Concepts in Pharmacogenomic

Cell Biology and Its Application BI-1202


GENOME

Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics

William E. Evans* and Mary V. Relling

SCIENCE VOL 286 15 OCTOBER 1999

REVIEW ARTICLE

DRUG THERAPY

Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects

William E. Evans, Pharm.D., and Howard L. McLeod, Pharm.D.

NEJM, Feb. 6, 2003

What is and why pharmacogenomics?

- **Pharmacology + Genetics/Genomics**
- ***Pharmacogenetics:*** the effect of genetic variation on drug response, including disposition, safety and tolerability, and efficacy. Pharmacogenetics is an old discipline
- **Pharmacogenomics**: branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphism with drug's efficacy or toxicity. Pharmacogenomics is the application of genome science (genomics) to the study of human variability in drug response.

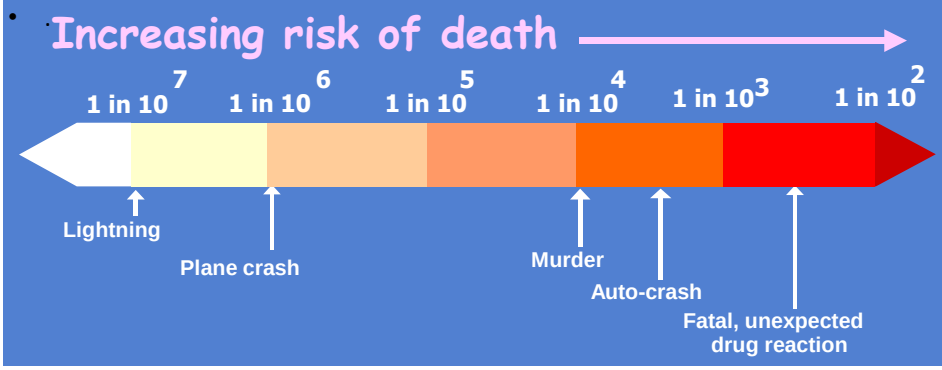
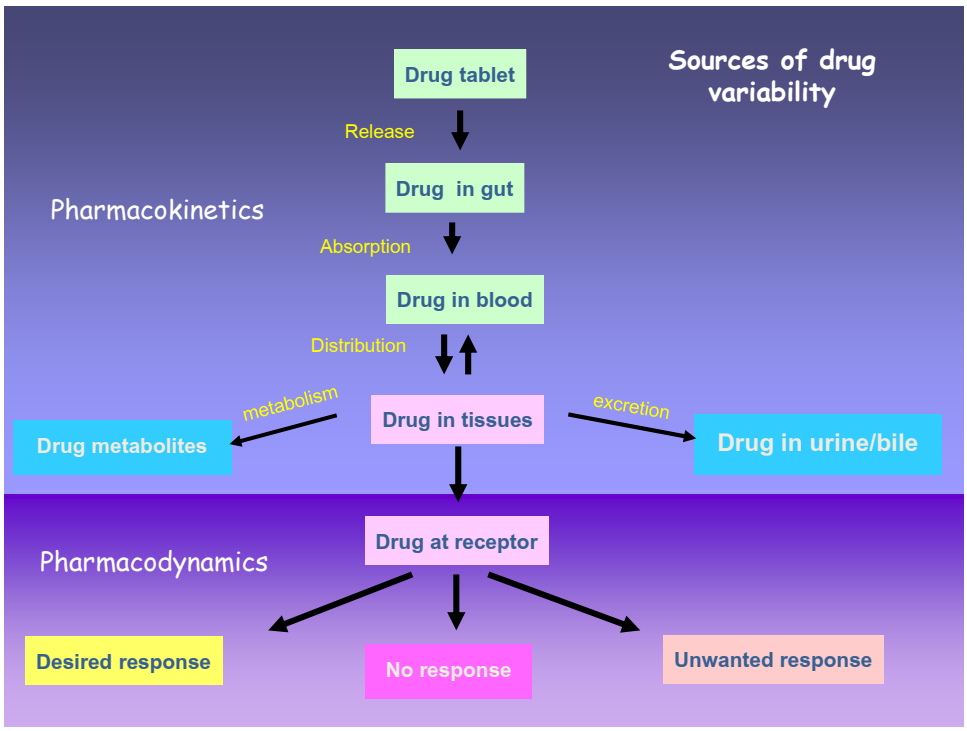


Table 1: The terms *pharmacogenetics* and *pharmacogenomics* as defined by different official organisations

Nuffield Council on Bioethics, UK[4]	
Pharmacogenetics	The study of the effects of genetic differences between individuals in their response to medicines.
Pharmacogenomics	The examination of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds.
The National Centre for Biotechnology Information (NCBI), USA[5]	
Pharmacogenetics	The study of inherited differences (variation) in drug metabolism and response.
Pharmacogenomics	The general study of all of the many different genes that determine drug behaviour.
Food and Drug Administration (FDA), USA[6]	
Pharmacogenetics	The influence of variations in DNA sequence on drug response
Pharmacogenomics	The investigation of variations of DNA and RNA characteristics as related to drug response.
European Medicines Agency (EMEA), UK[7]	
Pharmacogenetics	The study of interindividual variations in DNA sequence related to drug response.
Pharmacogenomics	The study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.
International Union of Basic and Clinical Pharmacology (IUPHAR), USA[8]	
Pharmacogenetics	The science about how heritability affects the response to drugs.
Pharmacogenomics	How the systematic identification of all the human genes, their products, interindividual variation, intraindividual variation in expression and function over time may be used both to predict the right treatment in individual patients and to design new drugs.

