Factors Influencing Racial/Ethnic Differences in Drug Response

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Ethnicity vs. Race

- Ethnicity / Ethnic group
  - people thought to have common ancestry who share a distinctive culture (Wikipedia.org)
  - a social category based on shared culture or cultural heritage
  - Korean, Japanese, Chinese, African

- Race
  - categorization of parts of a population based on physical appearance
  - no racial genotypes to delineate boundaries among races
  - socially defined based on appearance.
  - White, Black, White Hispanic, Asian (US FBI)

Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999

B. Evelyn, T. Toigo, D. Banks, D. Pohl, K. Gray, B. Robins, and J. Ernat
Rockville, Maryland

Few recent data are available from formal evaluations of approved new drug applications to address perceptions that racial and ethnic groups are under-represented in clinical trials of new drugs. This study reviews racial and ethnic group participation in clinical trials and race-related labeling for new molecular entities approved during a five-year period by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER)

Racial and ethnic groups appear to participate in clinical trials to varying degrees. African Americans participated in trials to the greatest extent; however, their participation steadily declined from 12% in 1995 to 6% in 1999. Among trials known to be conducted only in the U.S., African-American participation is comparable to their representation in the U.S. population. In all cases, participants designated as Hispanic appear to be far below their representation in the population. Some differences in participation for all racial and ethnic groups are seen when comparisons from year-to-year or among drug classes are made. Labeling for 45% (84/185) of the products contained some statement about race, although in only 8% (15/185) were differences related to race described. Fifty percent (50%) of the effects were pharmacokinetic, 39% were efficacy, and 11% were safety. One product label recommended a change in dosage based on racial differences. (*J Natl Med Assoc.* 2001;93(suppl):18S-24S).

Potential consequences of not accounting for ethnicity in new drug development…

- **Drug companies**
  - Efficacy & Safety: uncontrolled. Trial design. Trial failure
  - Dosing. Same for all.
  - Clinical trials: ↑ failure rate → delayed approval → ↓ revenue
  - Labeling. Local directions may not provide accurate information guiding use
  - ↓ market if product not well tolerated
- **Regulators** (CDE)
  - Ambiguous trial results making approval decision more difficult
  - Inaccurate estimates of true efficacy &/or toxicity
  - Potential post-market problems if significant toxicity issues occur….if they can be detected
- **Patients-Physicians**
  - Drug does not perform as advertised. Market may decrease

If there are true ethnic differences, we should:….

- Decide if ethnic differences (e.g., disease biology) are likely to be clinically significant
  - When unclear, possibly do further research to clarify significance

- Account for clinically significant differences in big decisions (e.g., development strategy, trial design, approval, labeling)

Do we do either in a systematic manner?

J Natl Med Assoc. 2002 Oct; 94(10 Suppl): 1–26
FDA, design consideration for pivotal clinical trial, 2013

Ethnic Factors Influencing
on Drug Response among ethnic populations

INTRINSIC		EXTRINSIC
Genetic	Physiological and Pathophysiological	Environmental
Gender	Age (Children–elderly)	Climate Sunlight Pollution
Height Body Weight	Liver Kidney CV function	Culture Socioeconomic factors Education status Language
Race ADME Receptor Sensitivity	Smoking Alcohol	Medical practice Disease definition/Diagnostic Therapeutic approach Drug Compliance
Pharmacogenomics		
Disease Genomics	Disease Food habits Stress	Regulatory practice/GCP Methodology/ Endpoints

Not only pharmacokinetics in different dosage among ethnics: medical culture

Different dose among different regions

Drugs	Daily dose		
	Japan	USA	EC
Antihypertensive			
Captopril	37.5−75mg	50−150mg	12.5−150mg
Enanalapril	5−10mg	10 − 40mg	10 − 40mg
Metoprolol	60−120mg	100−450mg	50−400mg
Doxazocin	1 − 4mg	1 − 10mg	1 − 16mg

Lower dose in Japan !

