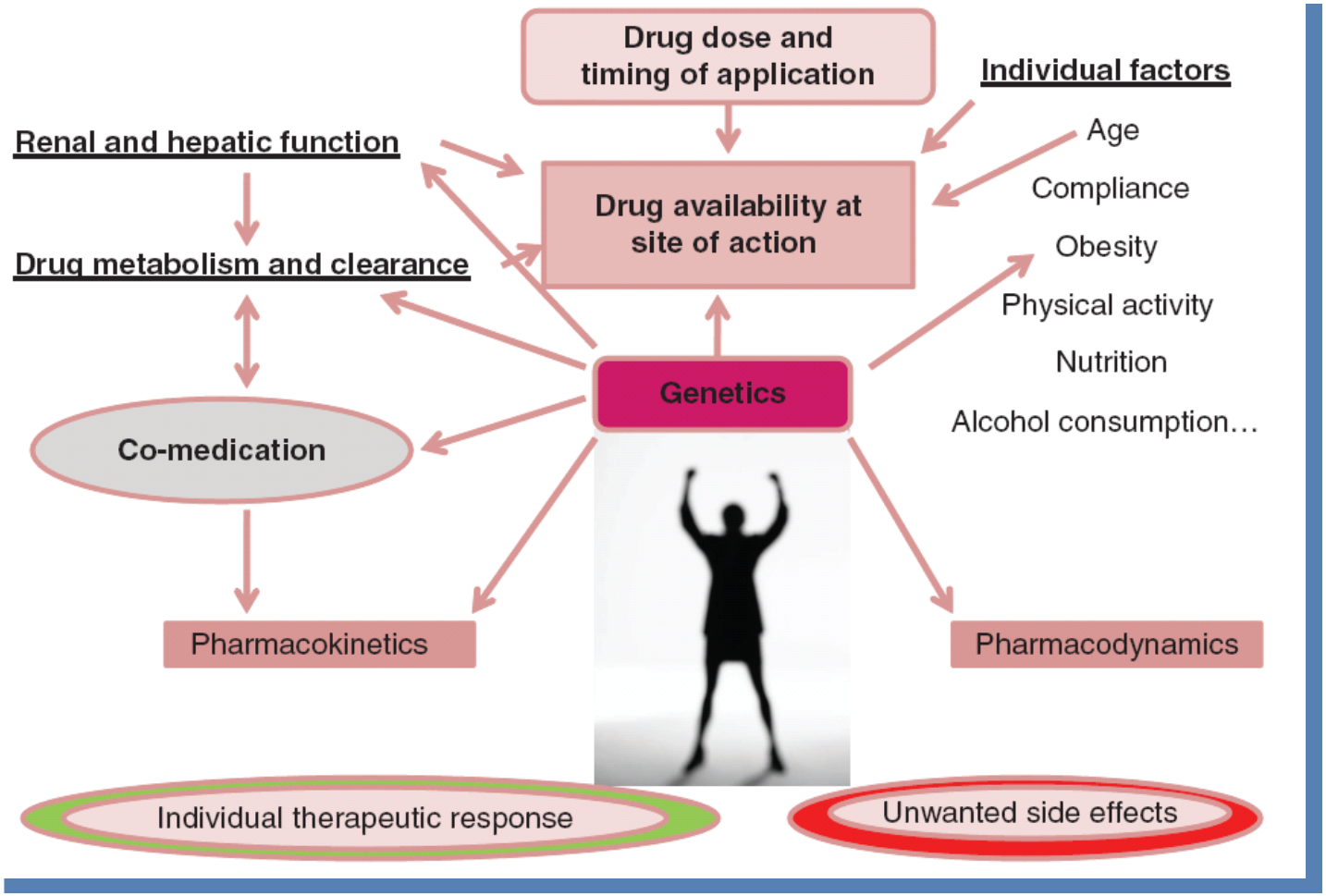
2012 Joint Conference of Drug Safety Research Centres
Hong Kong, 20 November 2012

Pharmacogenomic Tests for Improving Drug Safety and Effectiveness

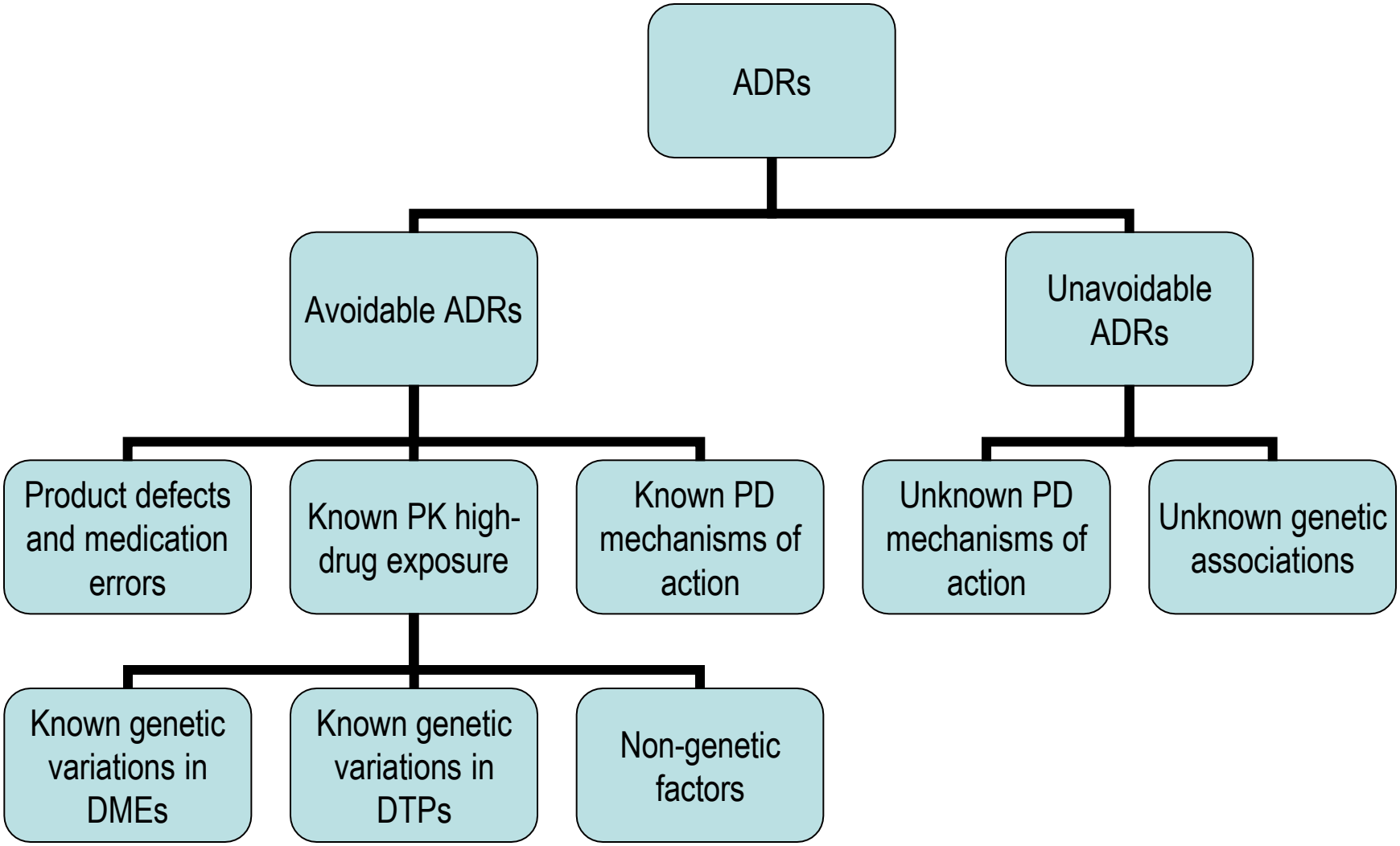
Brian Tomlinson
Professor of Medicine and Therapeutics
Division of Clinical Pharmacology
Department of Medicine & Therapeutics

Interaction of factors resulting in individual therapeutic drug response and side effects



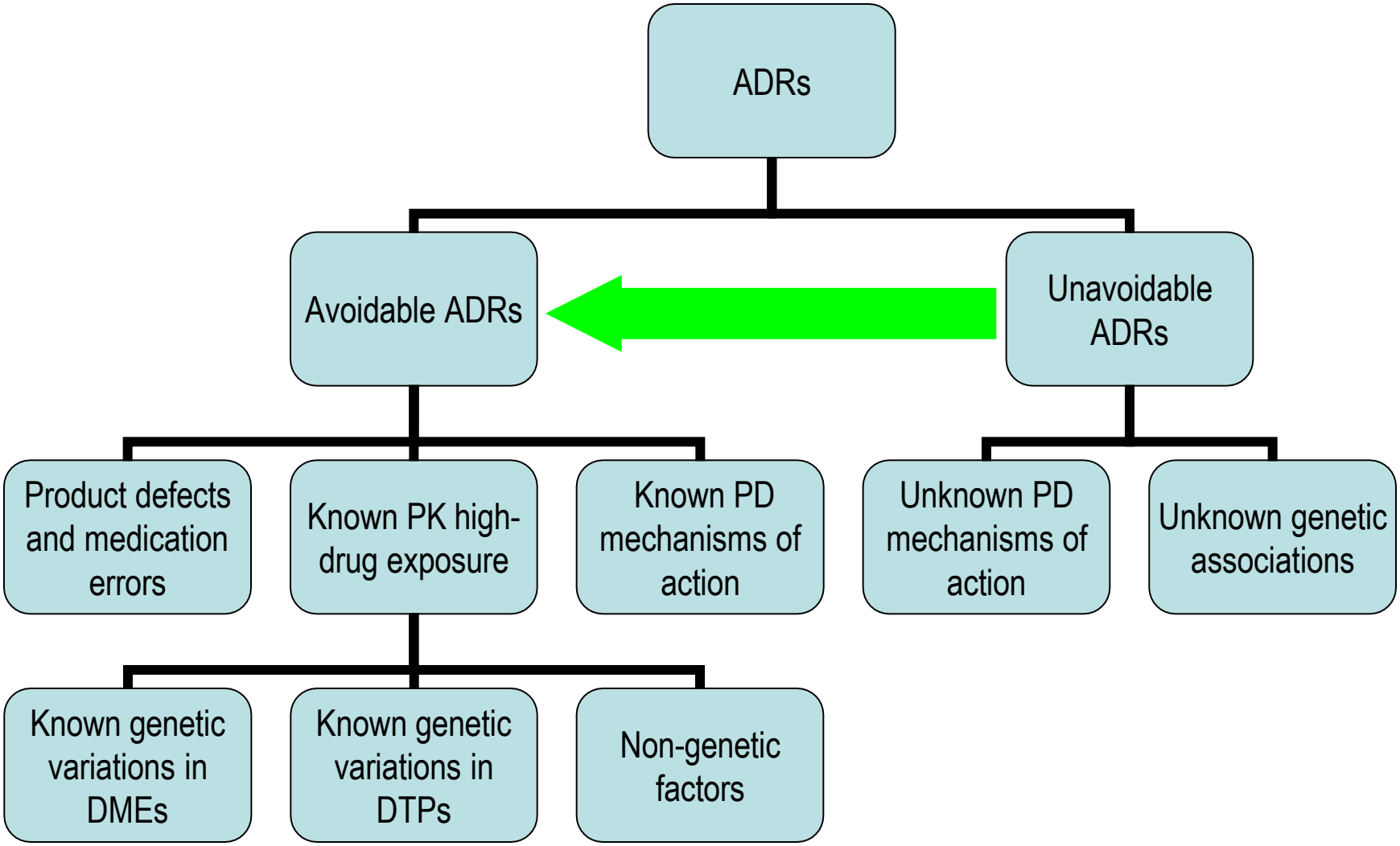
Holstein A, et al. Br J Diabetes Vasc Dis 2011;11:10-16.