(Fenech, 2007)



The Empirical Strategy for Drug Therapy

Treat
All Patients
with the
Same Diagnosis
with the
Same Medications

Evans et al, SJCRH, 2000

Genetic Predisposition to Toxicity or Poor Response to Therapy

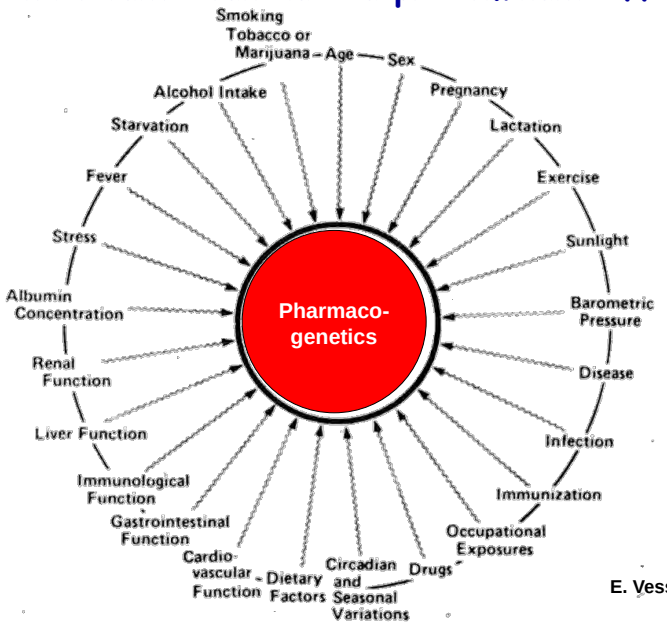
Non-Responders

Toxicity (ADR)

Adverse Drug Reactions (ADRs) are the fourth leading cause of hospitalization, fifth leading cause of mortality in the USA

Adapted from D. Grant (Orchid)

Many factors influence drug disposition & response but inheritance can have a predominant effect



E. Vessell, 1980s

Genetic variations in drug response and drug toxicity may result from

Variation in drug metabolizing enzymes

- Cytochromes P_{450}
- Thiopurine S-methyltransferase

Variation in drug targets

- $Beta_2$-adrenergic receptor
- ACE
- Dopamine receptor

Variation in drug transporters

- P-glycoprotein

Variation in disease modifying genes

- Apolipoprotein (APOE)

DNA alteration

Changes in the DNA sequence such as

- **Nucleotide mutation**
  - The most frequent DNA variation found in the human genome is single nucleotide polymorphism (SNP)
    - ✓ silent SNPs and non-coding SNPs can affect function
- **Nucleotide deletion**
- **Nucleotide insertion**

Deletions/ Insertions

A …G A G…..C A C A T …..

B …G A G T C A C A T …..

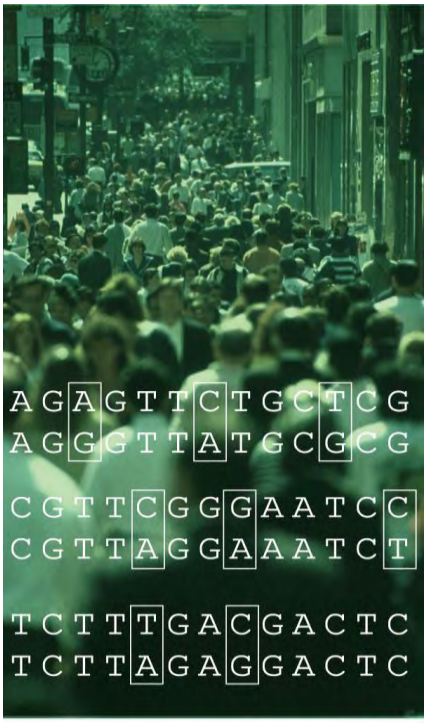
e.g. 68 bp insertion in CBS

- **Gene deletion**

e.g. entire GSTT1 and GSTM1

- **Gene duplication**

e.g. CYP2D6 up to 13 genes

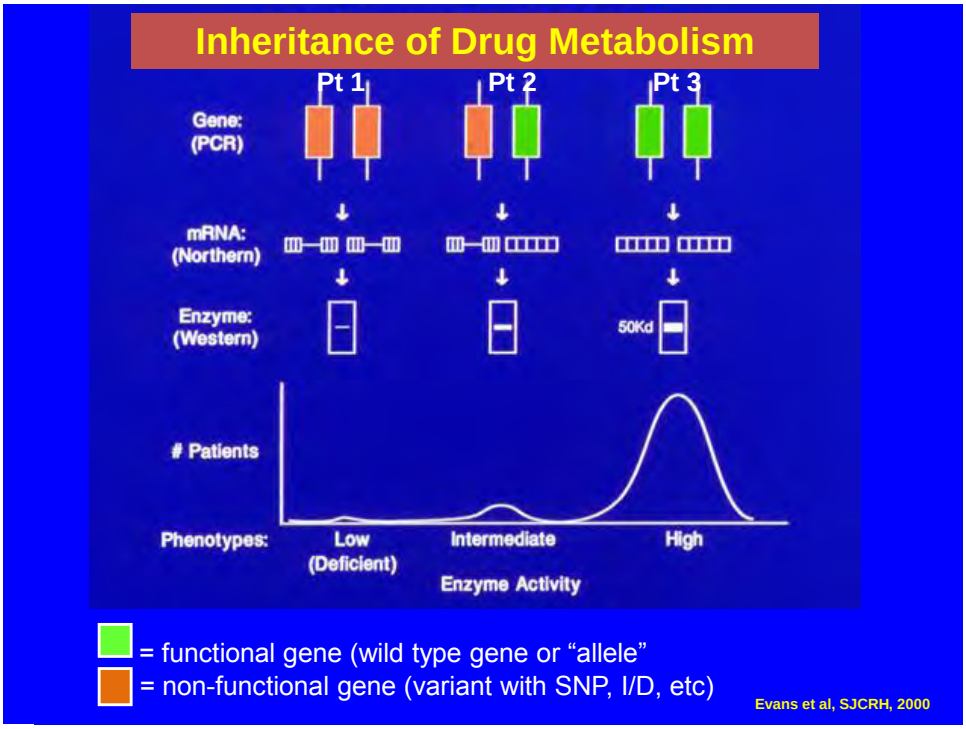


Inherited differences in drug metabolism and adverse drug effects (ADR)

59% of drugs in ADR-studies metabolised by polymorphic enzymes (86% are P450s) = INHERITED RISK

CYP2D6 involved in 38% of all ADR reports

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



PHARMACOGENETICS

Born in the 1950's

G6PD	→	chloroquine	→	hemolysis
NAT	→	isoniazid	→	p. neuropathy
cholinesterase	→	suxamethonium	→	muscle relax.

