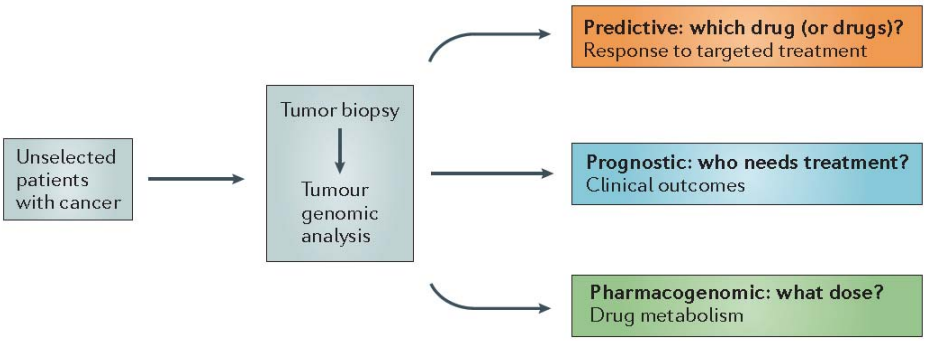
Pharmacogenetics in the evaluation of new drugs

Potential uses for pharmacogenetics data:

1. Elucidating the molecular or mechanistic basis for lack of drug efficacy or occurrence of adverse drug reactions (ADRs);
2. Clarifying variability in clinical response to drugs by ruling out the role of pathways involving the protein products of well-known polymorphic genes as clinically significant contributors to variable drug pharmacokinetics (PK) and/or pharmacodynamics (PD) parameters;
3. Estimating the magnitude of potential drug-drug interactions (DDIs);
4. Designing clinical trials to test for greater treatment effect in genetic subpopulations

Maliepaard M, et al. Nat Rev Drug Discov 2013;12:103-15.

Development and application of biomarkers for oncology



Simon R, Roychowdhury S. Nat Rev Drug Discov 2013;12(5):358-369.

Regulatory Agencies and Pharmacogenetics

Guidelines have been developed for the application of pharmacogenetics/pharmacogenomics in drug development by:

- **US Food and Drug Administration (FDA)**
- **European Medicines Agency (EMA)**
- **Pharmaceuticals and Medical Devices Agency (PMDA), Japan**

Pharmaceuticals and Medical Devices Agency, Japan

These Guidelines mainly focus on genetic aspects of drug metabolism:

- Presently, genes encoding proteins involved in drug metabolism have been the most extensively studied and are most often (~80%) referenced in drug labeling
- 30–50%of all clinically used drugs are metabolized by functionally polymorphic enzymes e.g. CYP2C9, CYP2C19, CYP2D6, UGTs etc.
- Current examples are based on research conducted after the regulatory approval of the drug.

Maliepaard M, et al. Nat Rev Drug Discov 2013;12:103-15.

European Medicines Agency (EMA)

12 December 2011
EMA/CHMP/37646/2009
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

US Food and Drug Administration (FDA)

Guidance for Industry

Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
January 2013
Clinical Pharmacology
Clinical/Medical

Beta-blockers in Hypertension

- Early studies found that black patients responded less well to beta-blockers.

Beta-blockers in Hypertension

- Early studies found that black patients responded less well to beta-blockers (and subsequently ACEI).
- This may be partly related to lower levels of plasma renin activity.

Beta-blockers in Hypertension

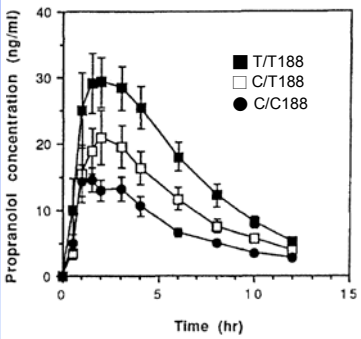
- Early studies found that black patients responded less well to beta-blockers (and subsequently ACEI).
- This may be partly related to lower levels of plasma renin activity.
- Empirical observation suggested Chinese patients were more sensitive to propranolol than Caucasians

Propranolol

Altered sensitivity to and clearance of propranolol in men of Chinese descent as compared with American whites

Zhou HH et al. N Engl J Med. 1989; 320(9): 565-70.