Enalapril

	Dose	Cmax	AUC	ADR (dose)
Japan	10mg	103.21	663.5	8.7% (2.5−10mg)
USA	10mg	90.4	682	28.5% (5−20mg)

Naito C. 1994

Cultural factors:
regional difference in prescription behavior

- In Japan, a medicine's safety profile is stressed more than its effectiveness.
  - This emphasis on safety may explain, in part, the general use of lower dosages, and the lower incidence of side effects reported by Japanese compared with American and European patients.
- Patients in Asian frequently are treated with multiple medications because Asian patients often believe that multiple drugs are more effective than monotherapy since multiple herbal ingredients are usually prescribed by traditional Asian doctors.
  - Possibility of drug interaction

The policy report. National Medical Association and National Pharmaceutical Council Web sites

Nongenetic/ Environmental/ Cultural Factors on Drug Response

- Drug metabolism/interaction
- Different diagnostics
- Rating Scale
- Efficacy – safety assessment
- Placebo effects
- Patient compliance

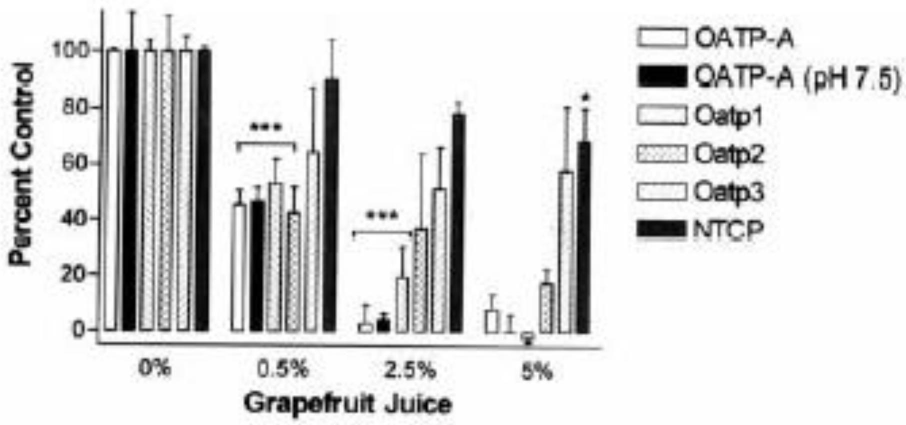
esp) Psychiatric drugs

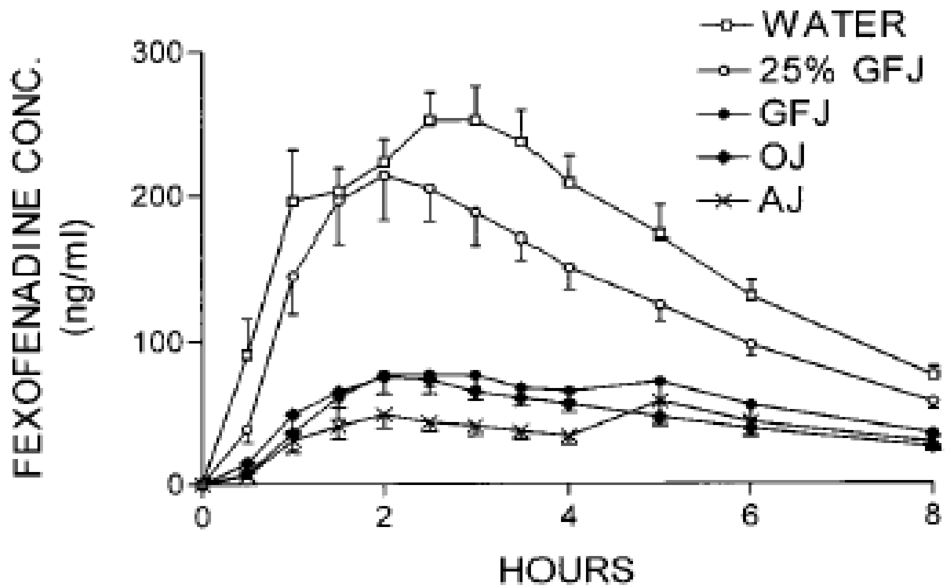
Cultural Factors on Drug Response

- Drug metabolism/interaction
  - different food, natural medicine, or environmental xenobiotics
  - switching of Indian vegetarian diet to British diet

