

- Boxed warning added in March 2010
  - Warns of reduced effectiveness of clopidogrel in CYP2C19 PMs.
  - States availability of genetic testing.
  - Advises consideration of alternative treatment strategies in PMs.
- Labeling does not provide recommendations on specific strategies for PMs or include recommendations for IMs.

HLA allele and Stevens Johnson Syndrome (SJS)

- SJS/Toxic epidermal necrolysis (TEN)
  - Severe adverse reactions to carbamazepine.
  - Serious blistering reactions of the skin and mucous membranes that can be permanently disabling or fatal.
  - ~10 times more common among Asians.
- Human Leukocyte Antigen-B*1502 allele
  - Found almost exclusively in patients with Asian ancestry.
  - Associated with increased risk of SJS/TEN from carbamazepine.

Carbamazepine Labeling

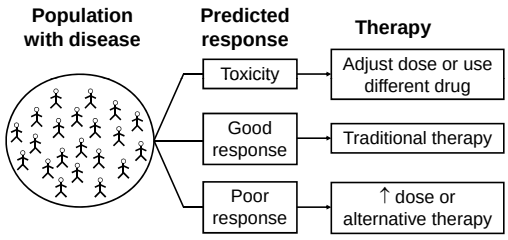
- Updated in 2007.
- Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions.
- Because this new data suggests a possible association between HLA-B*1502 and phenytoin – induced SJS, healthcare providers should consider avoiding phenytoin as alternative for carbamazepine in patients who test positive for HLA-B*1502.

Tegretol product labeling, rev 2-09

Clinical Application of Pharmacogenomics

- Individualize therapy based on genotype.
  - Predict likelihood of response and risk for toxicity based on DNA (e.g. warfarin, carbamazepine).
  - Choose drug therapy accordingly.
- Potential to eliminate trial-and-error approach to drug prescribing (e.g. antihypertensive drugs).
- Streamline treatment for complicated diseases (e.g. heart failure)

Clinical Application of Pharmacogenomics



Drugs with Genetic Labeling

Drug	Gene	Effect	Testing Status
Carbamazepine, Phenytoin	HLA-B	Increased risk for Stevens Johnson	Recommended for at-risk persons
Warfarin	CYP2C9; VKORC1	Altered metabolism and sensitivity	Suggested
Clopidogrel	CYP2C19	Determines efficacy	Suggested
Rasburicase	G6PD	Severe hemolysis	Recommended for at-risk persons
Trastuzamab	HER2	Determines efficacy	Mandated
Cetuximab	EGFR	Determines efficacy	Mandated
Azathioprine (6MP)	TPMT	Increased risk for myelotoxicity	Recommended

CASE 1: A 4 yo boy is diagnosed with acute lymphoblastic leukemia and is prescribed 6-mercaptopurine. Basing dosing decisions on TPMT genotype may result in which of the following?

1. Eliminate need for hematologic monitoring
2. Decreased risk for anemia
3. Shorten course of chemotherapy
4. Decreased need for multi-drug chemotherapy regimens

CASE 2: A 60 yo, 62 kg female is started on warfarin for stroke prevention in a. fib. Her other meds are metoprolol and atorvastatin. Genetic testing shows the *CYP2C9**1/*3 and *VKORC1* -1639 A/A genotypes. What is the most appropriate warfarin starting dose?

1. 2.5 mg/day
2. 5 mg/day
3. 7.5 mg/day
4. 10 mg/day

CASE 3: JM is a 55 yo male who suffers an ACS. He undergoes PCI with placement of a drug-eluting stent. He weighs 80 kg and has NKDA. Genotyping shows the *CYP2C19**2/*2 genotype. What do you recommend?

1. Standard dose clopidogrel
2. Prasugrel
3. High dose clopidogrel
4. Platelet aggregation testing

CASE 4: JB is an Asian male with newly diagnosed epilepsy. The physician is considering starting carbamazepine in this patient. What do you recommend?

1. Genotype for HLA-B*1502 allele and start carbamazepine if present
2. Genotype for the HLA-B*1502 allele and start phenytoin if present
3. Genotype for HLA-B*1502, and avoid both carbamazepine and phenytoin if present
4. Genotyping is not necessary as JB is at low risk for having the HLA-B*1502 allele

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