Linked to "idiosyncratic" drug reactions,
Motulsky, JAMA, 1959

Vogel coined term, "pharmacogenetics" in 1959

PHARMACOGENETICS

Inherited differences in drug disposition or drug effects

Expanded in the 1960's and 70's

Price-Evans	NAT
Smith; Eichelbaum	CYP2D6
Vessel	ALDH
Alexrod	COMT
Kupfer	CYP2C19

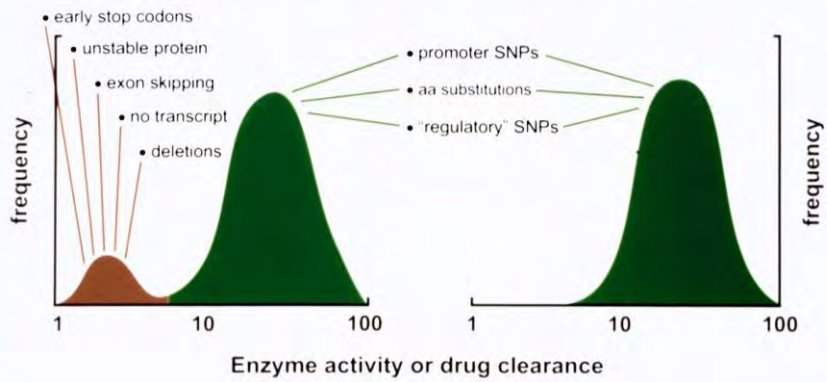
Became molecular in the 80's and 90's

Meyers & Gonzalez	*CYP2D6*	1987
Grant & Meyers	*NAT2*	1989
Wrighton & Goldstein	*CYP2C19*	1993
Liggett	*B2AR*	1993
etc		

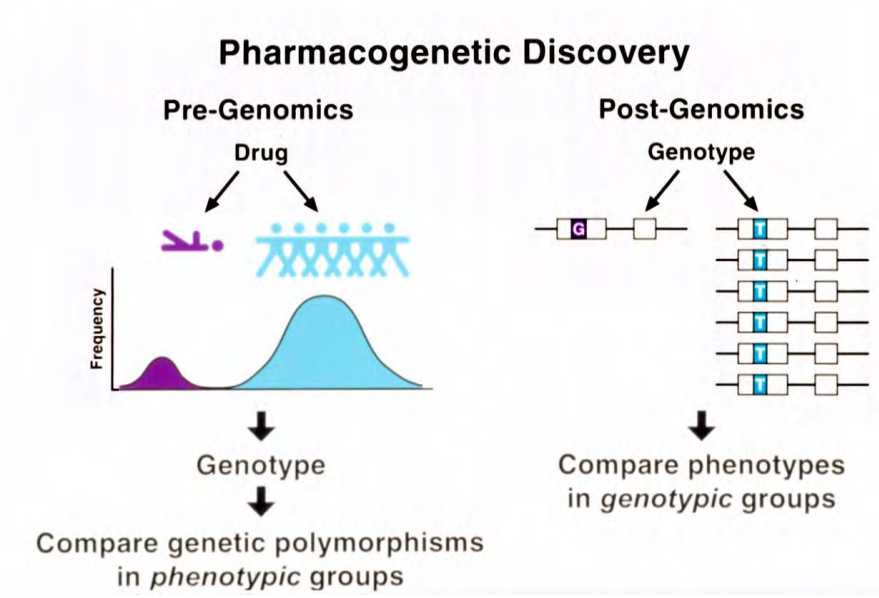
Becoming clinical in the 2000's

TPMT 1st PGEN Genotype	CLIA-certified

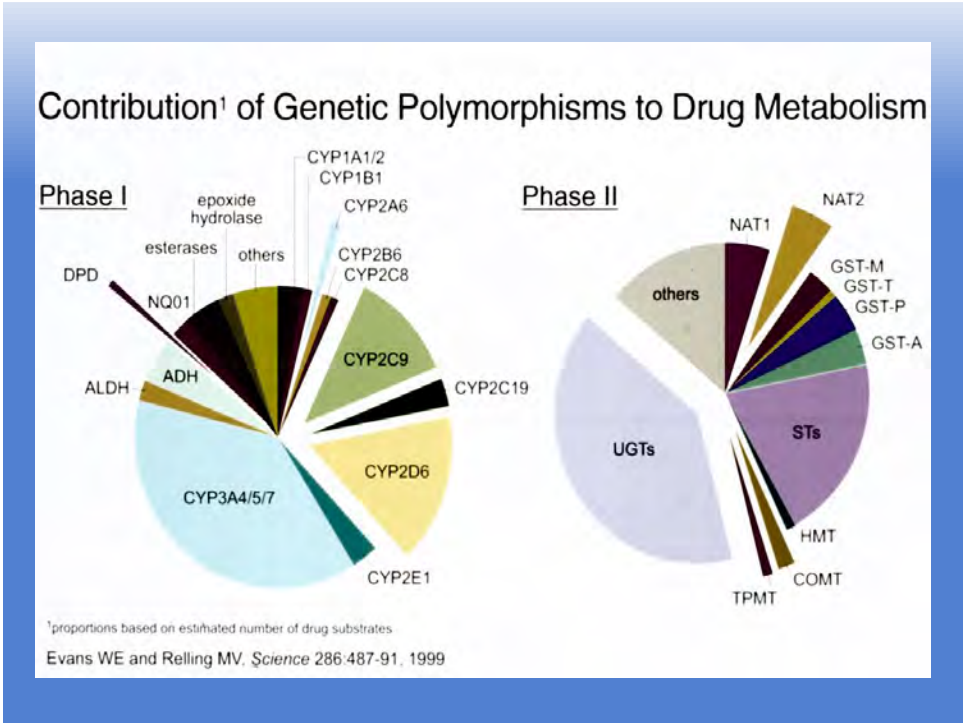
Inheritance (genetic polymorphisms) may result in different population distributions of phenotypes, depending on the type of polymorphism