Avoidable and unavoidable adverse drug reactions



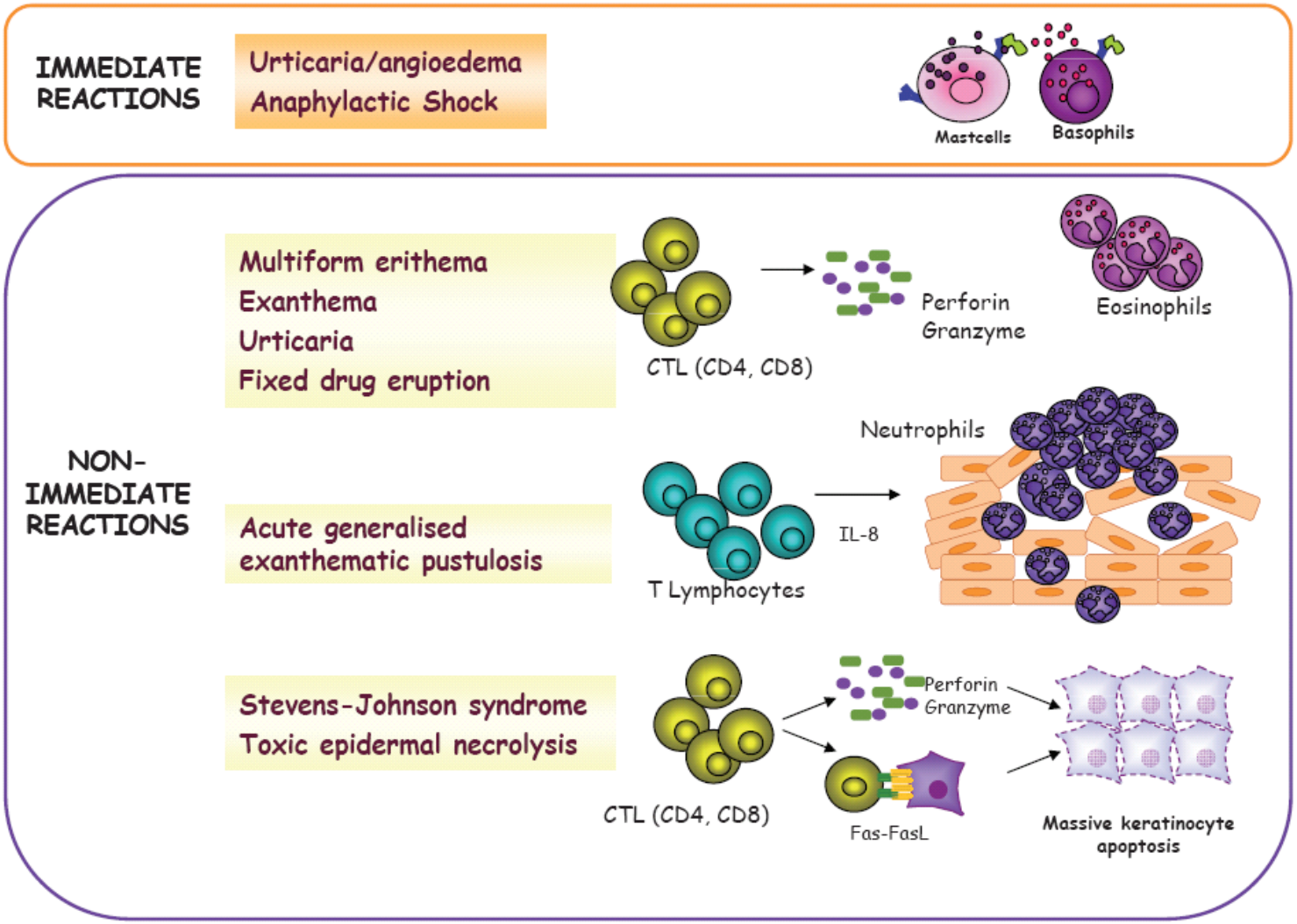
Adapted from Amur S et al, CDER, FDA. Personalized Medicine (2010) 7(6), 633–642.

Avoidable and unavoidable adverse drug reactions



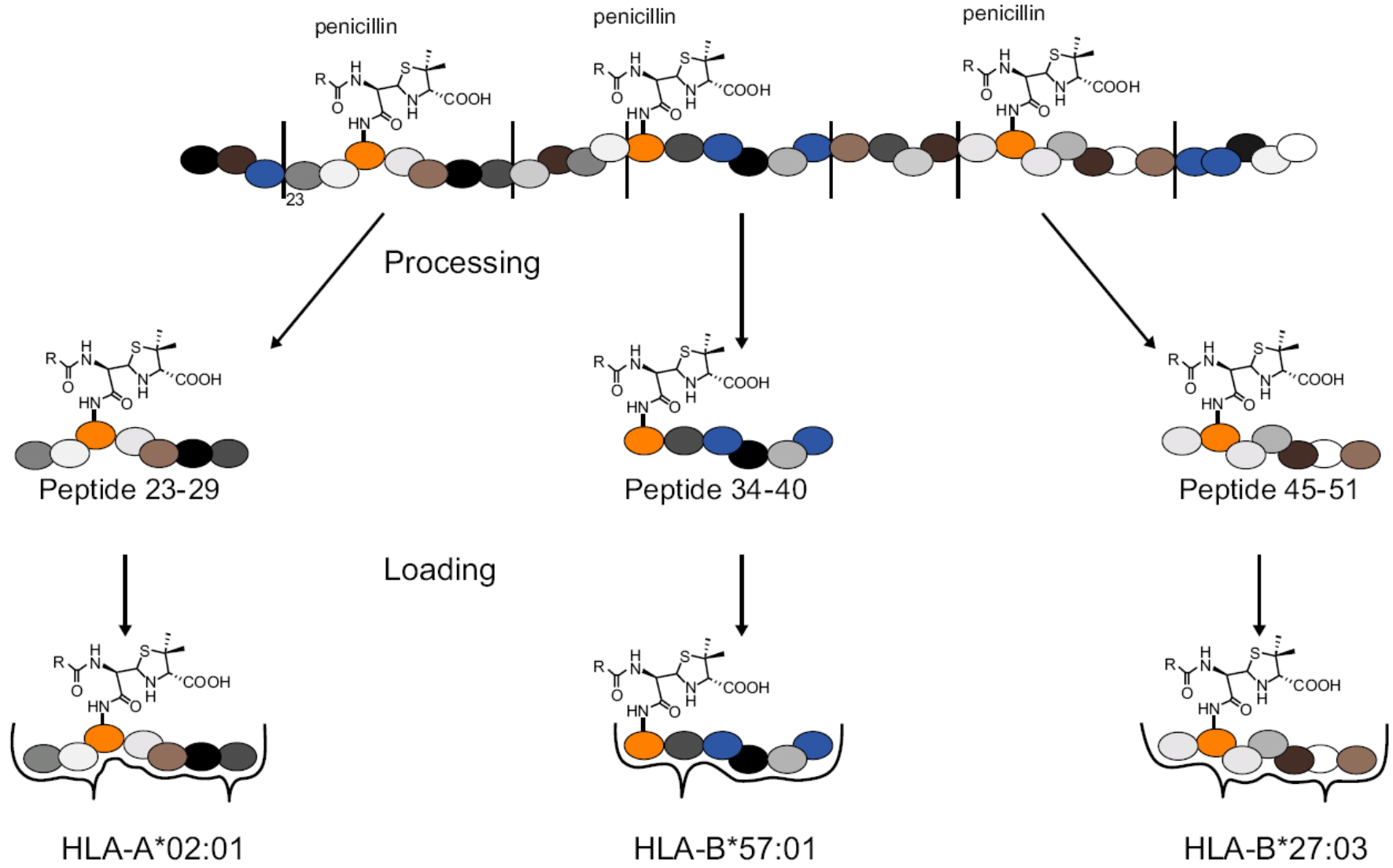
Adapted from Amur S et al, CDER, FDA. Personalized Medicine (2010) 7(6), 633–642.

Immunological mechanism in immediate and non-immediate reactions to drugs



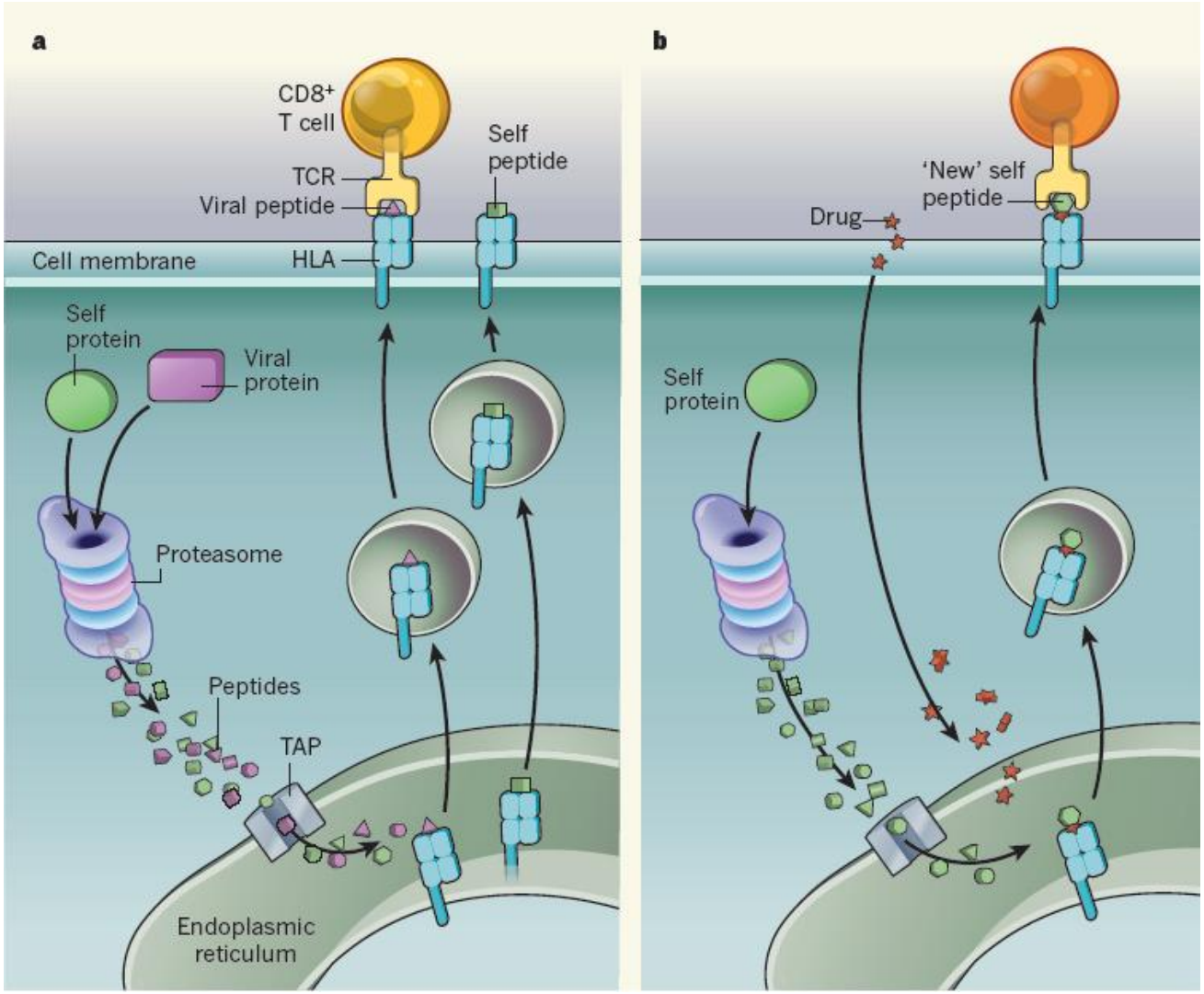
Adapted from Gómez E et al. Allergy Asthma Immunol Res 2012;4(5): 251-263.

Hapten–protein interaction and HLA restriction



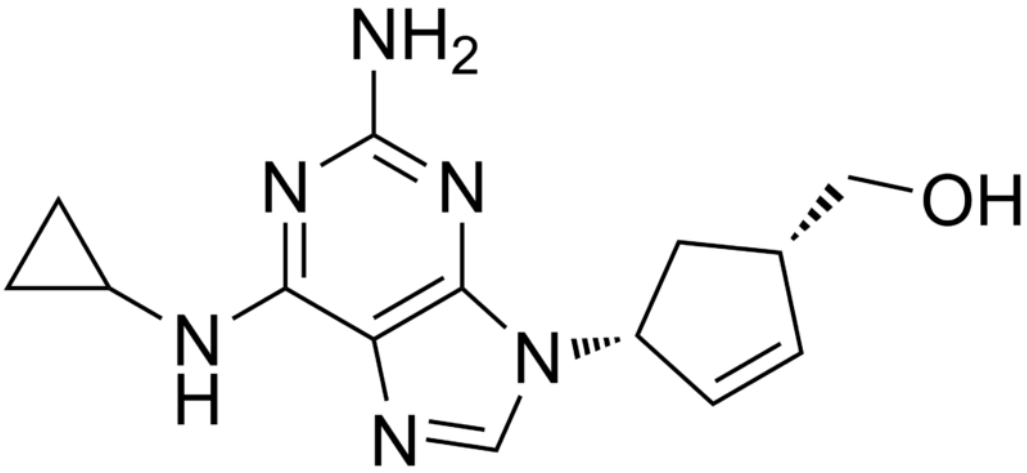
Yun J et al. Allergy 2012; DOI: 10.1111/all.12008.