Dietary Effect

- Effect of Juices on OATP

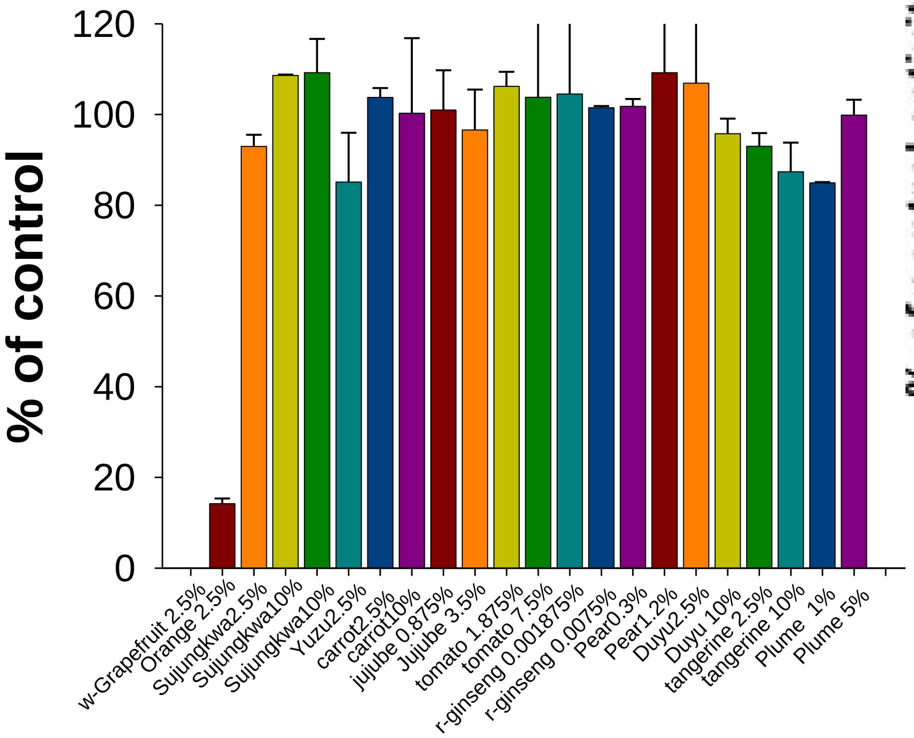


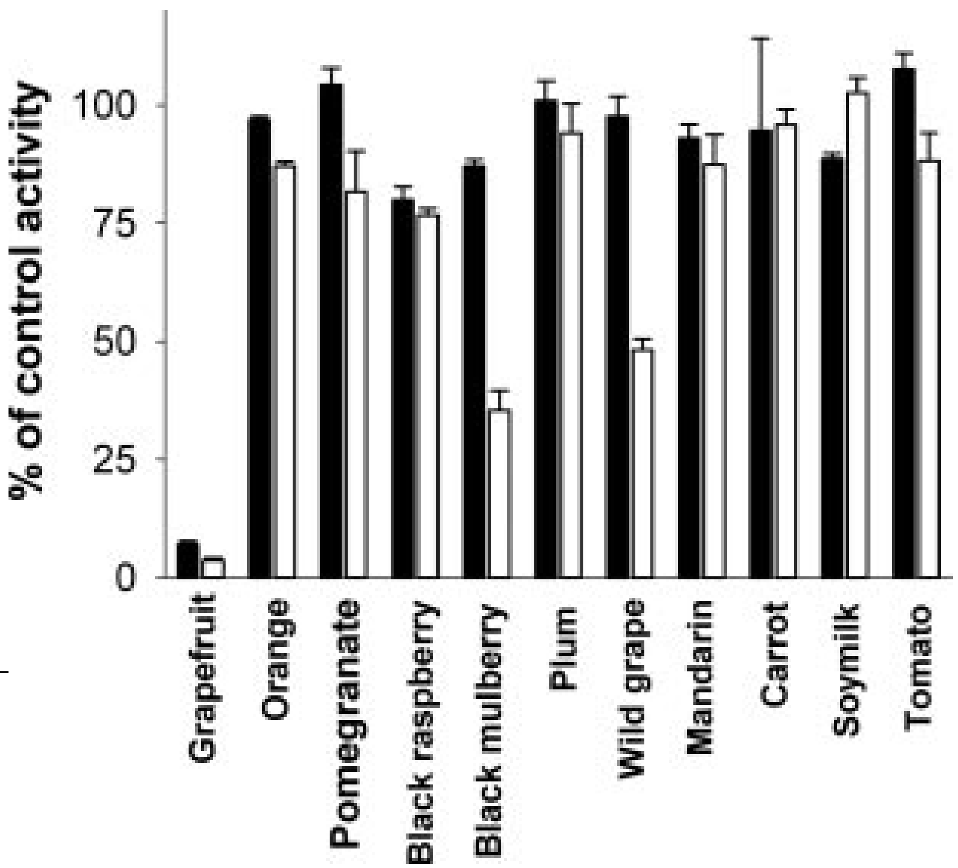


Effect of Juices on OATP *in vitro* and disposition of fexofenadine, an OATP substrate. (Dresser GK, Kim RB et al. 2002)