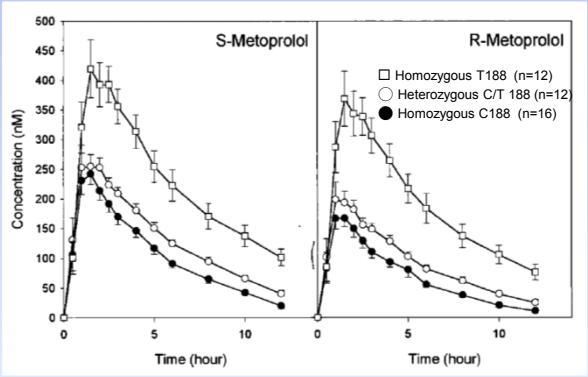
Propranolol pharmacokinetics and CYP2D6 genotype



- Chinese subjects with different CYP2D6*10 genotypes
- AUC values: 322.0, 481.6 and 766.1 nmol·hr/L, respectively, for C/C188, C/T188, and T/T188 subjects ($p < 0.05$)
- The 48-hour excreted amount of 4-hydroxy-S-propranolol-O-glucuronide, but not 4-hydroxy-R-propranolol-O-glucuronide, was significantly higher for C/C188 than for T/T188 subjects ($p < 0.05$)

Lai ML et al. Clin Pharmacol Ther. 1995; 58(3): 264-8.

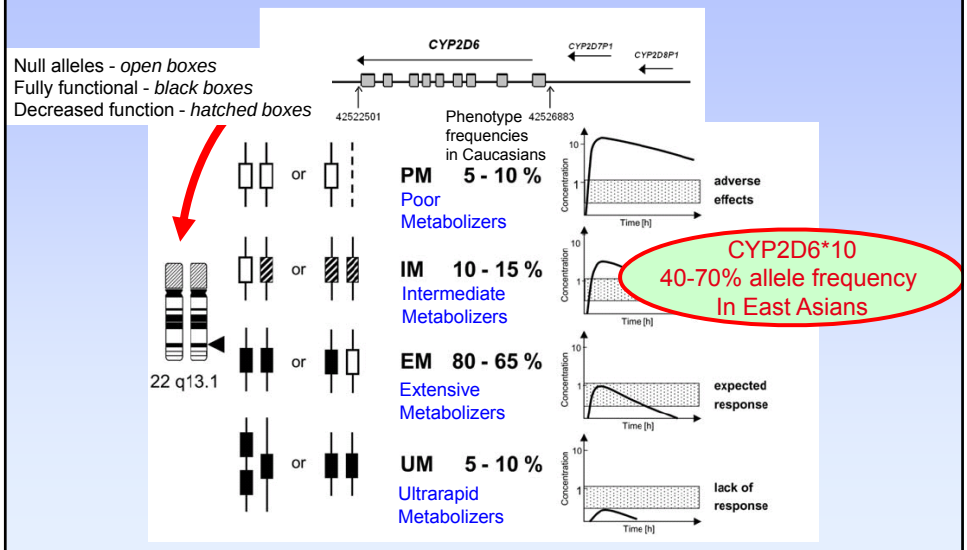
Metoprolol enantiomer pharmacokinetics in Chinese pharmacokinetics according to CYP2D6*10 genotypes



- There was a significant increasing trend of AUC, Cmax, and t½ among homozygous C188, heterozygous C/T188, and homozygous T188 subjects for both *R*- and *S*-metoprolol
- This suggests a lower dose of metoprolol may be used in subjects with the T188 genotype

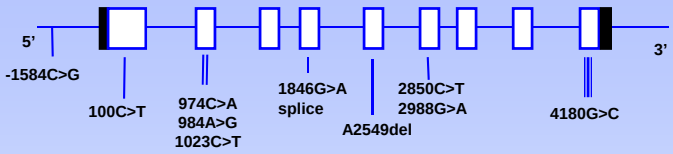
Huang JD et al. Clin Pharmacol Ther 1999; 65:402-7.

CYP2D6 genotype-phenotype relationships



Zanger UM et al. Naunyn Schmiedebergs Arch Pharmacol 2004; 369(1):23-37.