Mistaken identity



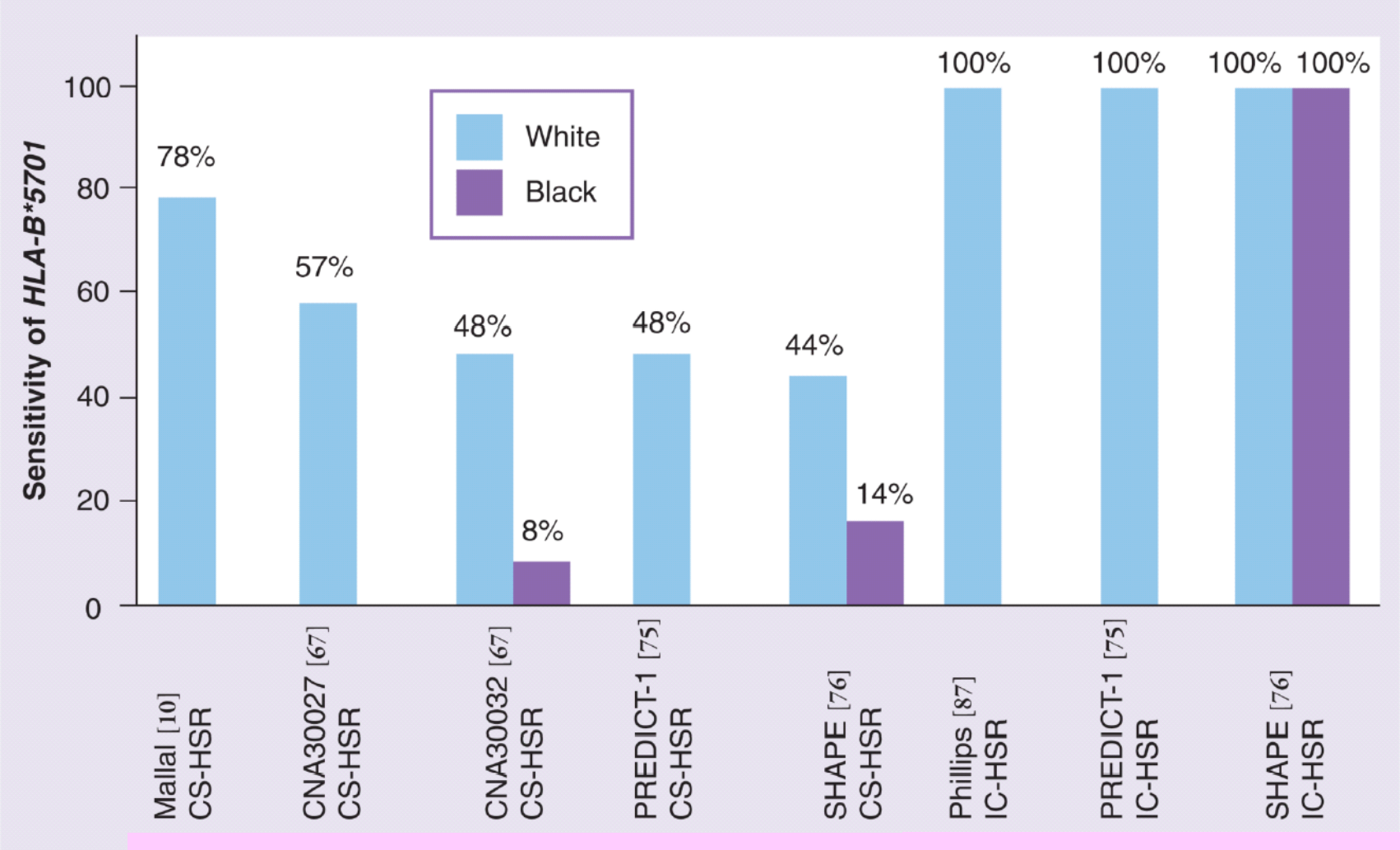
Adapted from Reinherz EL. Nature 2012; 486: 479-81.

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 - HLAB*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.)

Sensitivity of *HLA-B*5701* for abacavir hypersensitivity



Phillips EJ & Mallal SA. Pharmacogenomics. 2010; 11(7): 973–87.

Changes in the drug label for abacavir

Abacavir drug label change introduced by the EMEA in 2008

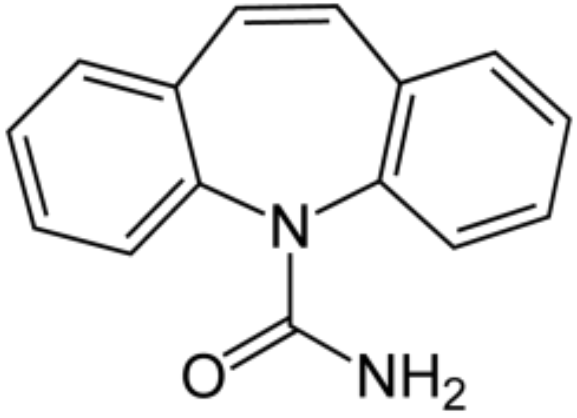
Before initiating treatment with abacavir, screening for carriage of the *HLA-B*5701* allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the *HLA-B*5701* allele, unless no other therapeutic option is available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

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

Hypersensitivity reactions

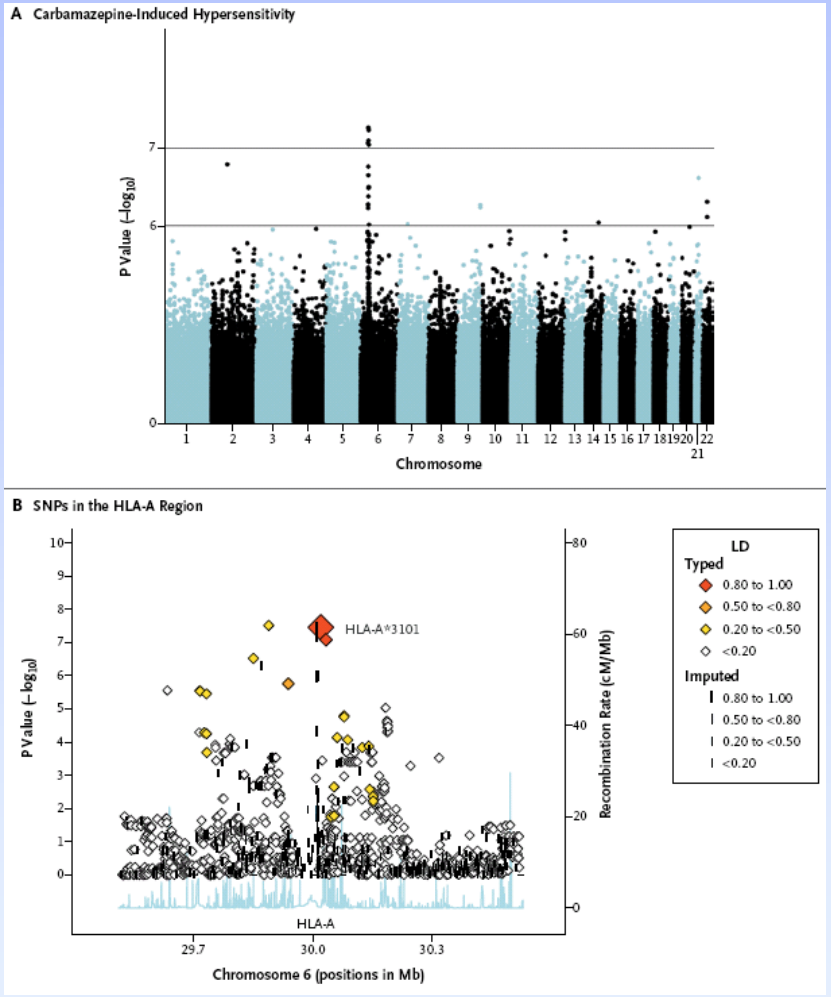


- Carbamazepine - cutaneous ADRs ranging from mild to severe (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- 2004 - *HLAB*1502* gene variant is highly associated with SCARs with carbamazepine (Chung WH, et al. Nature. 2004; 428(6982):486.)
- *HLAB*1502* genotype frequency varies in different areas
- 2011 - 4877 subjects genotyped in Taiwan – 7.7% positive for *HLAB*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.)

Area with high prevalence of HLA B*1502 (>5%)

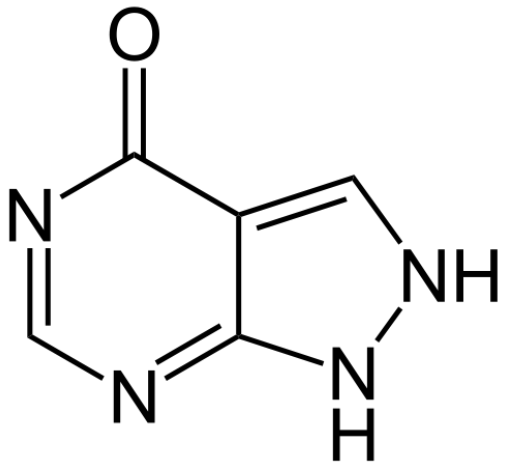
Lim KS et al. Neurology Asia 2008; 13:15-21.

HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans



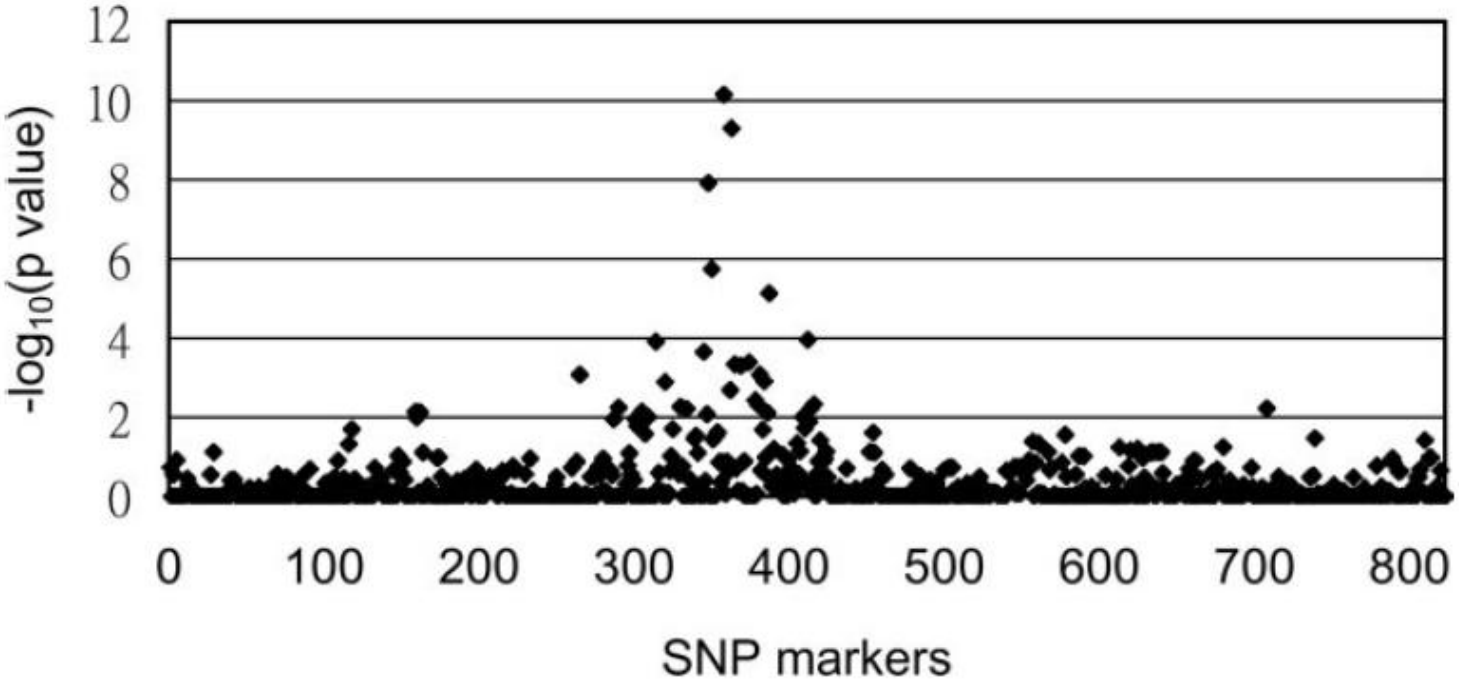
McCormack M et al. N Engl J Med 2011;364:1134-43.

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.)

SNPs association with allopurinol-induced SCAR



51 patients with allopurinol–SCAR and 228 control individuals (135 allopurinol-tolerant subjects and 93 healthy subjects)

823 SNPs ordered by their chromosome positions; 197 SNPs in the MHC region

*HLA-B*5801* allele present in all 51 patients with allopurinol–SCAR, but only in 20 (15%) of 135 tolerant patients [OR 580.3 (95% CI, 34.4–9780.9); corrected *P* value 4.7×10^{-24}]