Relling, SJCRH, 2001



Evans et al, SJCRH, 2000

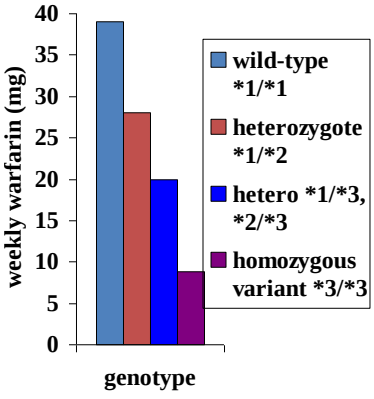


Warfarin is metabolized by *CYP2C9*

- Lower CYP2C9 = greater exposure to active (S) warfarin = higher INR (international normalized ratio)
- Higher CYP2C9 = lower exposure to active (S) warfarin =lower INR

- *CYP2C9* : 10% very low (v/v)
  40% intermediate (~wt/v)
  50% high activity (wt/wt)

Warfarin dosage depends upon CYP2C9 genotype



- 93 whites receiving long-term warfarin (a.fib, valvular dz, DVT)
- treated with warfarin with INR variation < 15% to maintain INR 2-3
- Pts genotyped for CYP2C9
- Warfarin PK

Clin Pharm Ther 2002;72:702-10

Drug receptors and targets can exhibit genetic polymorphisms influencing drug effects

Table 1. Examples of clinically relevant genetic polymorphisms influencing drug metabolism and effects. A comprehensive listing is available at www.sciencemag.org/feature/data/1044449.shl

Gene	Medications	Drug Effects Linked to Polymorphism
	Drug targets	
Angiotensin-converting-enzyme (ACE)	Enalapril, lisinopril, captopril	Renoprotective effects, cardiac indices, blood pressure, IgA nephropathy
Potassium channels		
HERG	Quinidine cisapride	Drug-induced long QT syndrome Drug-induced torsade de pointes
KvLQT1	Terfenadine, disopyramide meflaquine	Drug-induced long QT syndrome
hKCNE2	Clarithromycin	Drug-induced arrhythmia

Science, vol **286**, Oct 1999

Genes Encoding Drug Targets

Table 1. Genetic Polymorphisms in Drug Target Genes That Can Influence Drug Response.*

Gene or Gene Product	Medication	Drug Effect Associated with Polymorphism
Angiotensin-converting enzyme	ACE inhibitors (e.g., enalapril) Fluvastatin	Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function[32-40] Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression or regression of coronary atherosclerosis[41]
Arachidonate 5-lipoxygenase	Leukotriene inhibitors	Improvement in FEV_1[42]
β_2-Adrenergic receptor	β_2-Agonists (e.g., albuterol)	Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects[43-50]
Bradykinin B2 receptor	ACE inhibitors	ACE-inhibitor–induced cough[51]
Dopamine receptors (D2, D3, D4)	Antipsychotics (e.g. haloperidol, clozapine)	Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinsia (D3), antipsychotic-induced acute akathisia (D3)[52-56]
Estrogen receptor-α	Conjugated estrogens Hormone-replacement therapy	Increase in bone mineral density[57] Increase in high-density lipoprotein cholesterol[58]
Glycoprotein IIIa subunit of glycoprotein IIb/IIIa	Aspirin or glycoprotein IIb/IIIa inhibitors	Antiplatelet effect[59]
Serotonin (5-hydroxytryptamine) transporter	Antidepressants (e.g., clomipramine, fluoxetine, paroxetine)	5-Hydroxytryptamine neurotransmission, antidepressant response[60-62]

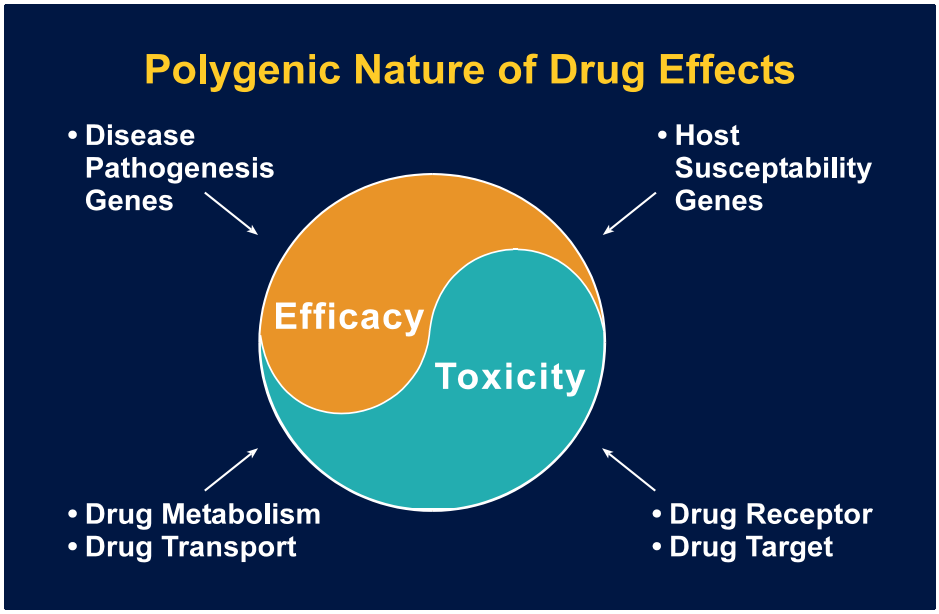
Evans and McLeod, *NEJM*, Feb. 2003

Disease or Rx-modifying Genes

Table 2. Genetic Polymorphisms in Disease-Modifying or Treatment-Modifying Genes That Can Influence Drug Response.*