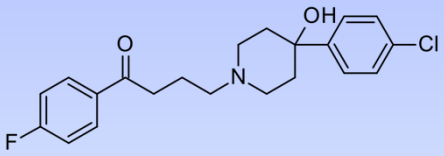
CYP2D6 Structure
Location: Chr. 22q13.1

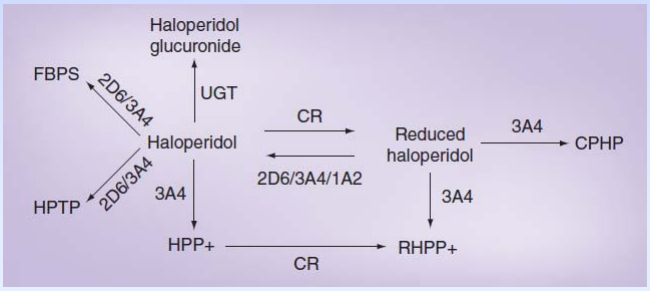


Allele	Enzyme Activity	Frequency distribution		
		Whites (%)	Blacks (%)	Asians (%)
*1 wild-type	Normal	33.4-83.8	27.8-90.4	22.7-49.0
*2 (-1584C>G, 2850C>T, 4180G>C)	Normal	32.4-35.3	9.9-40.0	8.0-13.4
*3 (A2549del)	Inactive	0.0-2.5	0.0-1.0	0.0
*4 (100C>T, 974C>A, 984A>G, 1846G>A splice, 4180G>C)	Inactive	11.3-28.6	0.9-9.3	0.2-0.8
*5 gene deletion	No Activity	0.6-7.3	3.3-9.0	1.2-6.2
*10 (100C>T, 4180G>C)	Decreased	1.4-6.1	1.0-8.6	38.1-70.0
*17 (1023C>T, 2850C>T, 4180G>C)	Decreased	0.0-1.1	9.0-34.0	0.0
*41 (-1584C>G, 2850C>T, 2988G>A, 4180G>C)	Decreased	10-20	14.9	2.6

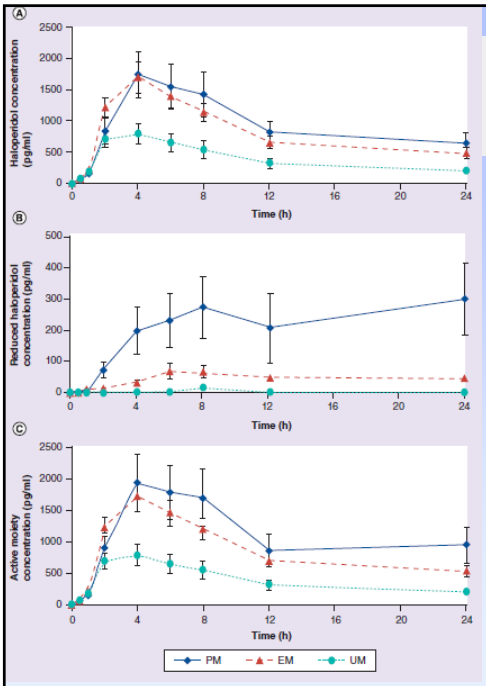
Refs: Cascorbi 2003, Xie 2001, Zanger UM 2004, Azuma 2009

Haloperidol





Gasso P et al. Pharmacogenomics 2013;14:1551-63.



Haloperidol

EM: Extensive metabolizer

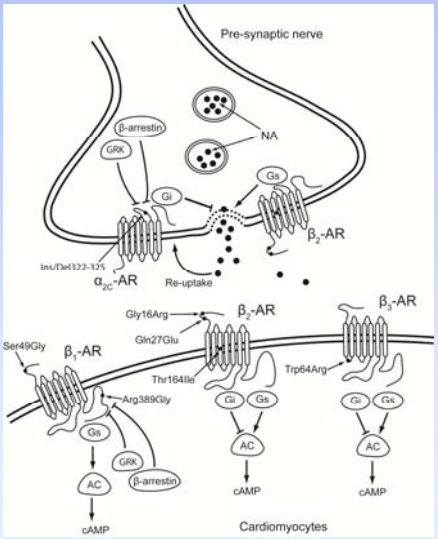
PM: Poor metabolizer

UM: Ultrarapid metabolizer

Gasso P et al. Pharmacogenomics 2013;14:1551-63.