Consumption of grapefruit juice? Korea < US

CYP3A Inhibitory potential of fruit juices *in vitro*
: screening from 20 fruit juices marked in Korea





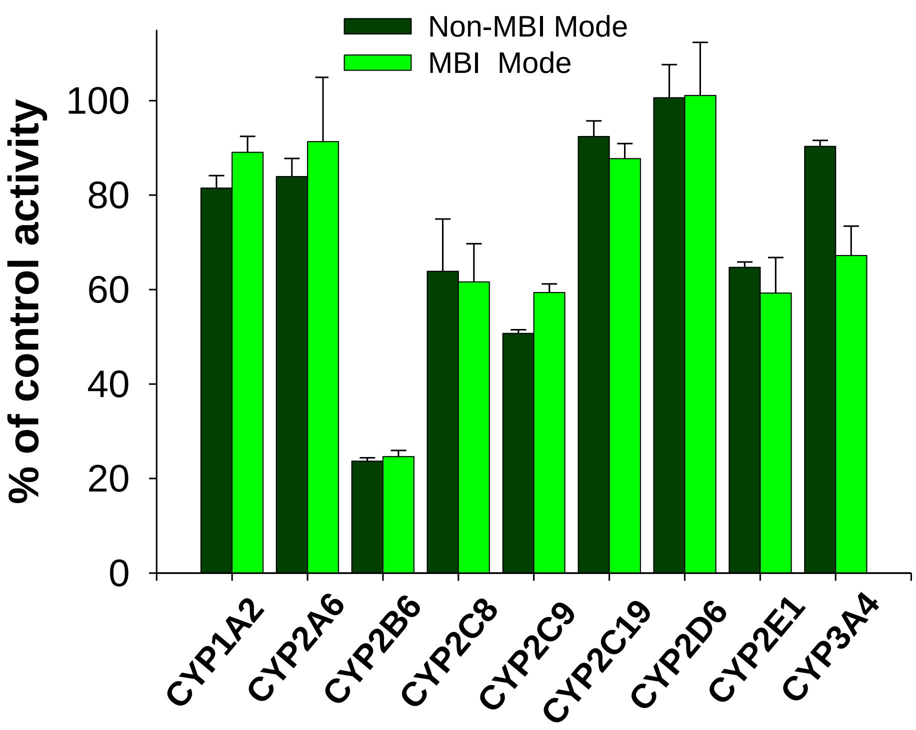
Kim HM, Shin JG et al. DMD 2006

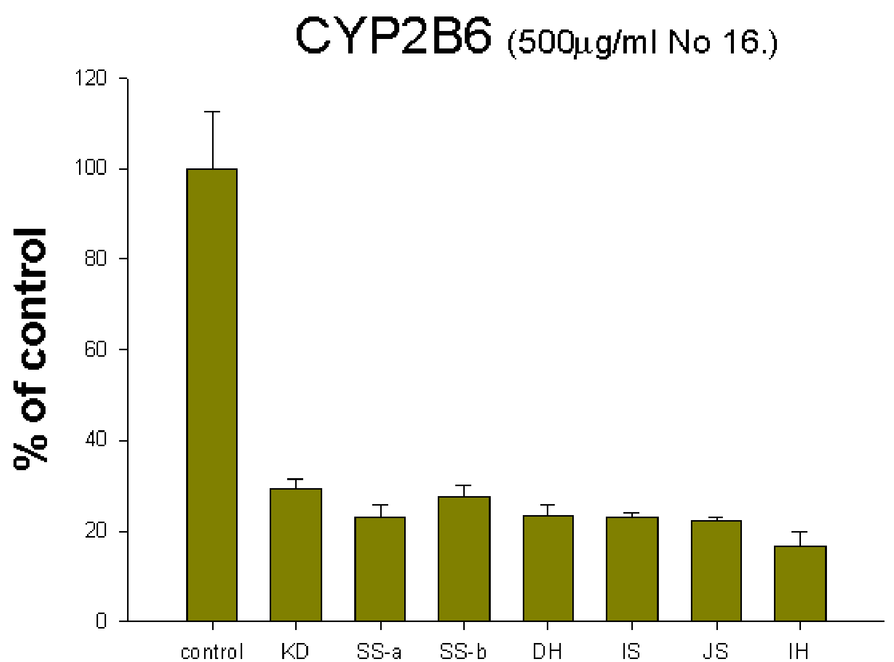
CYP inhibitory potential of herbal medicines marketed in Korea