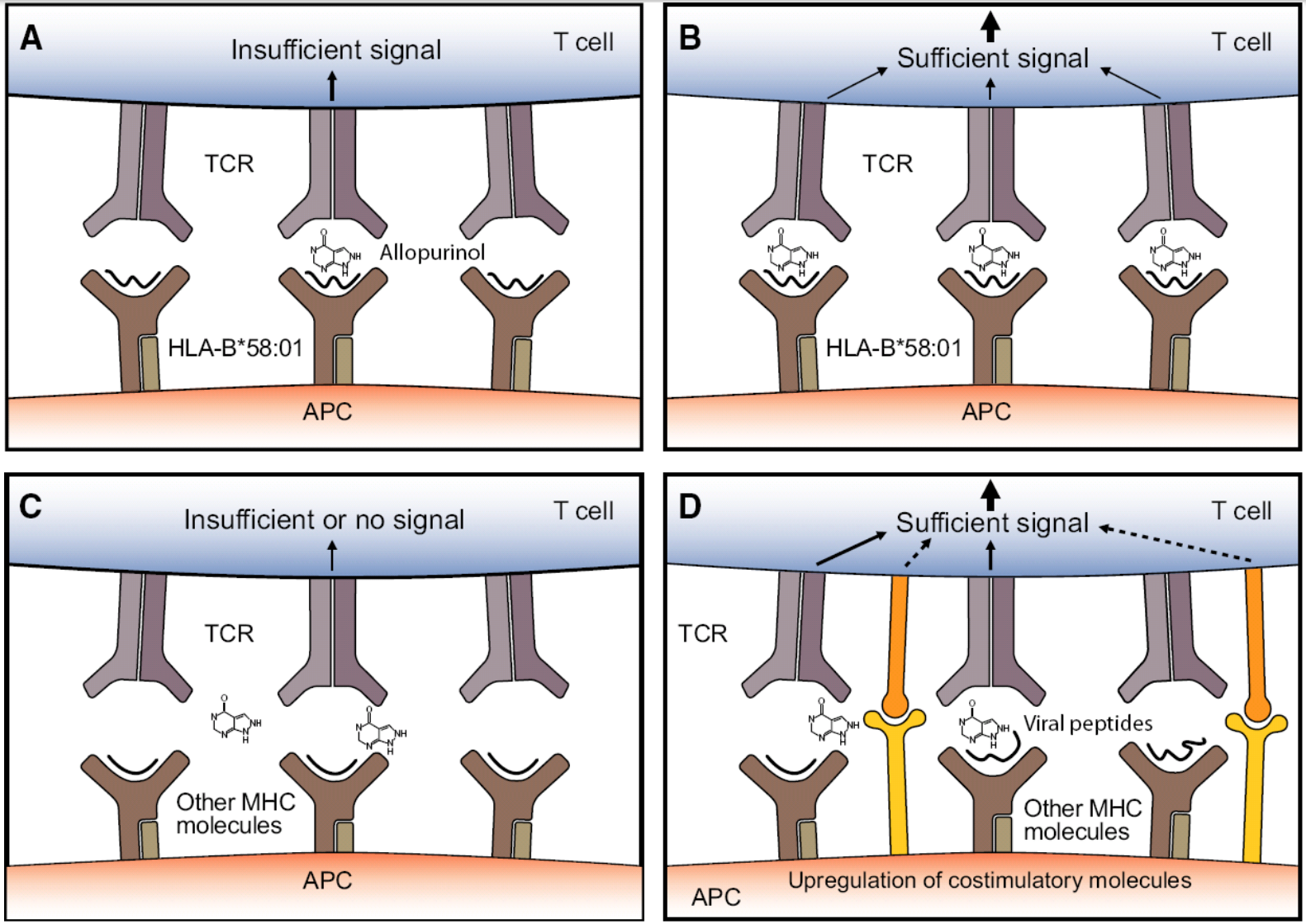
Hung SI, et al. Proc Natl Acad Sci U S A. 2005; 102(11): 4134-9.

Allele frequencies for *HLA-B*5801* in populations with allopurinol induced SJS/TEN

Country/region	Major population	HLA-B*5801 allele frequency (%)
Taiwan	Han-Chinese	10
Hong Kong	Han-Chinese	10.2
Thailand	Thai	7.7
China	Northern Han-Chinese	2.9
	Southern Han-Chinese	8.9
Japan	Japanese	4.0
US African American	African	6.4
France	European	4.5

Lee MT et al., Expert Opin. Pharmacother. 2010;11:2153-2162.

Possible mechanisms involved in allopurinol recognition by T cells



Yun J et al. Allergy 2012; DOI: 10.1111/all.12008.

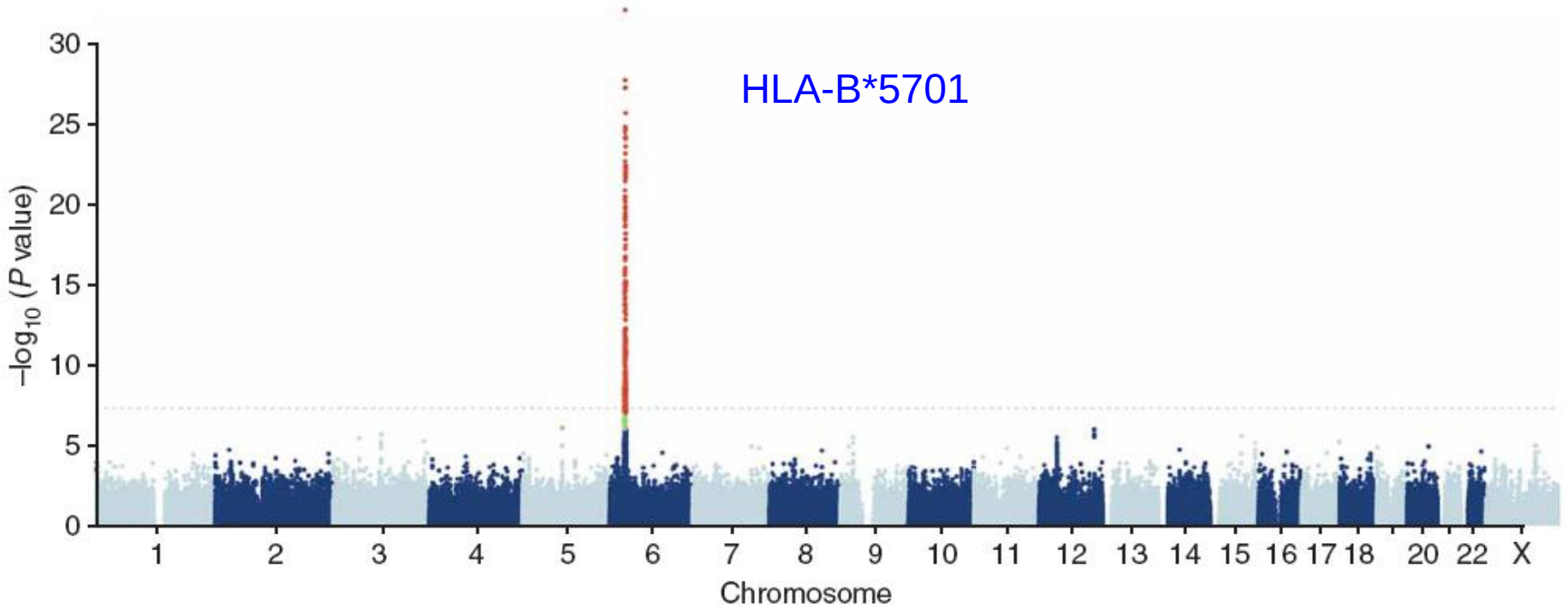
2012 American College of Rheumatology Guidelines for Management of Gout

- **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).**

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

Drug-induced liver injury due to flucloxacillin

- In the UK, the incidence of flucloxacillin-induced DILI has been estimated at 8.5 in every 100,000 new users in days 1 to 45 after starting treatment
- GWA study using 866,399 markers in 51 cases of flucloxacillin DILI and 282 controls matched for sex and ancestry.



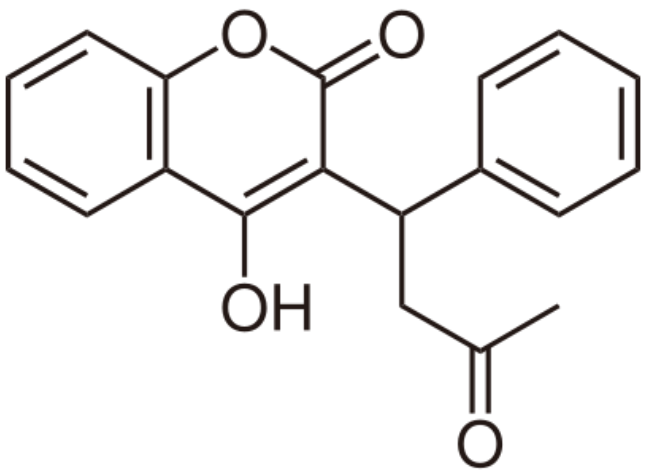
Daly AK et al. Nat Genet 2009;41:816-9.

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

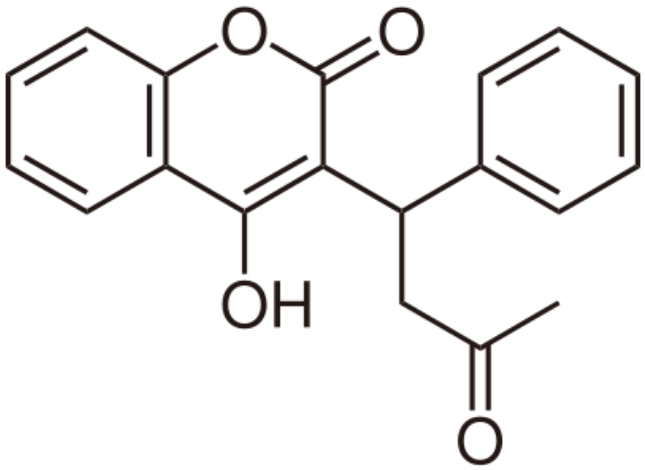
Drug	HLA allele	HLA carriage rate	Prevalence of diagnosis	Negative predictive value	Positive predictive value	NNT to prevent one case
Abacavir	B*5701	6-8% Caucasian, <1% African/Asian, 2.5% African American	8% (3% true HSR + 2-7% false positive Dx)	100% for patch test confirmed	55%	13
Carbamazepine	B*1502	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

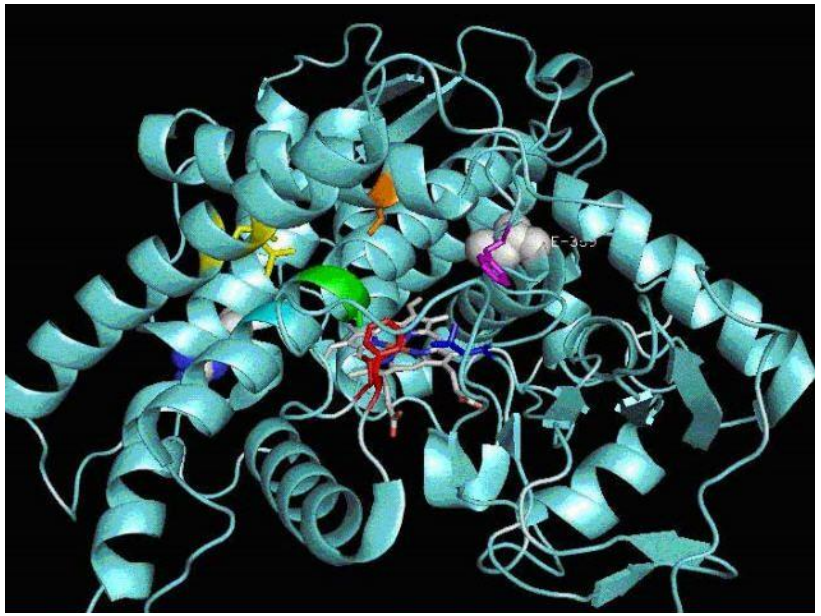
Phillips EJ, et al. J Allergy Clin Immunol. 2011; 127(3 Suppl): S60-6.

Warfarin Sensitivity



Warfarin Sensitivity





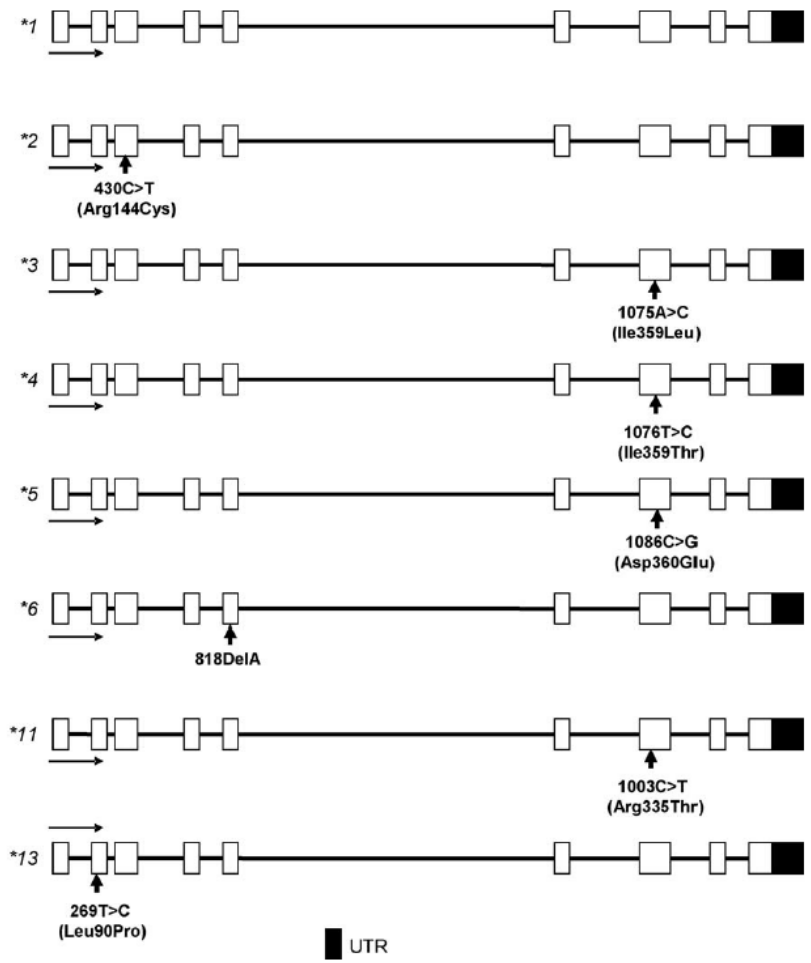
Cytochrome P450 2C9 (CYP2C9)

S-warfarin
R-warfarin

→ Metabolized by CYP2C9

← Metabolized by CYP1A1, CYP1A2, CYP3A4

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.