Adrenergic receptors (ARs) in the heart

- The ARs are G-protein coupled receptors that represent the major component of the sympathetic nervous system
- There are three alpha$_1$-AR subtypes, three alpha$_2$-AR subtypes and three beta-AR subtypes
- The human heart expresses beta$_1$ and beta$_2$ ARs at a ratio of about 70:30
- Beta$_1$ ARs are down-regulated in heart failure



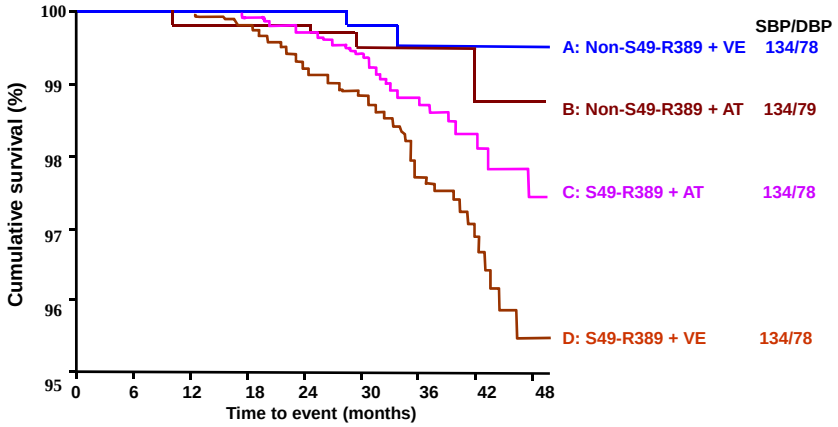
Chan S, Hu M, Tomlinson B. Ex Opin Drug Metab Tox 2012; 8(7):767-90

Functional consequences of the important ADRB1 genetic polymorphisms

Polymorphisms	Frequency				Functional consequences
	Caucasians	African-American	Hispanics	Asians	
Ser49Gly	12-6%	23-28%	20-21%	14%	•Gly49 allele has greater receptor down-regulation with agonist treatment •Gly49-β1-AR is more sensitive to the inhibitory effects of metoprolol than Ser49- β1-AR
Arg389Gly	24-34%	39-46%	31-33%	39%	•Arg389 allele has higher basal and agonist-stimulated AC activity •Lower AC activity upon agonist simulation in heart samples from HF patients with Arg389 allele than with Gly389 allele

Shin and Johnson. Heart Fail Rev 2010; 15(3):187-196.

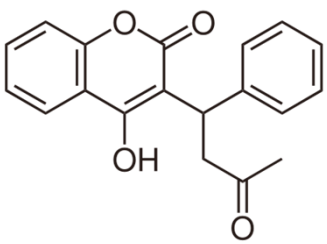
Beta-adrenergic receptor gene polymorphisms and treatment outcomes in hypertension: INVEST-GENES



β1-adrenergic receptor haplotype: S49-R389 is the more common and more responsive form

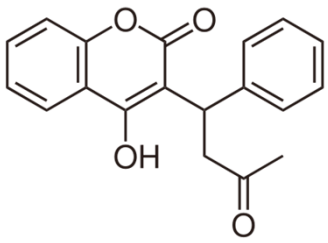
Adapted from: Pacanowski MA et al. Clin Pharmacol Ther. 2008;84(6):715-21.

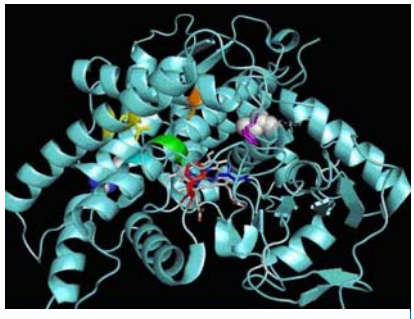
Warfarin Sensitivity



3 mg (blue), 5 mg (pink), 1 mg (brown)

Warfarin Sensitivity

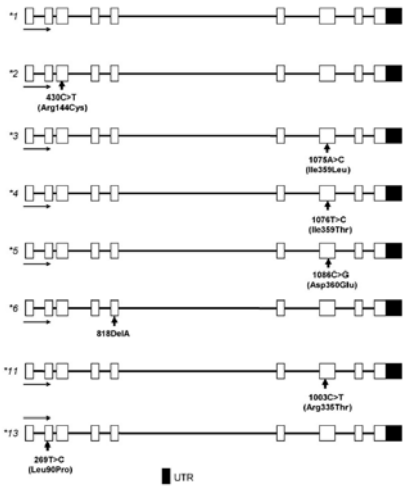




Cytochrome P450 2C9 (CYP2C9)