A. CYP isoform-specific inhibition

B. Product from different companies

Woowhangchungsimwon(500μg/ml)





Kim HM, Shin JG et al. DMD 2008

Effect of dietary salt on verapamil disposition

(in Caucasian and African American Subjects)

TABLE 1. Pharmacokinetic Data

	S-Verapamil		R-Verapamil	
	Low-Salt Diet	High-Salt Diet	Low-Salt Diet	High-Salt Diet
Intravenous data				
AUC_{IV}, ng · min · mL^{-1}	2149±504	1898±322	3742±789	3176±821
CL_s, mL/min	1358±300	1545±370	678±206	787±236
Oral data				
$AUC_{0-12\ h}$, ng · min · mL^{-1}	12 514±3527	7765±2591*	40 101±18 579	25 917±12 922*
$AUC_{0-4\ h}$, ng · min · mL^{-1}	4938±2220	2434±1060†	12 030±3480	8524±2854*
V_{ss}, L	162±44	157±52	187±49	201±94
Cl_o, mL/min	5237±1695	7990±5159	1560±1181	2319±1380
C_{max}, ng/mL	29.2±18	16.5±10*	115±46	80±36*
T_{max}, min	199±60	275±108	195±36	278±96
F, %	25.2±12.4	19.3±4.7*	44.7±29.5	33.7±18.0*

Data are mean±SD, determined after administration of 5 mg d_7-*S*/*R*-verapamil IV and of 120 mg d_0-*S*/*R*-verapamil PO to 8 volunteers on high- and low-salt diets, as described in the text.

*$P<0.05$, †$P<0.01$ low- versus high-salt diet.

Low salt diet: 10mEq/day
High salt diet: 400mEq/day

High salt diet in Koreans vs. low salt diet in Caucasians ??

Darbar D et al. (1998)

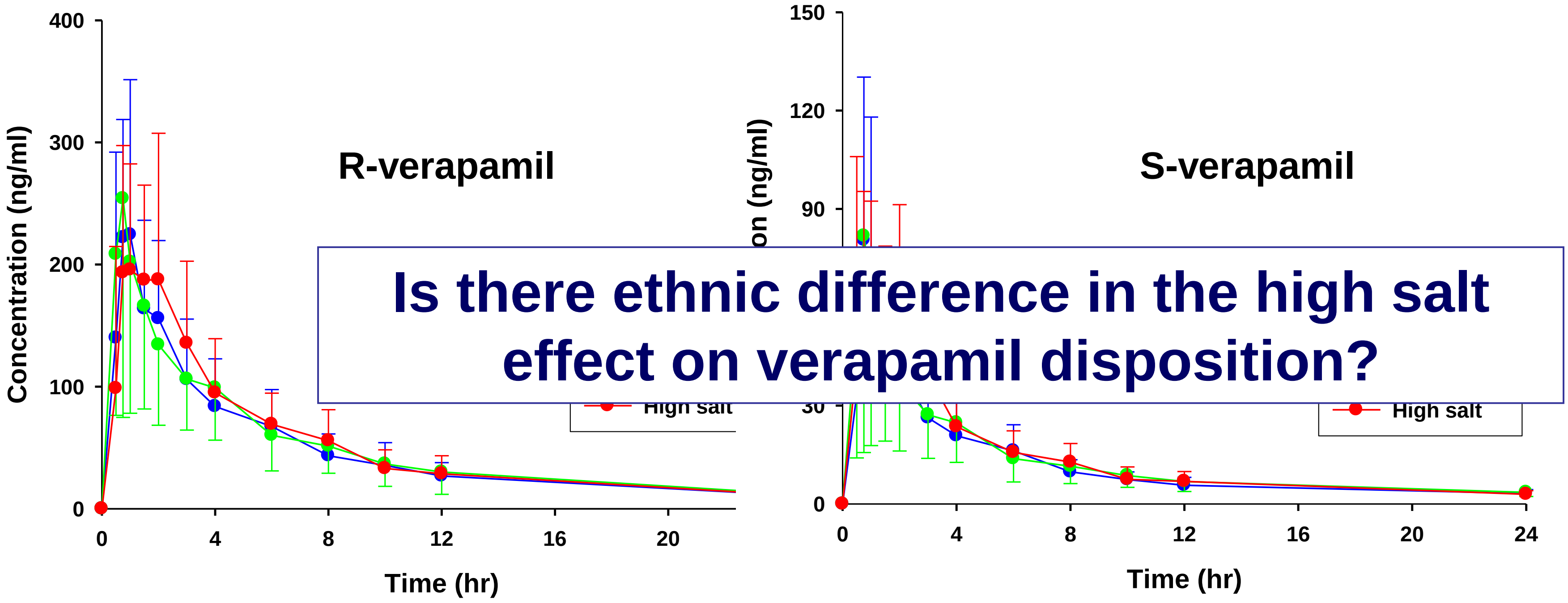
No significant effect of Salt-diet on verapamil disposition in Korean subjects