Gene or Gene Product	Disease or Response Association	Medication	Influence of Polymorphism on Drug Effect or Toxicity
Adducin	Hypertension	Diuretics	Myocardial infarction or strokes[69]
Apolipoprotein E (APOE)	Progression of atherosclerosis, ischemic cardiovascular events	Statins (e.g., simvastatin)	Enhanced survival[70,71]
Apolipoprotein E (APOE)	Alzheimer's disease	Tacrine	Clinical improvement[72]
HLA	Toxicity	Abacavir	Hypersensitivity reaction[73,74]
Cholesterol ester transfer protein (CETP)	Progression of atherosclerosis	Statins (e.g., pravastatin)	Slowing of progression of atherosclerosis by pravastatin[75]
Ion channels (HERG, KvLQT1, Mink, MiRP1)	Congenital long-QT syndrome	Erythromycin, terfenadine, cisapride, clarithromycin, quinidine	Increased risk of drug-induced torsade de pointes[76-78]
Methylguanine methyltransferase (MGMT)	Glioma	Carmustine	Response of glioma to carmustine[63]
Parkin	Parkinson's disease	Levodopa	Clinical improvement and levodopa-induced dyskinesias[79]
Prothrombin and factor V	Deep-vein thrombosis and cerebral-vein thrombosis	Oral contraceptives	Increased risk of deep-vein and cerebral-vein thrombosis with oral contraceptives[80]
Stromelysin-1	Atherosclerosis progression	Statins (e.g., pravastatin)	Reduction in cardiovascular events by pravastatin (death, myocardial infarction, stroke, angina, and others); reduction in risk of repeated angioplasty[81]

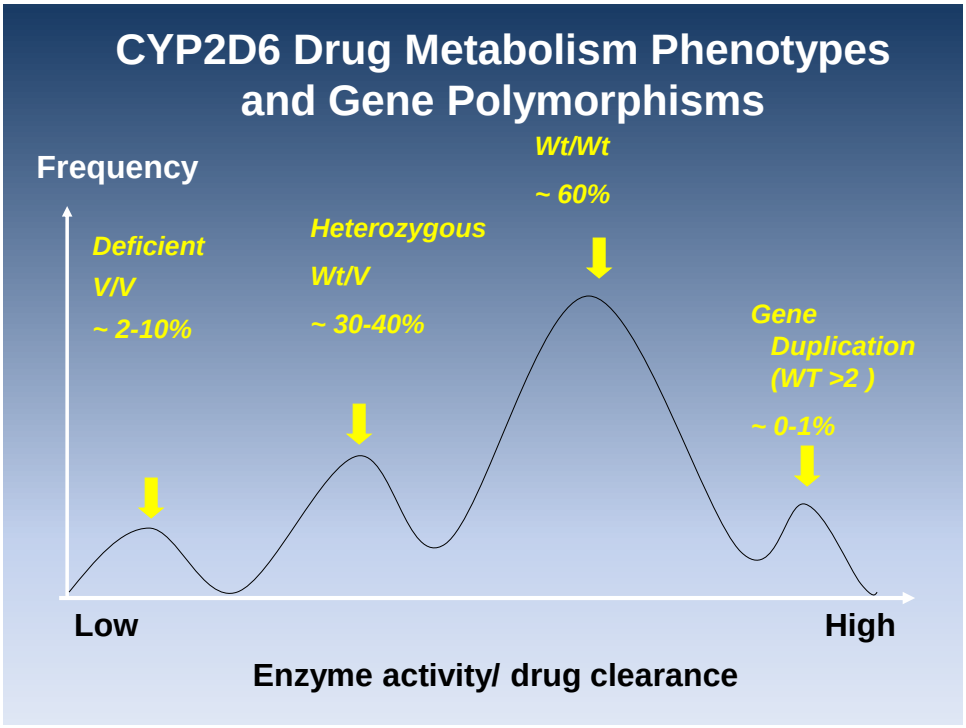
Evans and McLeod, *NEJM*, Feb. 2003



Evans et al, SJCRH, 2000

Common genetic polymorphism of human drug metabolizing enzymes

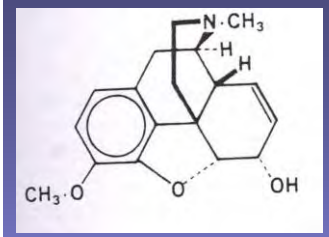
Enzyme	PM incidence	Drug substrates
CYP2D6	Caucasians 5-10% Asians 1%	Dextromethrophan beta-blockers Antiarrythmics Antidepressants Neuroleptics
CYP2C19	Caucasians 2-5% Asians 7-23%	Mephenytoin Mephobarbital Hexobarbital Diazepam Omeprazole Lansoprasole
CYP2C9	Caucasians < 1%	Tolbutamide (S)-Warfarin Phenytoin NSAIDs
Thiopurine S-methyltransferase	Caucasians & Asians 0.3%	Azathioprine 6-Mercaptopurine 6-Thioguanine



- **A 9-yr old boy was prescribed Prozac (Fluoxetine) to help control emotional outbursts.**
- **Child died suddenly ; toxicology tests show massive overdose of fluoxetine**
- **Adoptive parents investigated for homicide.**
- **Psychiatrist notices unusually high levels of Prozac indicatiing CYP2D6 deficiency.**
- **Subsequent genetic testing showed that child had CYP2D6 gene defect**

"After Michael died, we found out that there were tests to spot enzyme deficiencies that can cause adverse drug reactions. I felt devastated when I heard that. It should be the norm that the tests are used whenever there are concerns about possible side effects."