Metabolized by CYP1A1, CYP1A2, CYP3A4 ← **S-warfarin** **R-warfarin** → Metabolized by CYP2C9

Functionally important alleles of the human *CYP2C9* gene



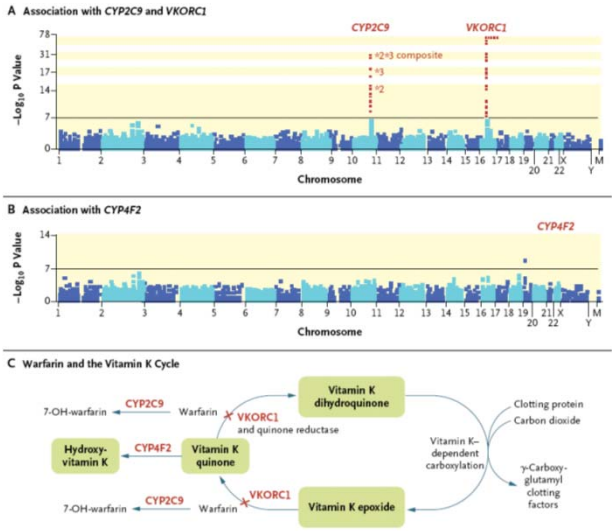
In Caucasians

CYP2C9*2
~1% homozygous
22% heterozygous.

CYP2C9*3
0.4% homozygous
15% heterozygous

Zhou SF, et al. Toxicology. 2010; 278(2): 165-88.

A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose



Takeuchi F et al. PLoS Genet 2009;5(3):e1000433

FDA U.S. Food and Drug Administration U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

FDA News

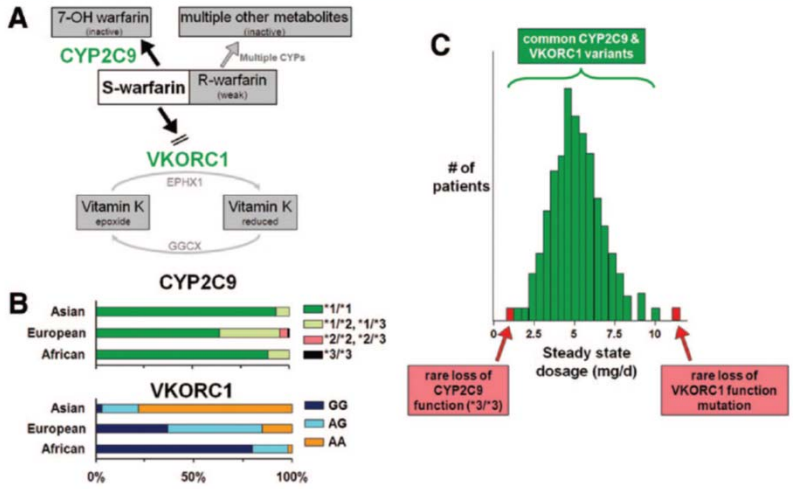
FOR IMMEDIATE RELEASE
September 17, 2007

FDA Clears Genetic Lab Test for Warfarin Sensitivity

The U.S. Food and Drug Administration today cleared for marketing a new genetic test that will help physicians assess whether a patient may be especially sensitive to the blood-thinning drug warfarin (Coumadin), which is used to prevent potentially fatal clots in blood vessels.

One-third of patients receiving warfarin metabolize it quite differently than expected and experience a higher risk of bleeding. Research has shown that some of the unexpected response to warfarin depends on variants of two genes, CYP2C9 and VKORC1. The Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test detects some variants of both genes.

Contributions of multiple genes to phenotype of warfarin maintenance dose requirement



Roden DM, et al. Circulation. 2011;123:1661-1670.

Rosuvastatin dose in Asians

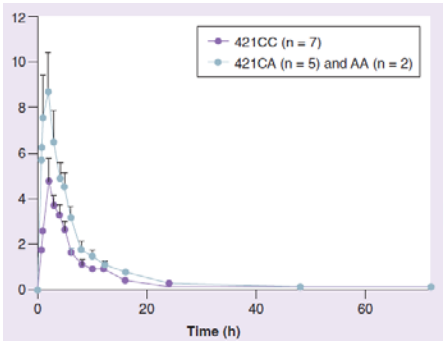
FDA issues rosuvastatin advisory highlighting revised label

March 2, 2005
Wilmington, DE - The **Food and Drug Administration** (FDA) issued a public-health advisory on **rosuvastatin** (Crestor®) today that highlights a revised package insert for the cholesterol-lowering medication.