Warfarin Sensitivity

Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2

Simone Rost[1,2]*, Andreas Fregin[1]*, Vytautas Ivaskevicius[3], Ernst Conzelmann[4], Konstanze Hörtnagel[2], Hans-Joachim Pelz[5], Knut Lappegard[6], Erhard Seifried[3], Inge Scharrer[7], Edward G. D. Tuddenham[8], Clemens R. Müller[1], Tim M. Strom[2,9] & Johannes Oldenburg[1,3]

Nature 2004;427:537-41.

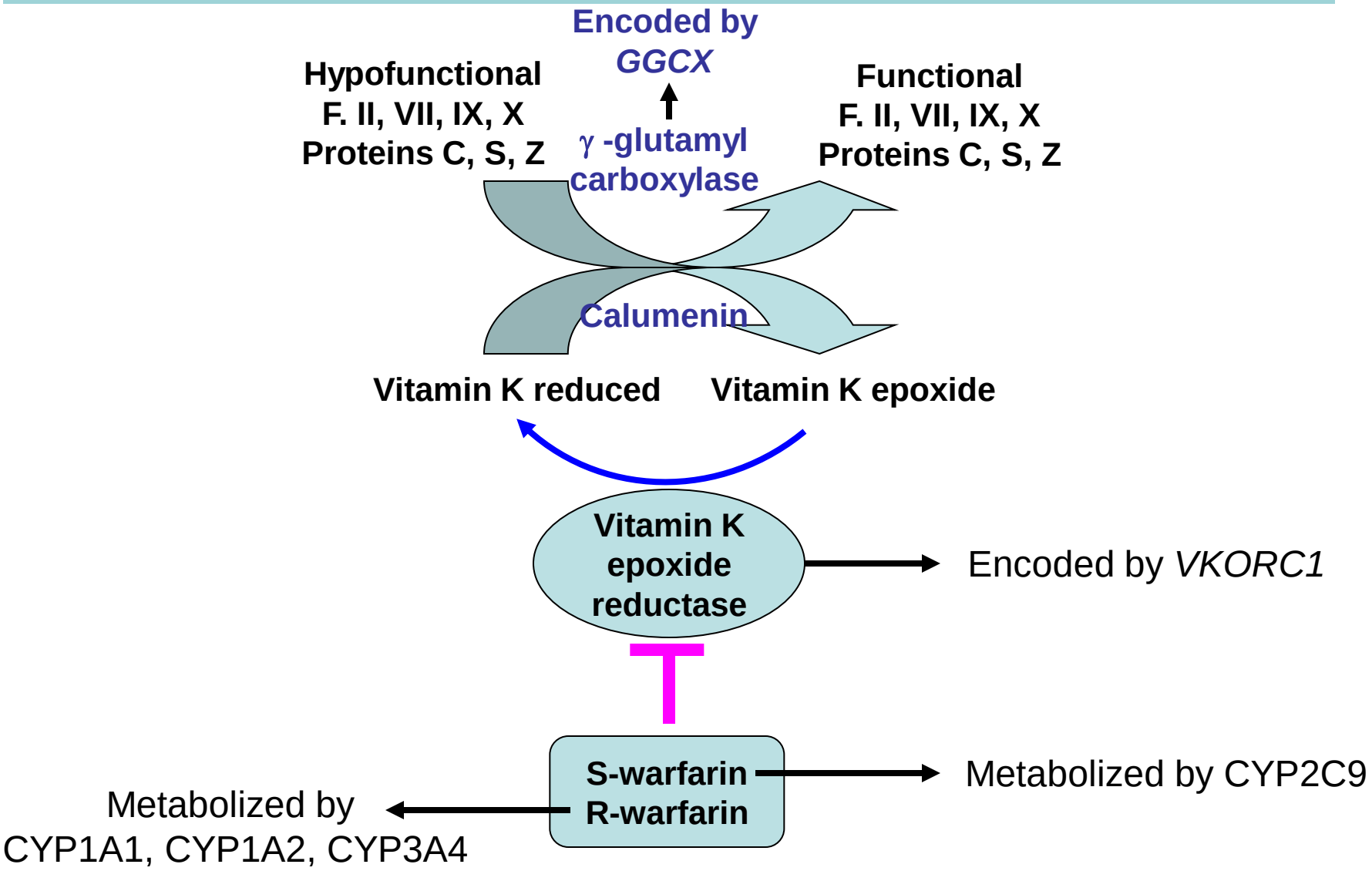
Identification of the gene for vitamin K epoxide reductase

Tao Li[1], Chun-Yun Chang[1], Da-Yun Jin[1], Pen-Jen Lin[1], Anastasia Khvorova[2] & Darrel W. Stafford[1]

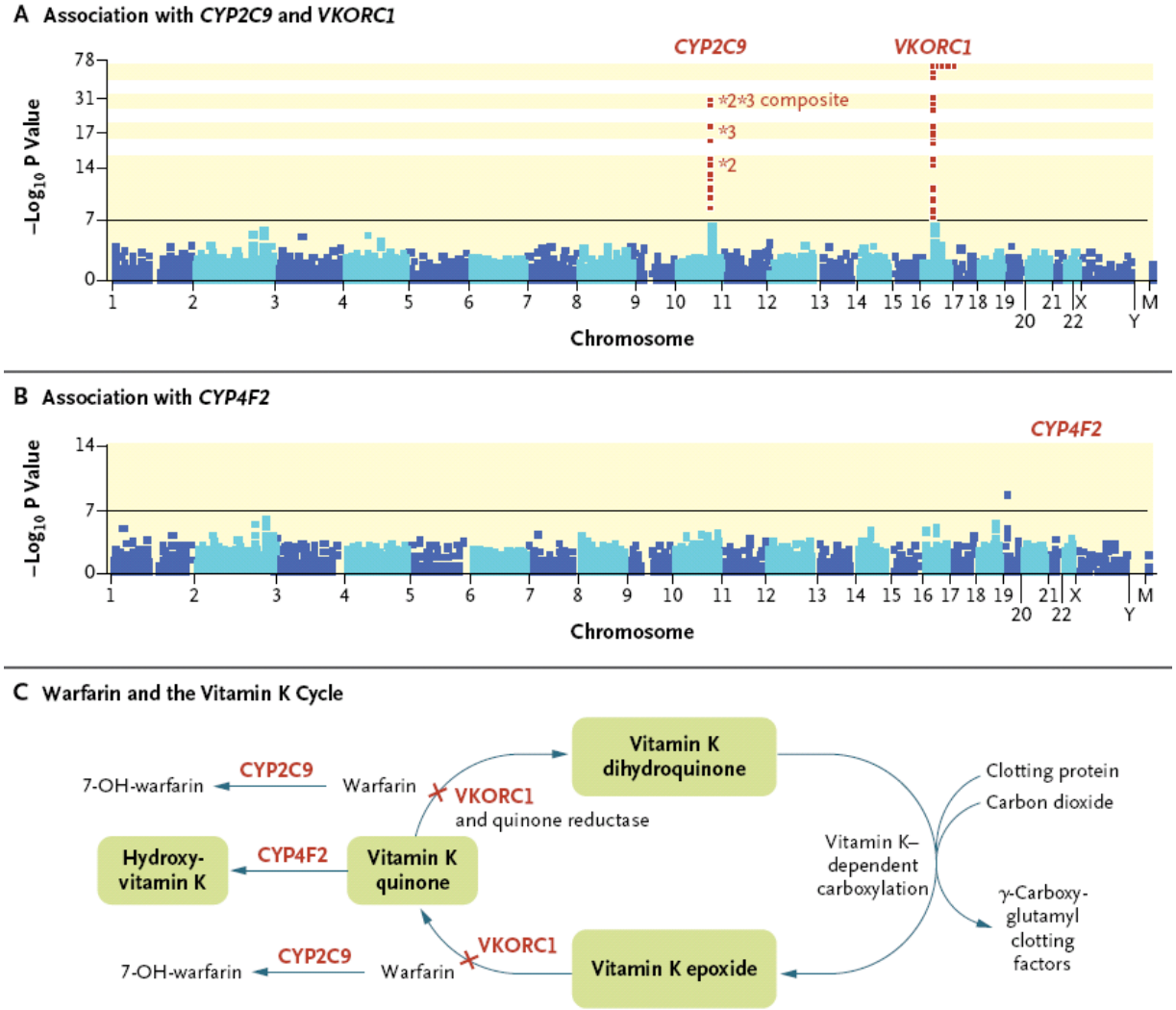
[1]*Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA*
[2]*Dharmacon, Inc., 1376 Miners Drive 101, Lafayette, Colorado 80026, USA*

Nature 2004;427:541-4.

Pharmacology of Warfarin



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 News

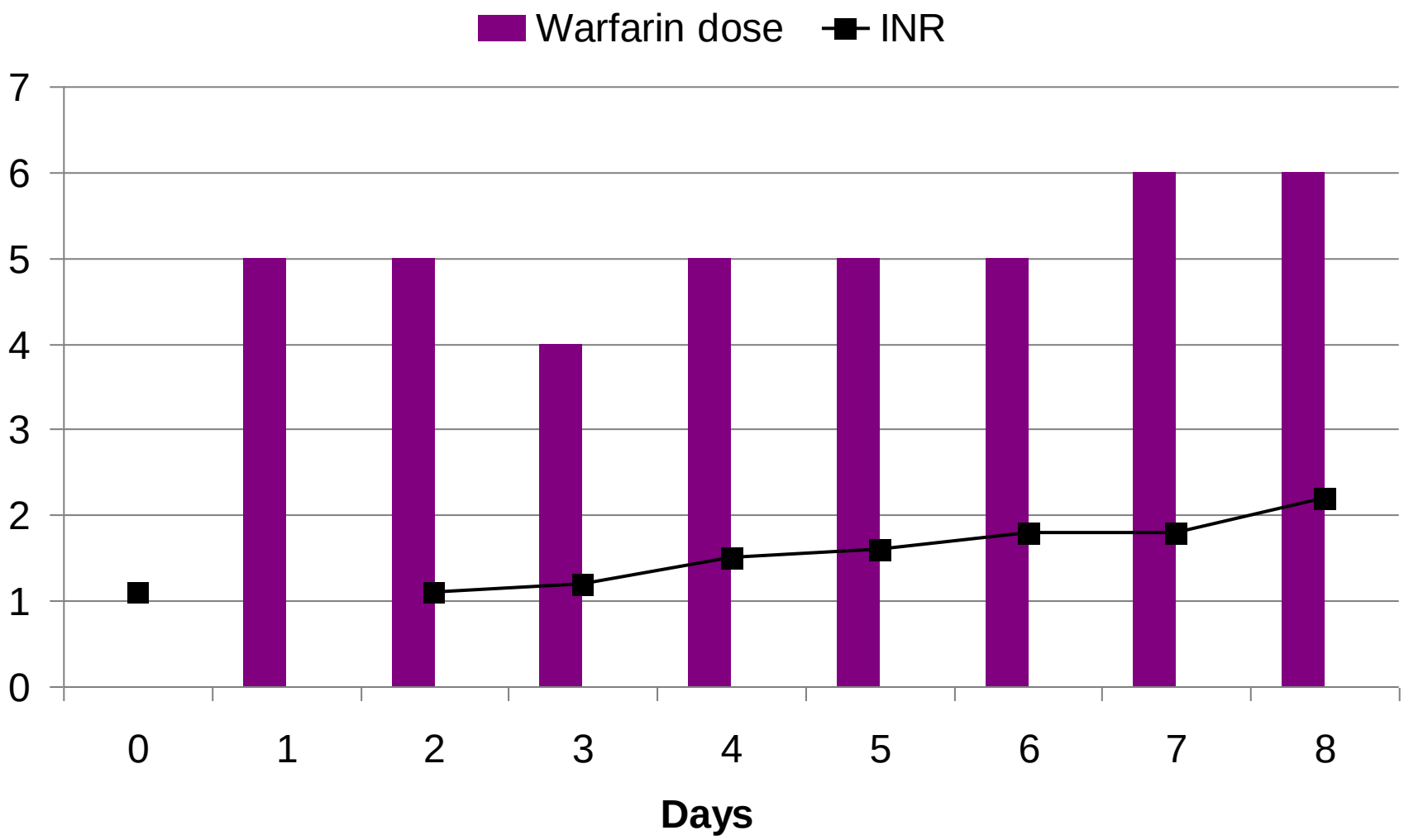
FOR IMMEDIATE RELEASE
September 17, 2007