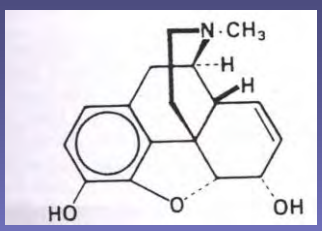
Codeine



O-demethylation

CYP2D6

Morphine



CYP2D6 PM fail to generate active metabolite

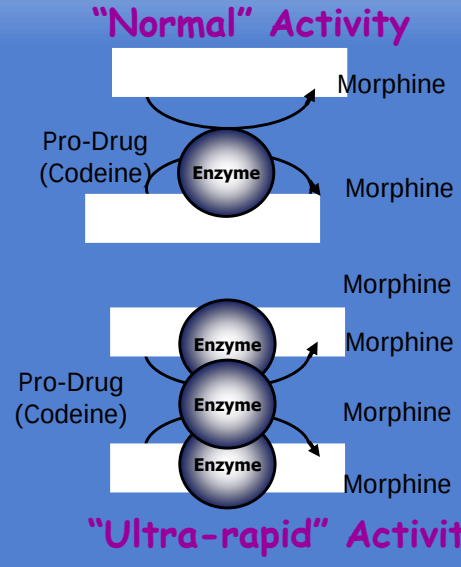
No analgesic effect

Life-threatening complication after cough suppression therapy with codeine

- **62 yr man with pneumonia treated with codeine (25 mg tid) for cough**
- **4 days after drug administration , the pt's consciousness rapidly deteriorated, and he became unresponsive.**
- **At the time of the pt's coma,**
  - **plasma morphine was 80 µg/L (normal 1-4 µg/L)**
  - **morphine-3-glucuronide was 580 µg/L (normal 8-70 µg/L)**
  - **morphine-6-glucuronide was 136 µg/L (normal 1-13 µg/L)**
- **CYP2D6 genotyping : ultra rapid metabolism**

N Engl J Med 2004;351:2827-31

Overactive metabolism can cause adverse events



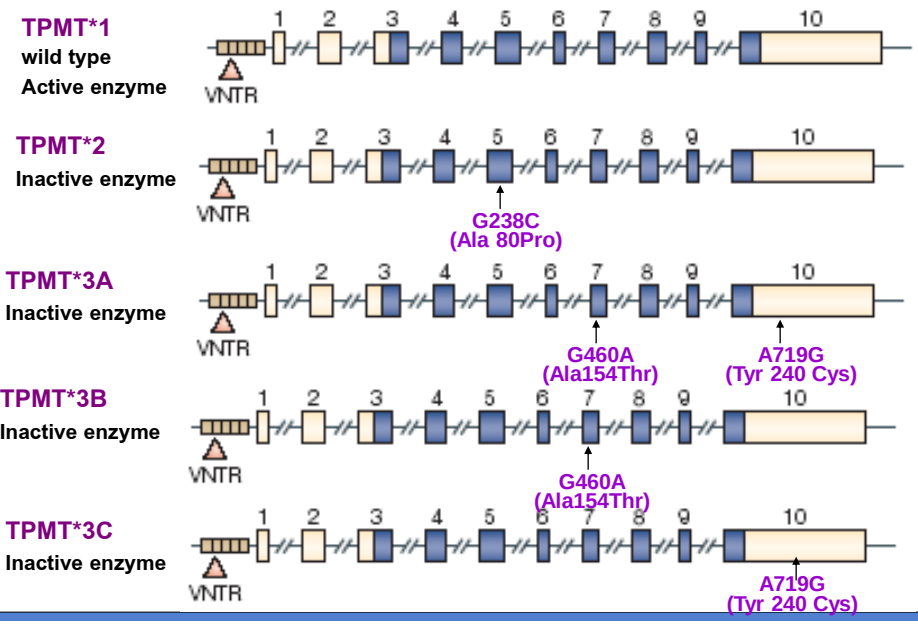
Thiopurine S-methyltransferase (TPMT) polymorphism

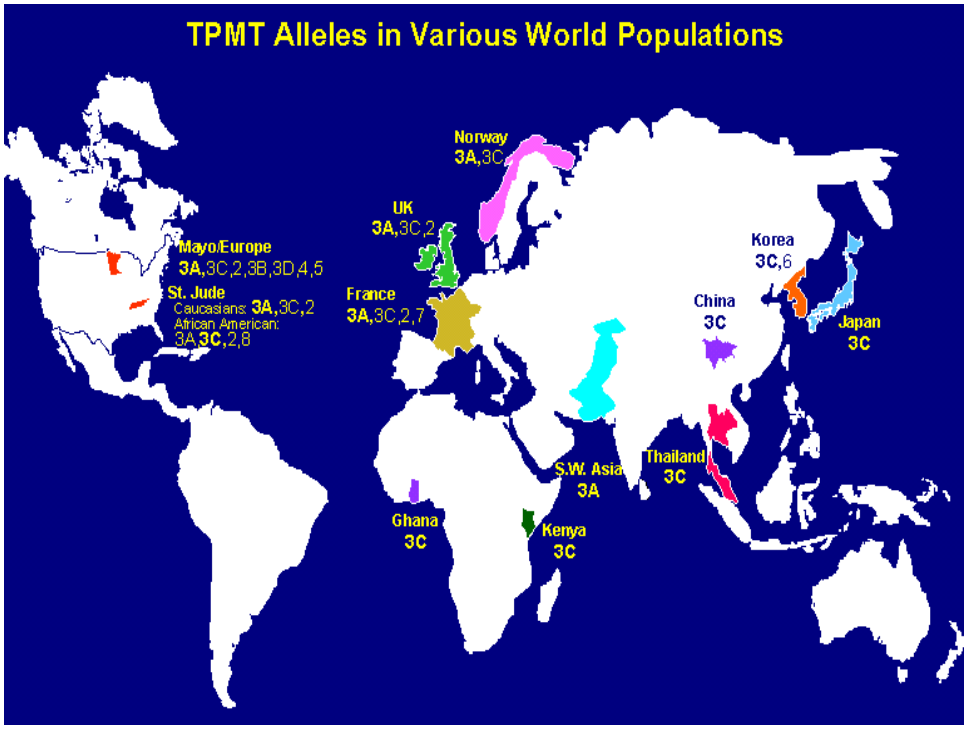
Cytosolic phase II enzyme involved in the metabolism of thiopurine and thioguanine anticancer drugs