Hospital Diet Salt Formulary

Low salt diet: 2.0 g/day
Normal salt diet: 7.5 g/day
High salt diet: 25 g/day
cf) usual Korean diet: 16 g/day

24-hour urinary sodium (mEq)

Low	Normal	High
43.1±22.9	114.1±42.7	232.0 ±73.7



Is there ethnic difference in the high salt effect on verapamil disposition?

Pan W, Shin JG et al. Xenobiotica, 2008

Cultural Factors on Drug Response

- Drug metabolism/interaction
  - different food, natural medicine, or environmental xenobiotics
  - switching of Indian vegetarian diet to British diet

- Different diagnostics

  : Language problem – problem of translation, minority
  Communication style – eye contact, gesture
  Cultural issues – depression
  (somatic complaints vs. suicidal manifestation)
  Socioeconomic issues – socioeconomic pressure

  - *bias in recruitment of patients*

    Far Eastern Asian vs. Western

Nongenetic/ Environmental/ Cultural Factors on Drug Response

- Rating Scale: issue of language translation
  - PANSS of Swedish vs. Chinese version
- Efficacy – safety assessment
  - Weight on safety relative to efficacy in Japan
  - more subjective judgement by physician in Japan
  - More aggressive evaluation of efficacy in USA
- Placebo effects
  - Color and shape of pharmaceutical product
    - white capsule – analgesics by Cauc stimulant by AA
- Patient compliance
  - Non-compliance rate
    - 2/3 for black, ½ for colored, ¼ for white patients for oral phenothiazines
    - Treatment expectation

Ethnic difference of docetaxel dose between Japanese vs. Western : PK vs. PD vs. Toxicity vs. Medical culture ?

Hirotsugu Kenmotsu and Yusuke Tanigawara, Cancer Sci 2015; 106: 497

Cancer Science
Japanese Cancer Association JCA
Open Access

Review Article

Pharmacokinetics, dynamics and toxicity of docetaxel: Why the Japanese dose differs from the Western dose

Hirotsugu Kenmotsu[1,2] and Yusuke Tanigawara[1]

[1]Department of Clinical Pharmacokinetics and Pharmacodynamics, Keio University School of Medicine, Tokyo; [2]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

- Recent Japanese clinical trials also used 75 mg/m^2 dose for breast cancer and non-small cell lung cancer. With an increasing number of medical oncologists in Japan with experiences and skills in toxicity management and with the significant progress in supportive care, a docetaxel dose of 75 mg/m^2 is likely to become a chemotherapy treatment option with curative intent in Japan.

Potential factor to cause dose difference in different ethnic countries:

- Global drug development pathways and strategy

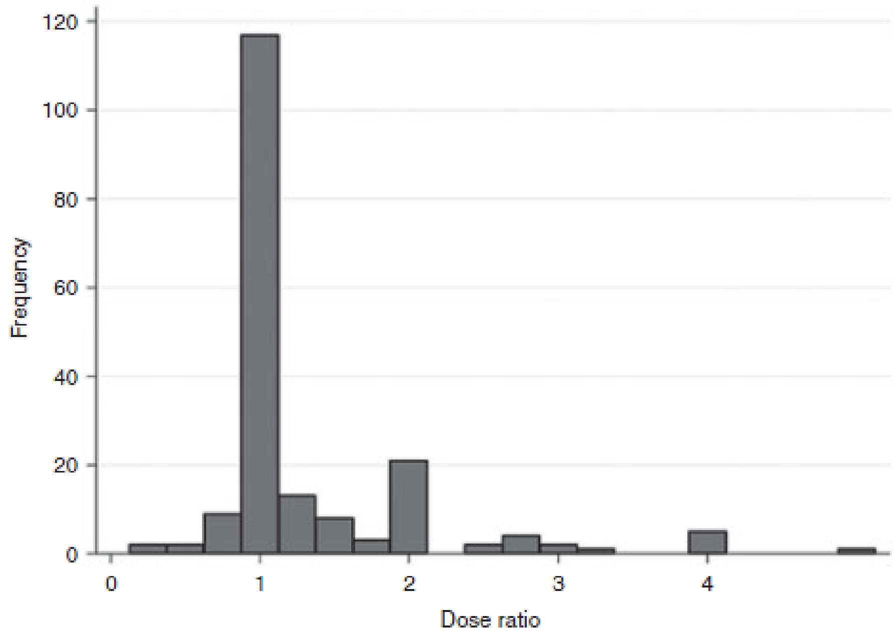


Figure 1 Distribution of dose ratios (US maximum dose/Japan maximum dose).

- Total drug formulation analyzed = 190
- US dose/Japanese dose > 1, 60 cases
- 36 showed dose ratio, >2
- Japanese dose higher in 13 cases
- 3 cases dose ratio 0.5 (2 fold than US)

Assessment of factors associated with dose differences between Japan and the United States.

Arnold FL, Clin Pharmacol Ther. 2014 May;95(5):542-9.

Assessment of Factors Associated With Dose Differences Between Japan and the United States

FL Arnold[1], S Fukunaga[1], M Kusama[1], N Matsuki[1] and S Ono[1]

Although it is well known that there are differences in approved doses between Japan and the United States, there has been no comprehensive research into the causes thereof. This study furthers the discussion of our previous investigation in 2010, with particular focus on pharmaceutical industry strategy and regulatory policy, among drugs approved in Japan between 2001 and 2009. Dose differences were observed in 73 of 190 drugs. Non-Japanese firms were more likely to have a similar dose approved between Japan and the United States, the association being more pronounced when limiting the analysis to drugs for which a Japanese dose-finding study was not conducted. Furthermore, dose differences were less frequent when non-Japanese efficacy data were included in the application data package. No relation between potential intrinsic ethnic difference and dose difference could be identified. The results suggest that the pathway of drug development is more strongly associated with dose difference than are drug characteristics.

CPT 2014;95:542

✓ Similar dose between tow countries

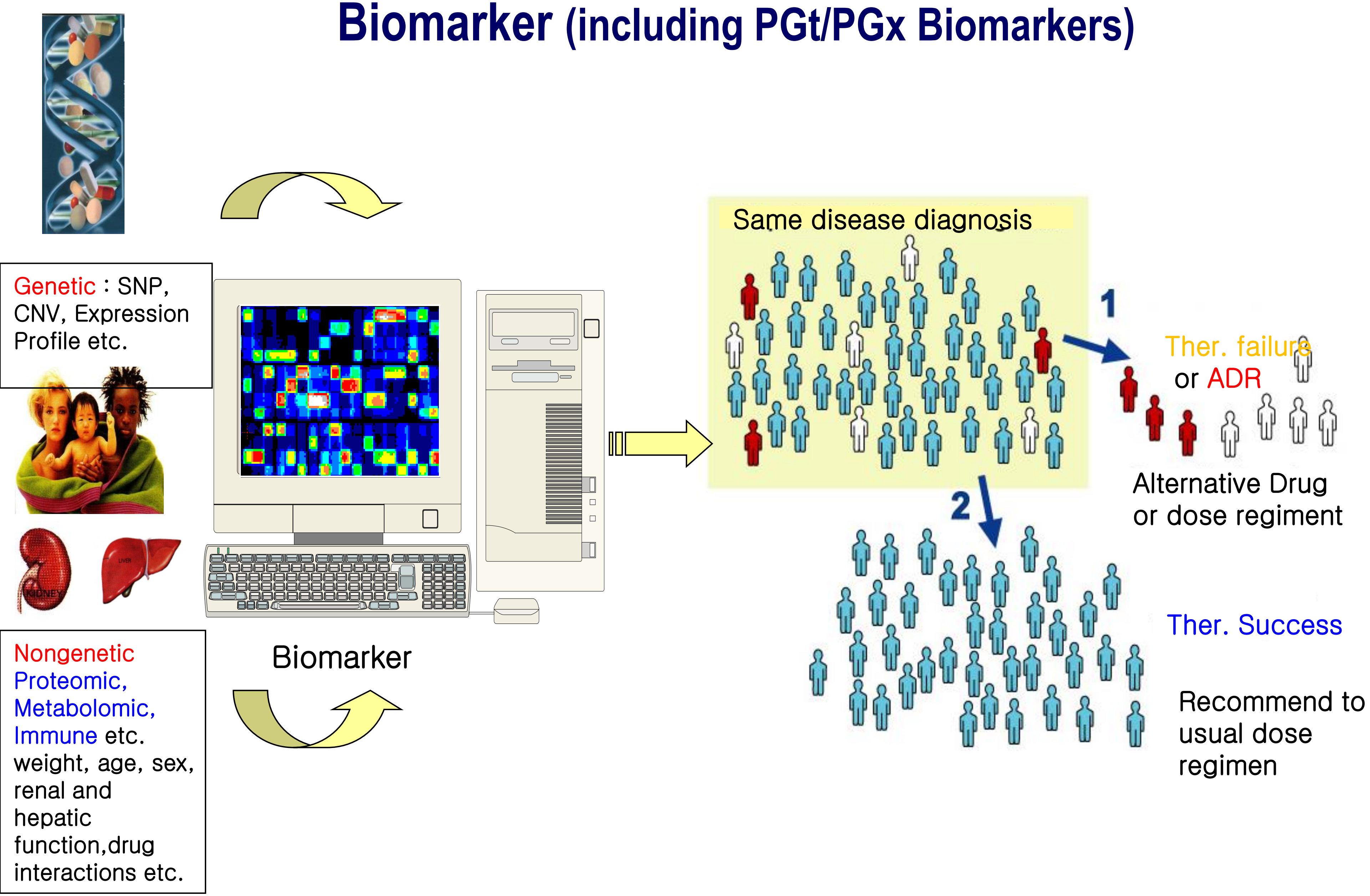
- Drugs developed by non-Japanese firms
- No-Japanese efficacy date were included for application data package