FDA Clears Genetic Lab Test for Warfarin Sensitivity

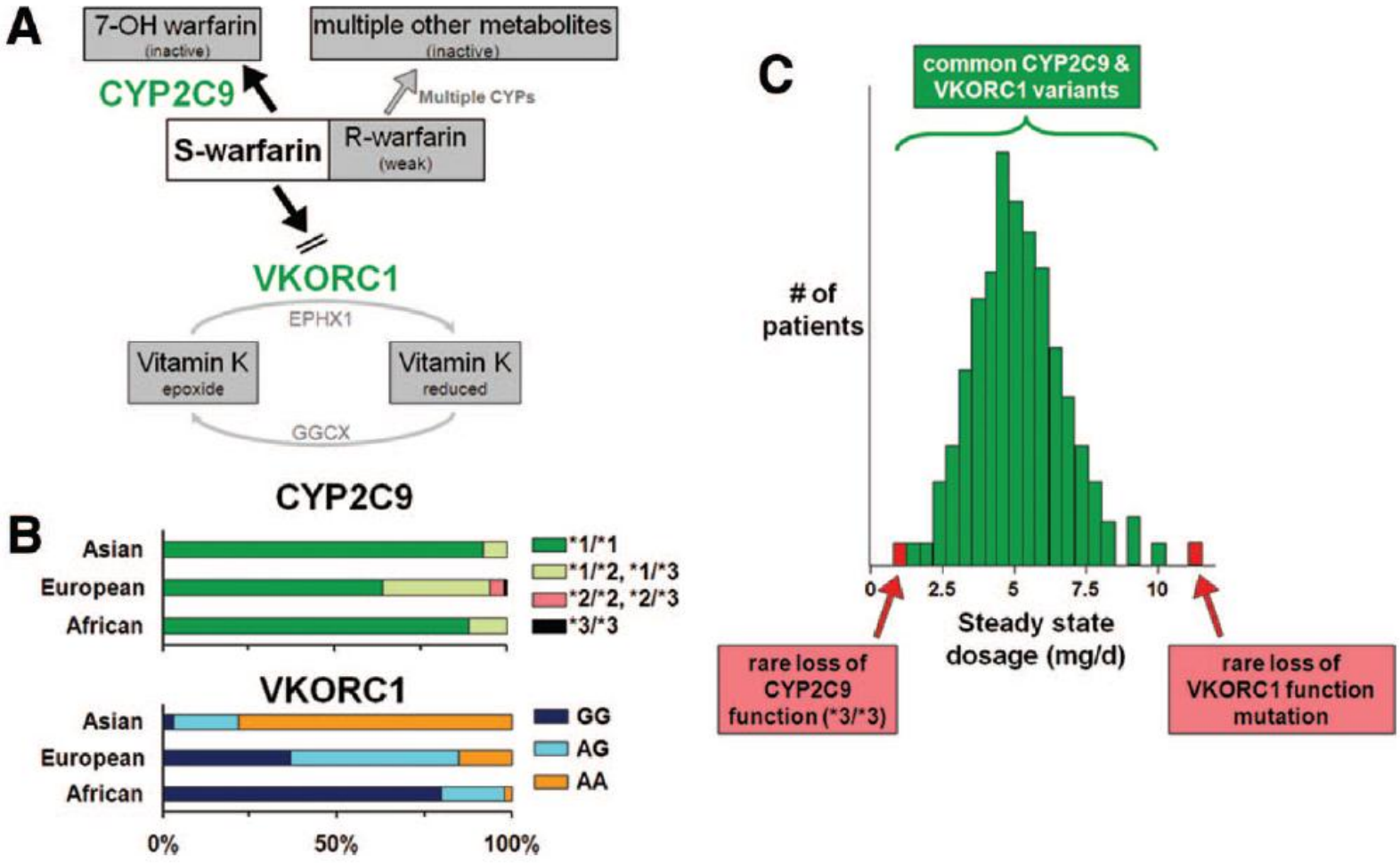
The U.S. Food and Drug Administration today cleared for marketing a new genetic test that will help physicians assess whether a patient may be especially sensitive to the blood-thinning drug warfarin (Coumadin), which is used to prevent potentially fatal clots in blood vessels.

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.

Warfarin titration



Contributions of multiple genes to phenotype of warfarin maintenance dose requirement



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

FDA guideline on 8 June 2011 on simvastatin 80 mg

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

Home> News & Events> Newsroom> Press Announcements

News & Events

FDA NEWS RELEASE

For Immediate Release: June 8, 2011
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA announces new safety recommendations for high-dose simvastatin
Increased risk of muscle injury cited

The U.S. Food and Drug Administration today is announcing safety label changes for the cholesterol-lowering medication simvastatin because the highest approved dose--80 milligram (mg)--has been associated with an elevated risk of muscle injury or myopathy, particularly during the first 12 months of use.

The agency is recommending that simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. It should not be prescribed to new patients. There are also new contraindications and dose limitations for when simvastatin is taken with certain other medications.

Simvastatin is used together with diet and exercise to reduce the amount of "bad cholesterol" (low-density lipoprotein cholesterol or LDL-C) in the blood. High levels of LDL-C are linked to a higher risk of heart attack, stroke and cardiovascular death. In 2010, about 2.1 million patients in the United States were prescribed a product containing simvastatin 80 mg.

"The FDA has completed its review of the safety of high-dose simvastatin and is making label changes to reduce the risk of statin-associated muscle injury," said Eric Colman, M.D., deputy director of the Division of Metabolism and Endocrinology Products in the FDA's Center for Drug Evaluation and Research. "We want to ensure that patients and health care professionals are aware of the new labeling changes to simvastatin, including the increased risk of myopathy when using the 80 mg dose of simvastatin."

The changes to the label for simvastatin-containing medications are based on the FDA's review of the results of the seven-year Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine clinical trial, other clinical trial data, and analyses of adverse events submitted to the FDA's Adverse Event Reporting System. All showed that patients taking simvastatin 80 mg daily had an increased risk of muscle injury compared to patients taking lower doses of simvastatin or other statin drugs. The risk of muscle injury is highest during the first year of treatment with the 80 mg dose of simvastatin, is often the result of interactions with certain other medicines, and is frequently associated with a genetic predisposition for simvastatin-related muscle injury.

Simvastatin is sold under the brand-name Zocor and as a single-ingredient generic product. It is also sold in combination with ezetimibe as Vytorin and in combination with niacin as Simcor.

FDA News

Simvastatin Used With Amiodarone

Audience: Cardiologic healthcare professionals, pharmacists, other healthcare professionals

[Posted 08/08/2008] FDA notified healthcare professionals of the risk of muscle injury, rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone. This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. Although a revision of the simvastatin labeling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily, FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

[August 08, 2008 - Drug Information Page - FDA]

[August 08, 2008 - Information for Healthcare Professionals - FDA]

Changes in dose limitations for simvastatin to reduce drug-drug interactions following FDA guideline on 8 June 2011.

Interacting Drug	Previous daily dose limit	New daily dose limit
Posaconazole	No DDI restriction	Contraindicated with simvastatin
Gemfibrozil	10mg Simvastatin	Contraindicated with simvastatin
Cyclosporine		
Danazol		
Amiodarone	20mg Simvastatin	10mg Simvastatin (Later changed to 20mg for amiodarone)
Verapamil		
Diltiazem	40mg Simvastatin	10mg Simvastatin
Amlodipine	No DDI restriction	20mg Simvastatin
Ranolazine		

Available at: http://www.fda.gov/ Drugs/DrugSafety/ucm256581.htm

SLCO1B1 Variants and Statin-Induced Myopathy - a Genomewide Study

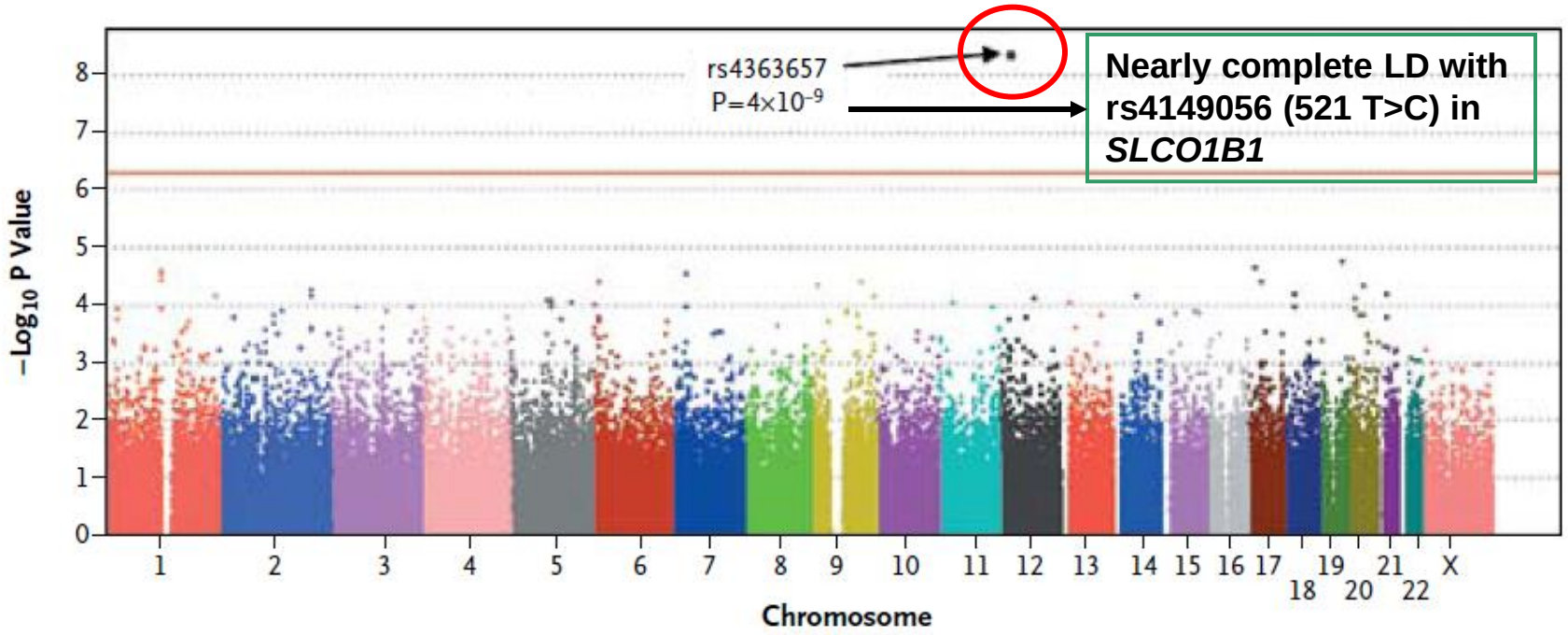
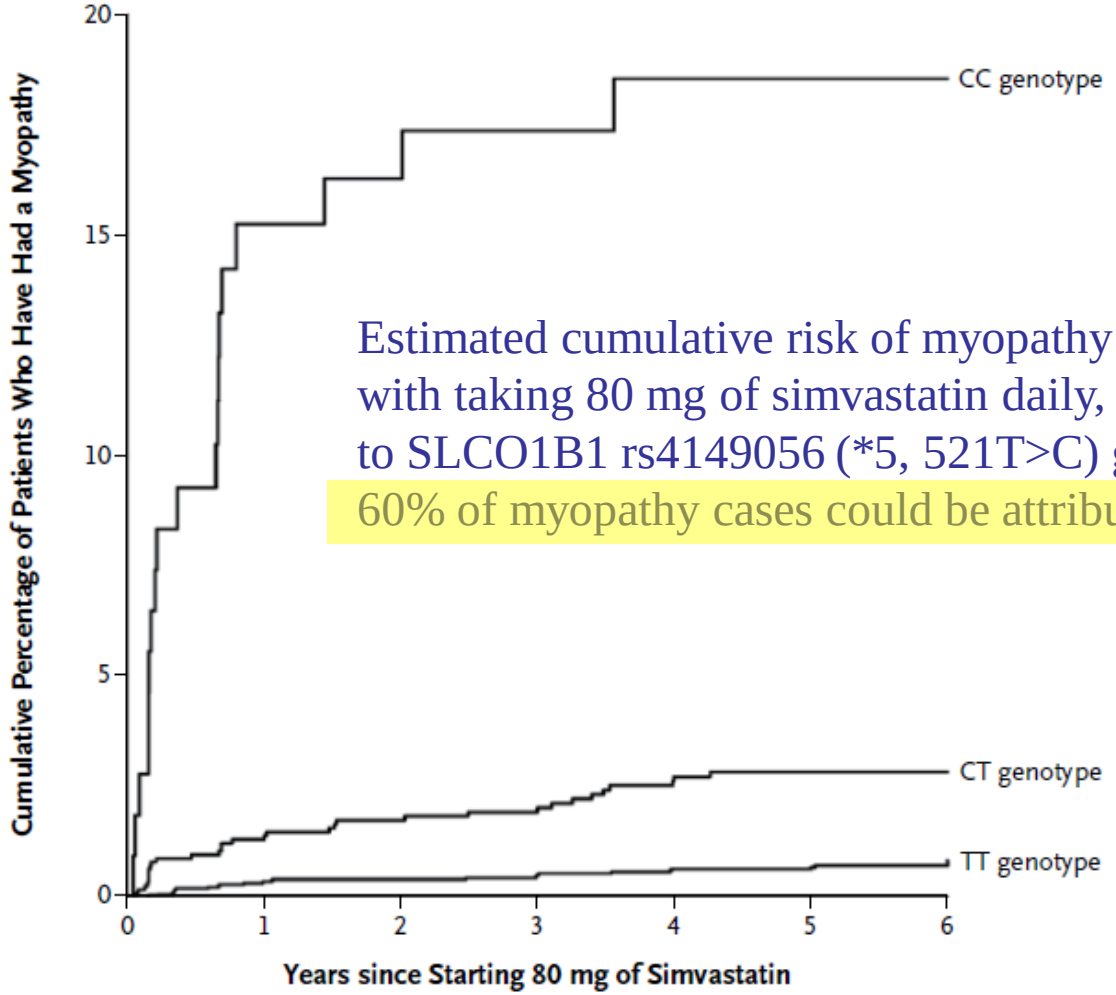


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<5\times10^{-7}$).