- **Azathioprine**
- **6-Mercaptopurine**
- **6-Thioguanine**

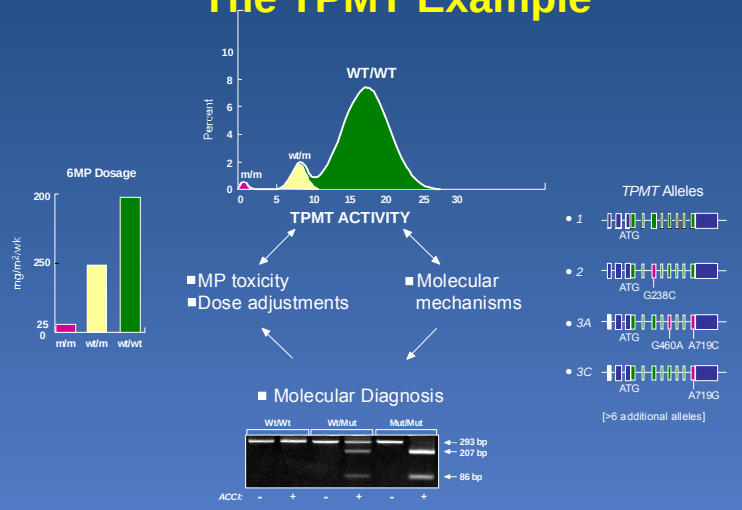
exhibits genetic polymorphism

Common TPMT alleles



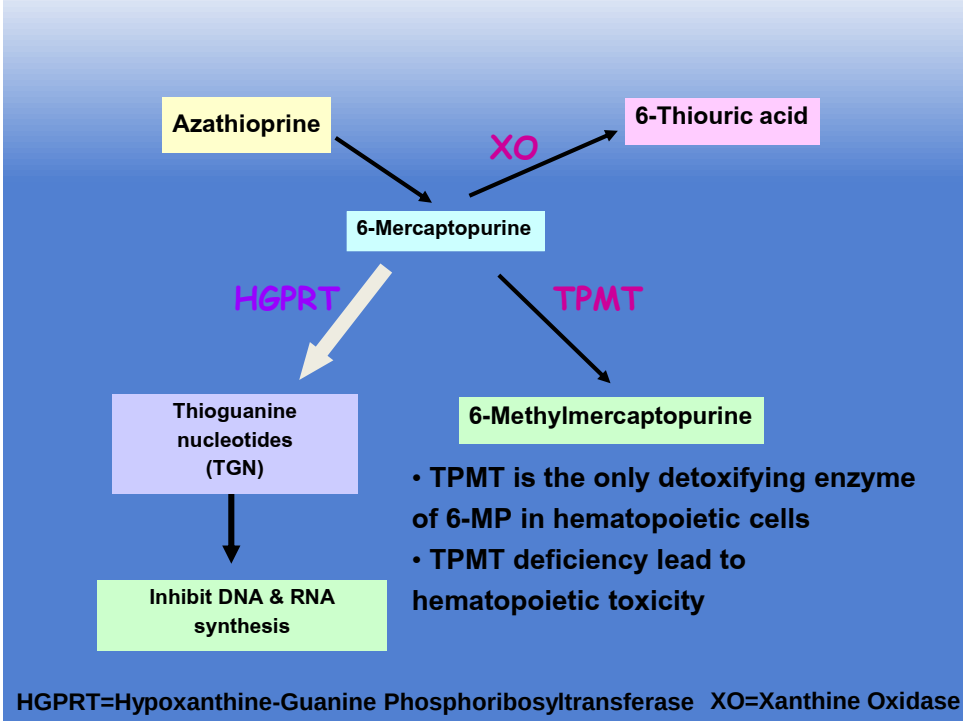


Polymorphic Drug Metabolism
The TPMT Example



CLIA Certified from Reference Labs

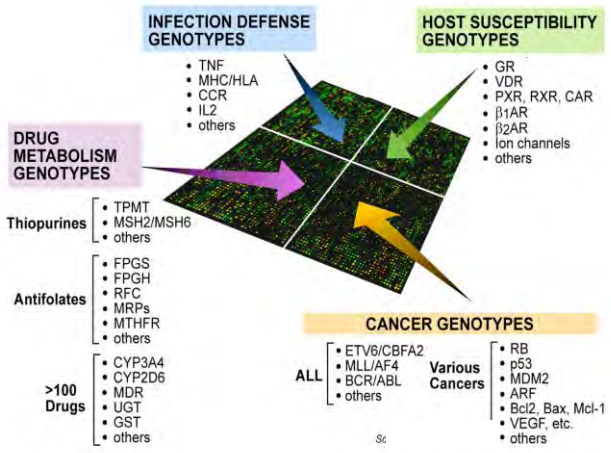
Evans and Krynetski
Am. J. Hum. Gen. 1998



GENOME
REVIEW

Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics

William E. Evans* and Mary V. Relling



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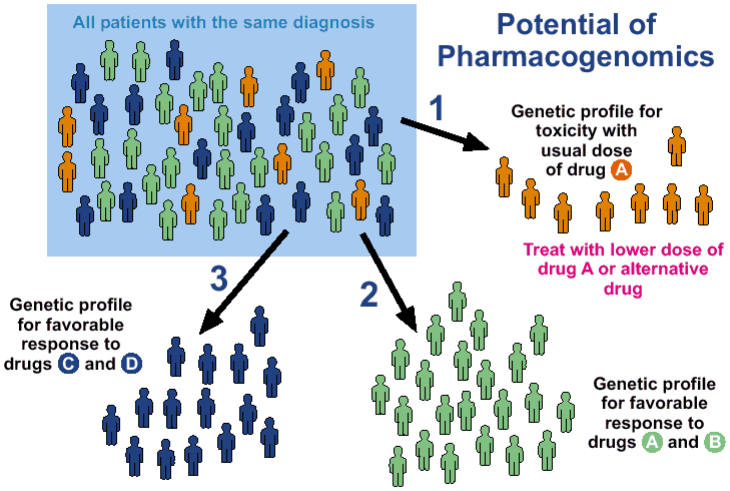