Also, based on a pharmacokinetic study that found elevated drug levels in a population of Asian patients, the "Dosage and Administration" section of the label now advises that the 5-mg dose of rosuvastatin be considered the starting dose in this population.

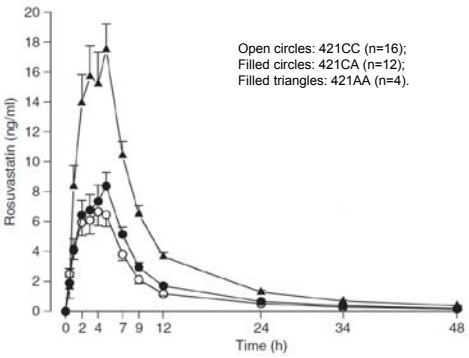
Effect of the ABCG2 421 C>A Polymorphism on the Pharmacokinetics of Rosuvastatin in Chinese and Caucasians

Chinese



Zhang A et al., Clin Chim Acta 2006; 373: 99-103.

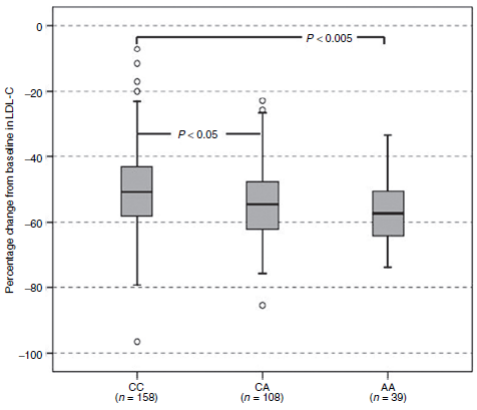
Caucasians



Keskitalo JE, et al. Clin Pharmacol Ther 2009; 86:197-203.

ABCG2 Polymorphism Is Associated With the Low-Density Lipoprotein Cholesterol Response to Rosuvastatin

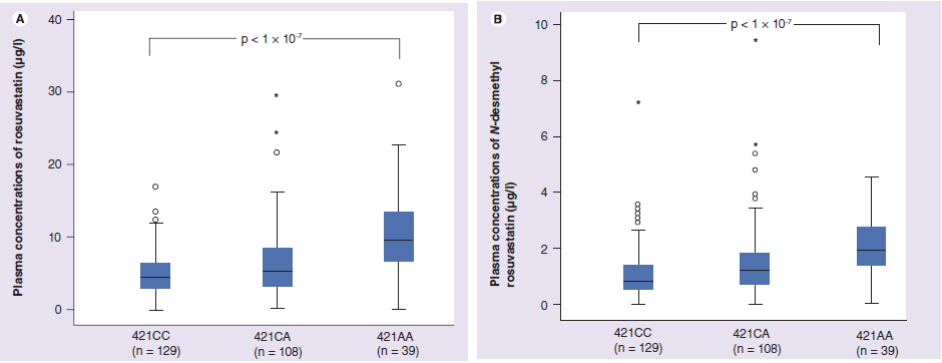
Clinical Pharmacology & Therapeutics



Tomlinson B, Hu M, Lee VWY et al., Clin Pharmacol Ther 2010; 87(5): 558-62.

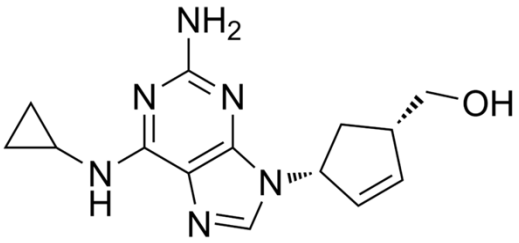
Effect of the *ABCG2* 421C>A polymorphism on the plasma concentration of Rosuvastatin in Chinese Patients with hypercholesterolaemia

ABCG2 421C>A polymorphism



Lee HK, Hu M,….Tomlinson B. *Pharmacogenomics* 2013; 14(11): 1283–94

Hypersensitivity reactions



- Abacavir - a potent HIV-1 reverse transcriptase inhibitor. Approved since 1998.
- Hypersensitivity reactions - fever, rash and gastrointestinal problems in 5–10% of patients after median of 9 days. Symptoms resolve within 72 h of discontinuation but re-exposure can result in severe hypotension and death.
- 2002 – HLA-B*5701 gene variant is highly associated with hypersensitivity reactions to abacavir. (Mallal S, et al. Lancet 2002;359:727-32; Hetherington S, et al. Lancet 2002;359:1121-2.)
- 2008 - prospective genotyping prevented hypersensitivity reactions. (Mallal S, et al. N Engl J Med 2008;358:568-79.)