The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-99.

SLCO1B1 Variants and Statin-Induced Myopathy - a Genomewide Study

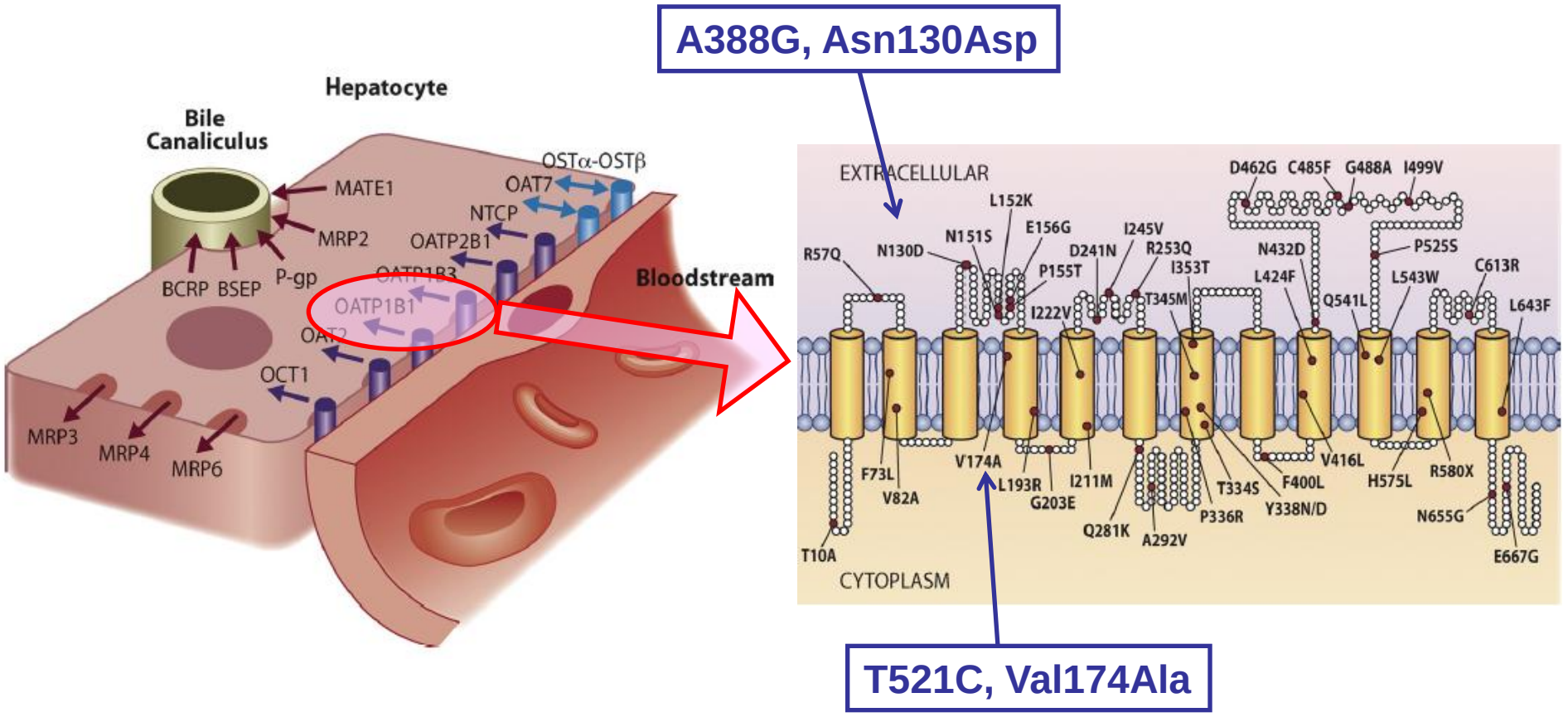


Estimated cumulative risk of myopathy associated with taking 80 mg of simvastatin daily, according to SLCO1B1 rs4149056 (*5, 521T>C) genotype.

60% of myopathy cases could be attributed to the C variant

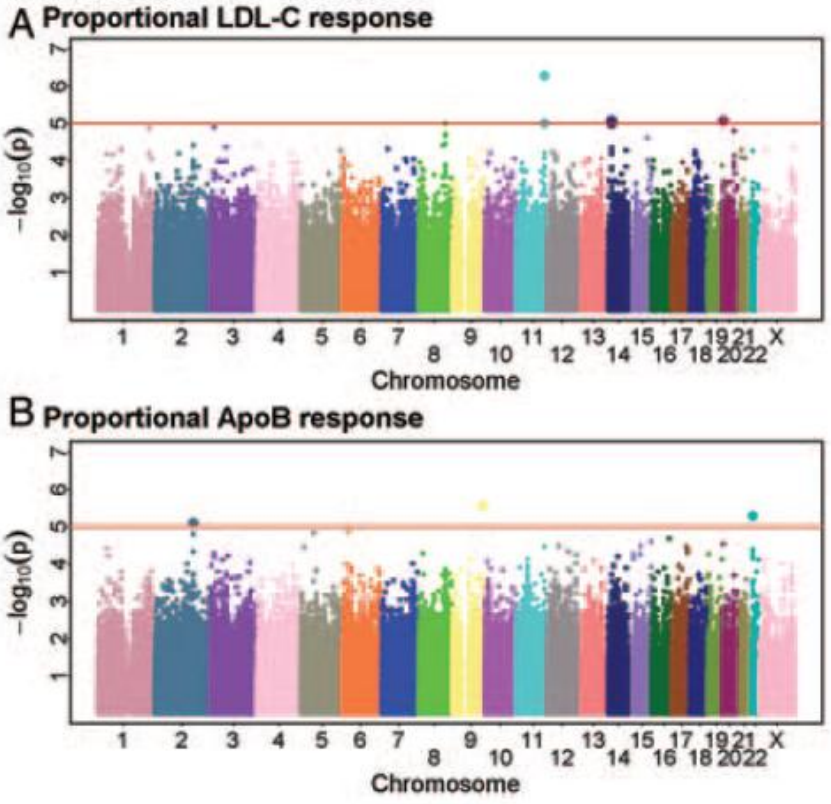
The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-99.

SLCO1B1 - Organic Anion Transporting Polypeptide 1B1



Niemi M et al. Pharmacol Rev 2011; 63:157–181.

LDL cholesterol and ApoB response to simvastatin



Gene/locus (SNP)	N	LDL–C (mmol/L) Mean off-statin (SE)	Per cent reduction (SE)	Absolute reduction (SE)
LPA score				
0 variants	11480	3.36 (0.008)	43.2% (0.1%)	1.41 (0.006)
1 variant	2794	3.43 (0.015)	40.0% (0.3%)	1.34 (0.012)
2 variants	185	3.56 (0.060)	37.5% (1.1%)	1.28 (0.047)
Per variant effect (SE)		*0.08 (0.015)* $P=1.1\times10^{-7}$	*−3.11 (0.27)* $P=4.4\times10^{-32}$	*−0.069 (0.012)* $P=7.8\times10^{-9}$
APOE (rs7412)				
0 ε2 variants	12305	3.45 (0.007)	42.1% (0.1%)	1.42 (0.006)
1 ε2 variant	2060	2.96 (0.016)	44.6% (0.3%)	1.28 (0.014)
2 ε2 variants	90	1.80 (0.056)	48.1% (1.3%)	0.85 (0.066)
Per ε2 variant effect (SE)		*−0.55 (0.017)* $P=2.1\times10^{-215}$	*2.55 (0.29)* $P=4.8\times10^{-18}$	*−0.159 (0.014)* $P=2.7\times10^{-30}$
SLCO1B1 score				
Lower third	3686	3.38 (0.013)	43.3% (0.2%)	1.42 (0.010)
Middle third	4322	3.35 (0.012)	42.6% (0.2%)	1.39 (0.010)
Upper third	4059	3.39 (0.013)	41.5% (0.2%)	1.37 (0.010)
Per group effect (SE)		*0.00 (0.009)* $P=0.62$	*−0.88 (0.16)* $P=2.6\times10^{-8}$	*−0.025 (0.007)* $P=4.9\times10^{-4}$

35% 40% 45% 50%
Percent reduction (95% CI)

Hopewell JC et al. Eur Heart J. 2012.

VANDERBILT UNIVERSITY MEDICAL CENTER

Vanderbilt doctors to screen patients taking cholesterol-lowering drugs for harmful genetic variation

October 28, 2011
Vanderbilt University Medical Center doctors announced today they will begin screening patients who take commonly prescribed statin drugs for a rare genetic variation that can increase risks for side effects from these drugs such as muscle aches, kidney damage and even death.
Statin drugs are among the world's most commonly prescribed medications and are used to lower cholesterol levels in the blood.
Simvastatin, the generic form of the statin Zocor, is one of the most widely prescribed drugs in the United States and is effective in reducing LDL-cholesterol levels and lowering the risk for heart attacks and strokes.

But growing evidence indicates that about 2 percent of patients taking 80 milligrams of simvastatin per day will experience muscle aches that could lead to muscle damage. In extreme cases complications can be more severe, such as kidney damage and even death.
The risk for developing complications is increased when a patient carries even a single genetic variation, according to Vanderbilt's Dan Roden, M.D., assistant vice chancellor for Personalized Medicine.

"If you have two copies of the SLC01B1 gene, you're at an almost 20-fold increased risk of muscle toxicity," he said.

http://www.mc.vanderbilt.edu/news/releases.php?release=2263

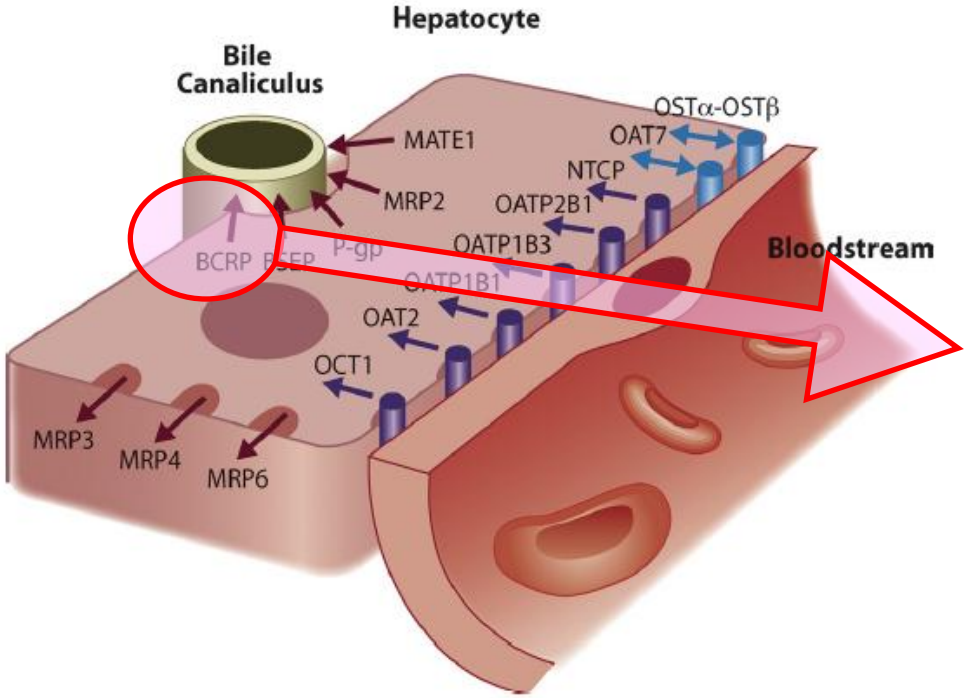
Rosuvastatin dose in Asians

FDA issues rosuvastatin advisory highlighting revised label

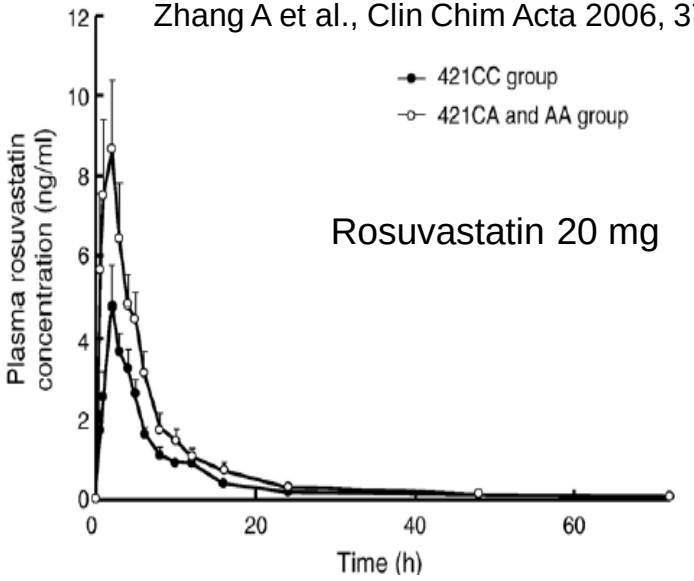
March 2, 2005
Wilmington, DE - The **Food and Drug Administration** (FDA) issued a public-health advisory on **rosuvastatin** (Crestor®) today that highlights a revised package insert for the cholesterol-lowering medication.

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.