October 23-24, 2003

GENOMIC MEDICINE

NEWS

Preventing Toxicity With a Gene Test

To test or not to test? That is the question clinicians are asking about screening for genes that affect how the body metabolizes drugs

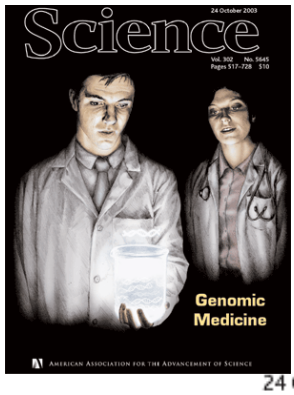
For more than 30 years, doctors have been using a powerful cell-killing compound to cure leukemia in children. This wonder drug—6-mercaptopurine (6MP), synthe-

community remains skeptical. Like other promised benefits of genomic medicine, this one has run into complaints about its cost ($100 to $300 per test), technical issues

U.S. Food and Drug Administration (FDA) seems unlikely to recommend one.

The resistance has surprised champions of genomic medicine. A leader in pharmacogenetic studies, Russ Altman of Stanford University, acknowledges that genotyping for drug risks has been a hard

But the medical community remains skeptical…



First Check My Genome, Doctor

The dangerous reactions some people have to the cancer drug 6MP may offer the most dramatic case for gene testing (see main text), but many other vulnerabilities may soon be checkable with a simple DNA test.

The biggest player in this DNA diagnostics market is Roche Molecular Diagnostics in Pleasanton, California. It is seeking U.S. and European regulatory clearance for a battery of gene tests to be included on a single device, the "AmpliChip CYP450," a microarray developed with the genomics company Affymetrix of Santa Clara, California. The chip will test for variations in two genes: *CYP2D6* and *CYP2C19*. They affect how people process about 25% of drugs on the market, says Walter H. Koch, the company's senior director of pharmacogenomics. Initially, Roche plans to market it primarily for patients using antipsychotic and antidepressant drugs, the efficacy of which varies greatly depending on *CYP2D6* genes. Some people with *CYP2D6* variations also get no pain relief from codeine or related drugs. The company will translate the results for physicians into metabolic function categories, from poor to ultrarapid.

In January 2003, Seryx of New York City launched a genotyping service called Signature Genetics that also zeroes in on similar "cy-

24 OCTOBER 2003 VOL 302 SCIENCE www.sciencemag.org

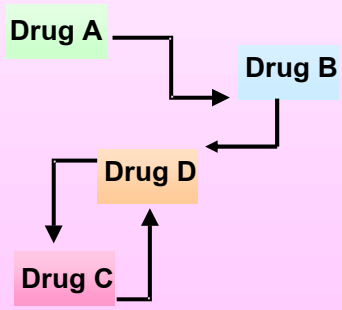
AmpliChip CYP450 Test
Use for routine diagnosis of CYP2C9 and CYP2D6 gene

Targeted prescription of medicine: applied pharmacogenomics

Today

empirical prescription

"One drug fit all"



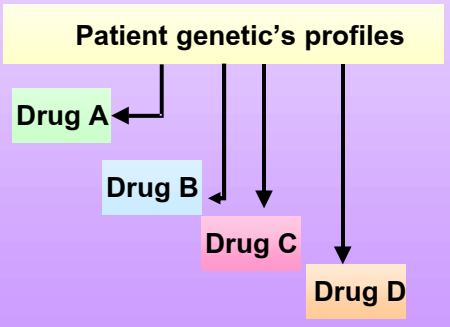
Individual physician experience

Cost: time, money & well-being

Future

Rational prescription

"individualized"



Informed physician diagnosis

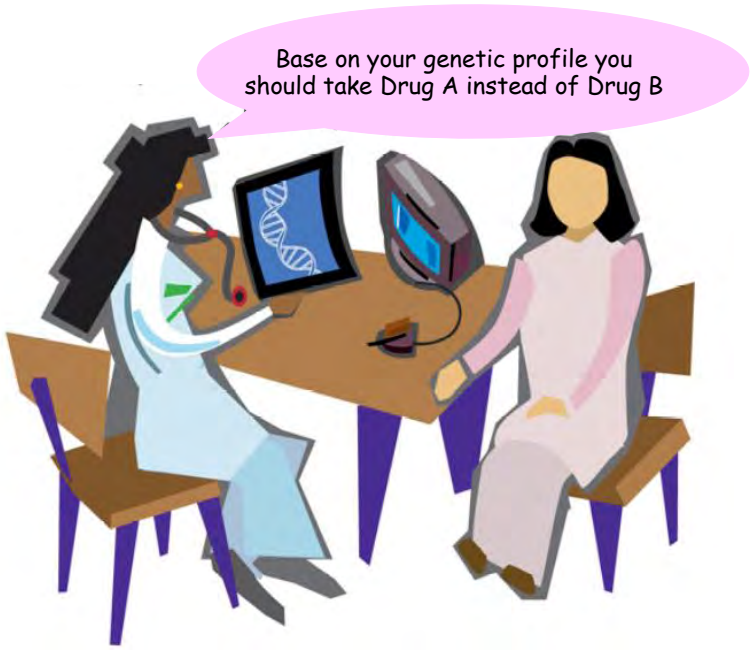
Saving : time, money & patient's life

Personalized medicine:

✓develop drugs that target persons of specific genotypes

✓prescribe existing drugs tailored to specific genotypes

January 20, 2003


Base on your genetic profile you should take Drug A instead of Drug B