Changes in the drug label for abacavir

Abacavir drug label change introduced by the EMEA in 2008

Before initiating treatment with abacavir, screening for carriage of the *HLA-B*5701* allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the *HLA-B*5701* allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing

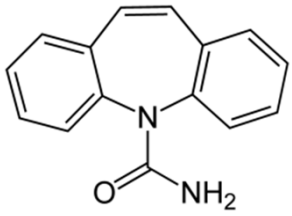
Abacavir drug label change introduced by the FDA in 2008

Patients who carry the *HLA-B*5701* allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the *HLA-B*5701* allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown *HLA-B*5701* status who have previously tolerated abacavir. *HLA-B*5701*-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in *HLA-B*5701*-positive patients.

Hong Kong label
Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing

Adapted from Pirmohamed M. Handb Exp Pharmacol 2010: 477-491

Hypersensitivity reactions



- Carbamazepine - cutaneous ADRs ranging from mild to severe (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- 2004 – *HLA-B*1502* gene variant is highly associated with SCARs with carbamazepine (Chung WH, et al. Nature. 2004; 428(6982):486.)
- *HLA-B*1502* genotype frequency varies in different areas
- 2011 - 4877 subjects genotyped in Taiwan – 7.7% positive for *HLA-B*1502* not given carbamazepine. 0.1% of *HLA-B*1502*-negative subjects hospitalized for rash but no SJS-TEN ~10 cases prevented (Chen P, et al. N Engl J Med 2011;364:1126-33.)

FDA Boxed Warning for Carbamazepine

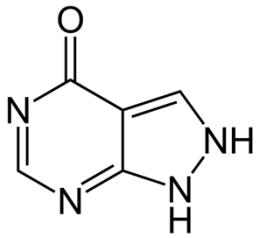
WARNINGS
SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE
SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS**, **LABORATORY TESTS**).

Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared t o about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea.

Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present.

FDA label approved on 03/06/2013 for TEGRETOL

Hypersensitivity reactions



- Allopurinol - structural isomer of hypoxanthine - inhibits xanthine oxidase.
- Cutaneous ADRs ranging from mild to severe (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- More common with renal impairment – dose/plasma concentration-dependent
- 2005 - *HLA-B*5801* allele highly associated with allopurinol SCARs (Hung SI, et al. Proc Natl Acad Sci U S A. 2005; 102(11): 4134-9.)
- In Han Chinese patients in Hong Kong 19/19 with allopurinol-induced SCAR carried HLA-B*58:01 vs. 4/30 (13%) allopurinol-tolerant controls – OR 229.7, 95% CI 11.7-4520.4 (Chiu ML, et al. Br J Dermatol. 2012; 167(1): 44-9.)

2012 American College of Rheumatology Guidelines for Management of Gout

- **Prior to initiation of allopurinol, rapid polymerase chain reaction–based HLA-B*5801 screening should be considered as a risk management component in subpopulations where both the HLA-B*5801 allele frequency is elevated and the HLA-B*5801–positive subjects have a very high hazard ratio ("high risk") for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD and all those of Han Chinese and Thai descent).**

  Not listed in FDA
  Table of Pharmacogenomic Biomarkers in Drug Labels
  http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Arthritis Care & Research 2012; 64 (10): 1431–1446.

Number needed to test (NNT) to prevent 1 case of specific drug reaction

Drug	HLA allele	HLA carriage rate	Prevalence of diagnosis	Negative predictive value	Positive predictive value	NNT to prevent one case
Abacavir	B*5701	6-8% Caucasian, <1% African/Asian, 2.5% African American	8% (3% true HSR + 2-7% false positive Dx)	100% for patch test confirmed	55%	13
Carbamazepine	B*1502	10-15% Han Chinese, <0.1% Caucasian	<1-6/1000	100% in Han Chinese	3%	1000
Allopurinol	B*5801	9-11% Han Chinese, 1-6% Caucasian	1/250-1/1000	100% in Han Chinese	3%	250
Flucloxacillin	B*5701	As for abacavir	8.5/100,000	99.99%	0.12%	13819

Phillips EJ, et al. J Allergy Clin Immunol. 2011; 127(3 Suppl): S60-6.