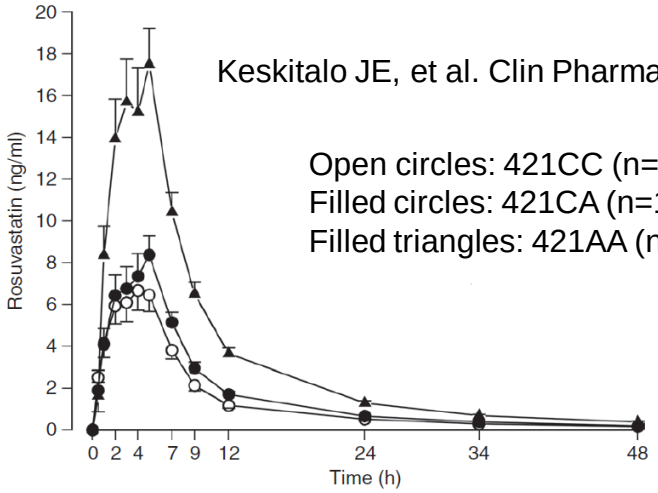
BCRP - *ABCG2* – ATP binding cassette G2 efflux transporter



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



Rosuvastatin 20 mg



Keskitalo JE, et al. Clin Pharmacol Ther 2009

Open circles: 421CC (n=16);
Filled circles: 421CA (n=12);
Filled triangles: 421AA (n=4).

Niemi M et al. Pharmacol Rev 2011; 63:157–181.

ABCG2 polymorphism increases rosuvastatin plasma levels and efficacy

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

B Tomlinson[1], M Hu[1], VWY Lee[2], SSH Lui[1], TTW Chu[1], E Poon[1], GTC Ko[3], L Baum[2], LS Tam[1] and EK Li[1]

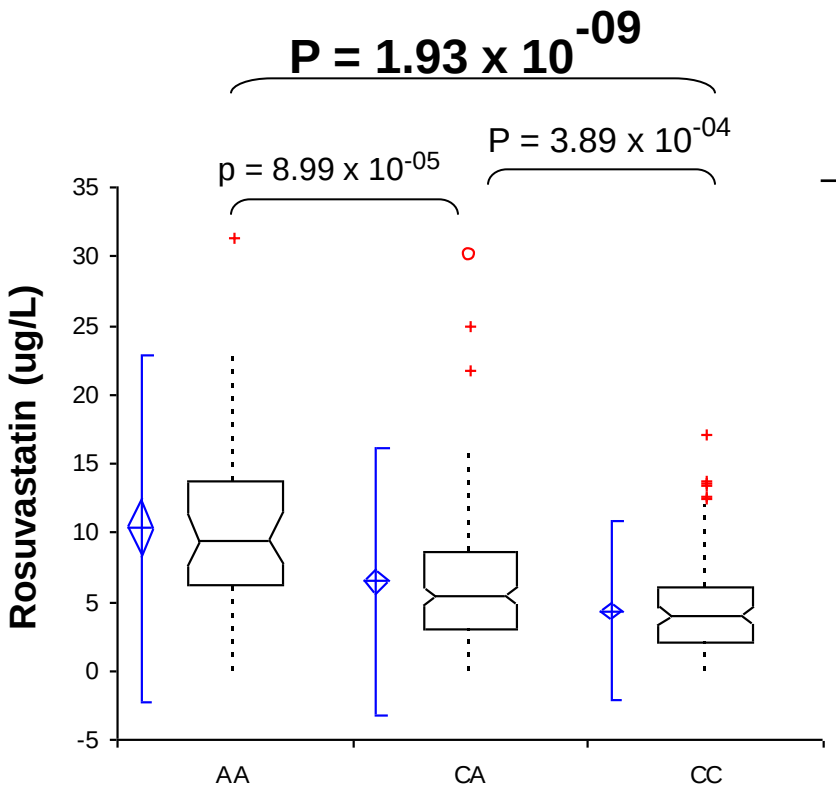
The ATP-binding cassette G2 (*ABCG2*) c.421C>A (rs2231142) polymorphism influences the pharmacokinetics of rosuvastatin. We examined whether this polymorphism influences the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of the drug. In 305 Chinese patients with hypercholesterolemia who were treated with rosuvastatin at a dosage of 10 mg daily, the c.421A variant was found to be significantly associated with greater reduction in LDL-C level, in a gene-dose-dependent manner. As compared with subjects with the c.421CC genotype, those with the c.421AA genotype showed a 6.9% greater reduction in LDL-C level, which would be equivalent to the effect obtained by doubling the dose of rosuvastatin.

in drug metabolizing enzymes, given that rosuvastatin undergoes relatively little enzymic modification and is a substrate for a number of drug transporters that influence its disposition.[5,6]

The efflux transporter ATP-binding cassette G2 (ABCG2) plays a significant role in the disposition of rosuvastatin *in vitro*.[7] The c.421C>A (rs2231142, Gln141Lys) single-nucleotide polymorphism of *ABCG2* influences the pharmacokinetics of rosuvastatin in Chinese and Caucasian subjects.[8,9] We examined whether this *ABCG2* single-nucleotide polymorphism influences the reduction of LDL-C levels when rosuvastatin is administered to Chinese patients with hypercholesterolemia, including some with familial hypercholesterolemia (FH).

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

Relationship of Genetic Variation and Pharmacokinetics of Rosuvastatin



ABCG2 c.421C>A

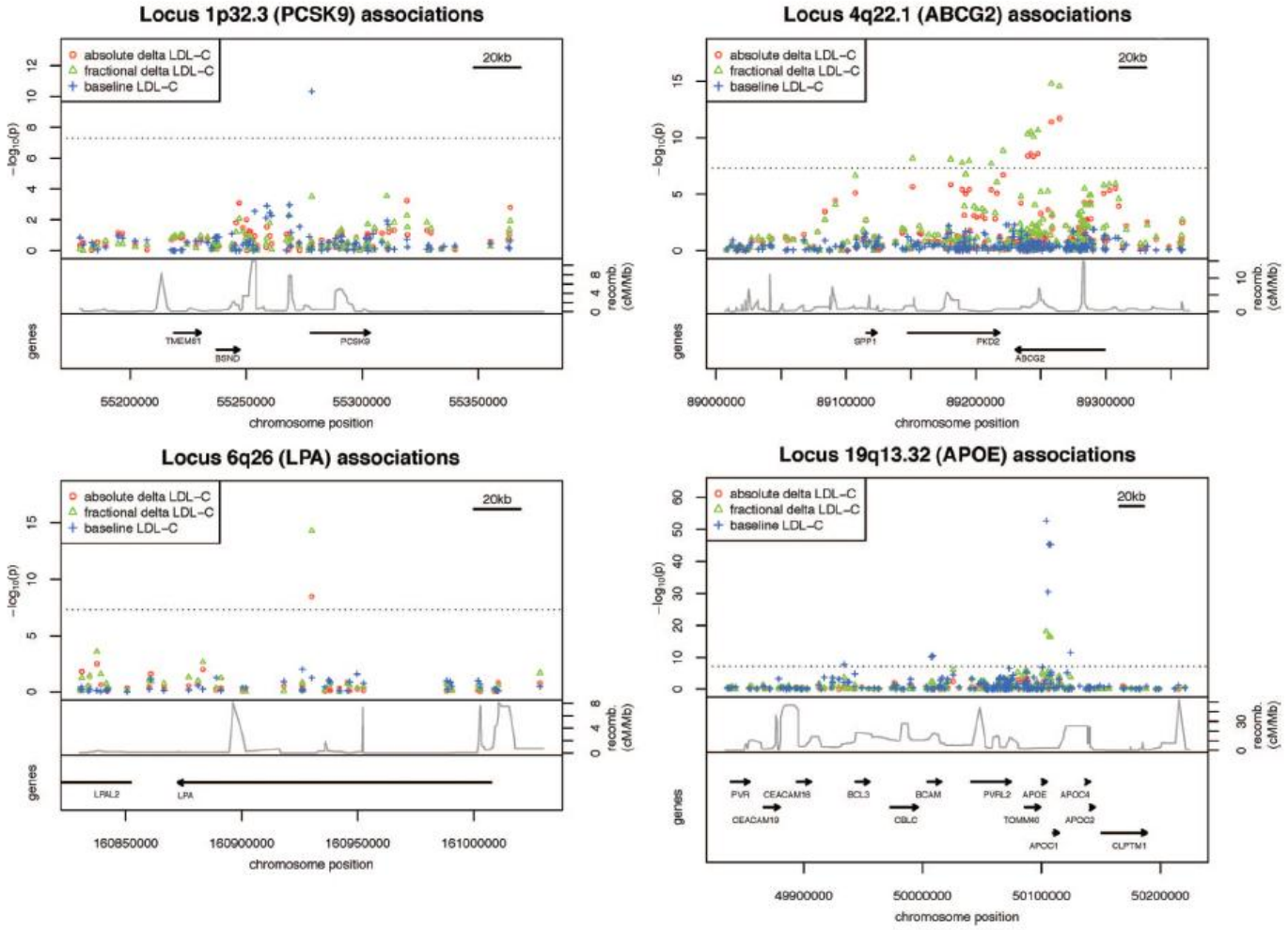
variant results in lower expression levels of the efflux transporter

Rosuvastatin by ABCG2	n	Mean	SD
AA	40	10.32	6.398
CA	112	6.44	4.979
CC	143	4.35	3.325

8% additional reduction of LDL-C (AA vs. CC) is **more than the double dose effect** (6%) – well matched to **2.4-fold increment** of blood rosuvastatin concentration.

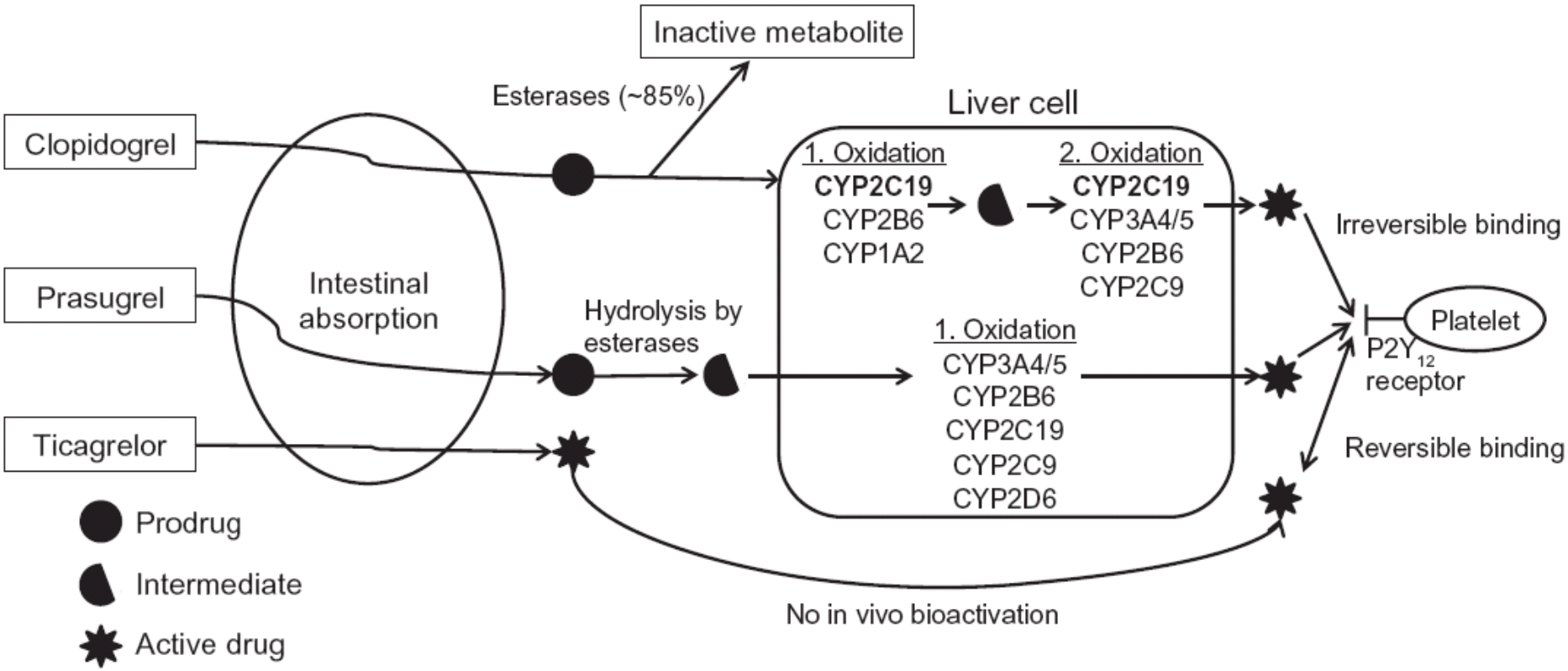
Lee M, Tomlinson B, et al., unpublished data

ABCG2 polymorphism was in the top 4 SNPs for the LDL-C response to rosuvastatin in the GWAS of the JUPITER trial



Chasman DI, et al., Circ Cardiovasc Genet. 2012; 5(2): 257-64.

Bioactivation and mechanism of action of clopidogrel, prasugrel, and ticagrelor



Cavallari LH et al, Pharmacogenomics and Personalized Medicine 2011:4 123–136.

Pharmacogenetic tests for improving drug safety and effectiveness in Hong Kong

Safety

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

Effectiveness

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