Pharmacogenetic tests for improving drug safety and effectiveness in Hong Kong

Safety

- Abacavir - *HLA-B*5701* X
- Carbamazepine – *HLA-B*1502* ✓
- Carbamazepine – *HLA-A*3101* X
- Allopurinol - *HLA-B*5801* X
- Flucloxacillin - *HLA-B*5701* X
- Irinotecan - *UGT1A1*28*
- 6-Mercaptopurines - *TPMT*

Effectiveness

- Propranolol *CYP2D6*
- Metoprolol *CYP2D6*
- Warfarin *CYP2C9, VKORC1*
- Clopidogrel *CYP2C19*
- Simvastatin *SLCO1B1*
- Rosuvastatin *ABCG2*
- Tamoxifen *CYP2D6*

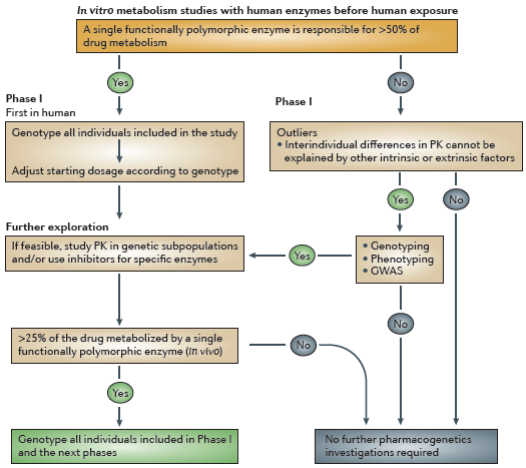
European Medicines Agency (EMA)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2011
EMA/CHMP/37646/2009
Committee for Medicinal Products for Human Use (CHMP)

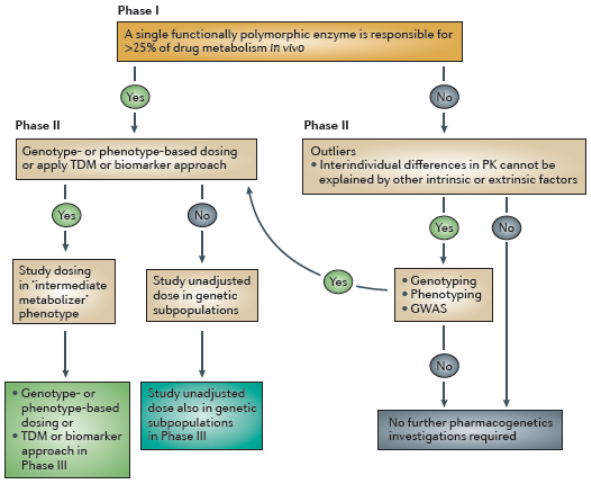
Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

European Medicines Agency (EMA) decision-making tree for in vitro studies prior to human exposure and Phase I studies



Maliepaard M, et al. Nat Rev Drug Discov 2013;12:103-15.

European Medicines Agency (EMA) decision-making tree for Phase I and Phase II studies



Maliepaard M, et al. Nat Rev Drug Discov 2013;12:103-15.

Summary of differences between the three regulatory guidelines on pharmacogenetics

Issue	EMA	PMDA	FDA
Development phases covered in guideline or guidance	Preclinical and clinical (Phases I–IV; focusing on PK)	Clinical development (Phases I–IV)	Early clinical development (Phases I and II)
Banking of DNA samples	Highly recommended	Encouraged	Strongly encouraged
Genomic testing	Required‡	Recommended	Recommended
In vitro cut-off values§	>50%	None	None
In vivo cut-off values§	>25%	None	None

‡Is a firm requirement only when *in vitro* (>50%) or *in vivo* (>25%) cut-off values are met.
§For when pharmacogenetics-related testing is required in pharmacokinetics (PK) studies.

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For more information:

- http://www.fda.gov/default.htm
- http://www.pmda.go.jp/english/
- http://www.ema.europa.eu/ema/

Thank you for your attention

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