✓ Higher dose ratio of US/Japan

- US upper dose is not tested in Japanese dose finding study

✓ No significant relationship: in drug characteristics (drug class, route of administration, unit of dosing, PK related genetic polymorphisms)

Era of Personalized Pharmacotherapy from Predictive Biomarker (including PGt/PGx Biomarkers)



Drug product labeling includes ethnicity factor

Table 1 Examples of recent FDA drug product labeling that included ethnicity or genetic information

Therapeutic area	Drug products: generic (brand) names	Ethnicity information	Genetics information
Cardiorenal	Isosorbide dinitrate–hydralazine (BiDil)	Indicated for self-identified blacks	
	Angiotensin II antagonists and ACE inhibitors	Smaller effects in blacks[a]	
Metabolic	Rosuvastatin (Crestor)	Lower dose for Asians	
Transplant	Azathioprine (Imuran)		Dose adjustments for TPMT variants
	Tacrolimus (Protopic)	Higher dose for blacks	
Oncology	Trastuzumab (Herceptin)		Indicated for HER2 overexpression
	Irinotecan (Camptosar)		Dose reduction for *UGT1A1*28*
	6-Mercaptopurine (Purinethol)		Dose adjustments for TPMT variants
	Erlotinib (Tarceva)		Different survival and tumor response in EGFR-positive and -negative patients reported
Antiviral	Maraviroc (Selzentry)		Indicated for CCR5-positive patients
	Oseltamivir (Tamiflu)	Neuropsychiatric events mostly reported in Japan	
	Abacavir (Ziagen)		Boxed warning for HLA-B*5701 allele
Pain	Codeine		Warnings for nursing mothers that CYP2D6 UM metabolized codeine to morphine more rapidly and completely[b]
Hematology	Warfarin (Coumadin)	Lower dose for Asians	Lower initial dose for CYP2C9- and VKORC1-sensitive variants
Psychopharmacological	Thioridazine (Mellaril)		Contraindication for CYP2D6 PM
	Atomoxetine (Strattera)		Dosage adjustments for CYP2D6 PM; no drug interactions with strong CYP2D6 inhibitors expected for PM
Neuropharmacological	Carbamazepine (Tegretol)	Box warning for Asians with variant alleles of *HLA-B*1502*	Box warning for Asians with variant alleles of *HLA-B*1502*

ACE, angiotensin-converting enzyme; CCR5, chemokine (C-C motif) receptor 5; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; PM, poor metabolizer; TPMT, thiopurine methyl transferase; UGT, uridine diphosphate glucuronosyl transferase; UM, ultra-rapid metabolizer; VKORC, vitamin K reductase complex. Data from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

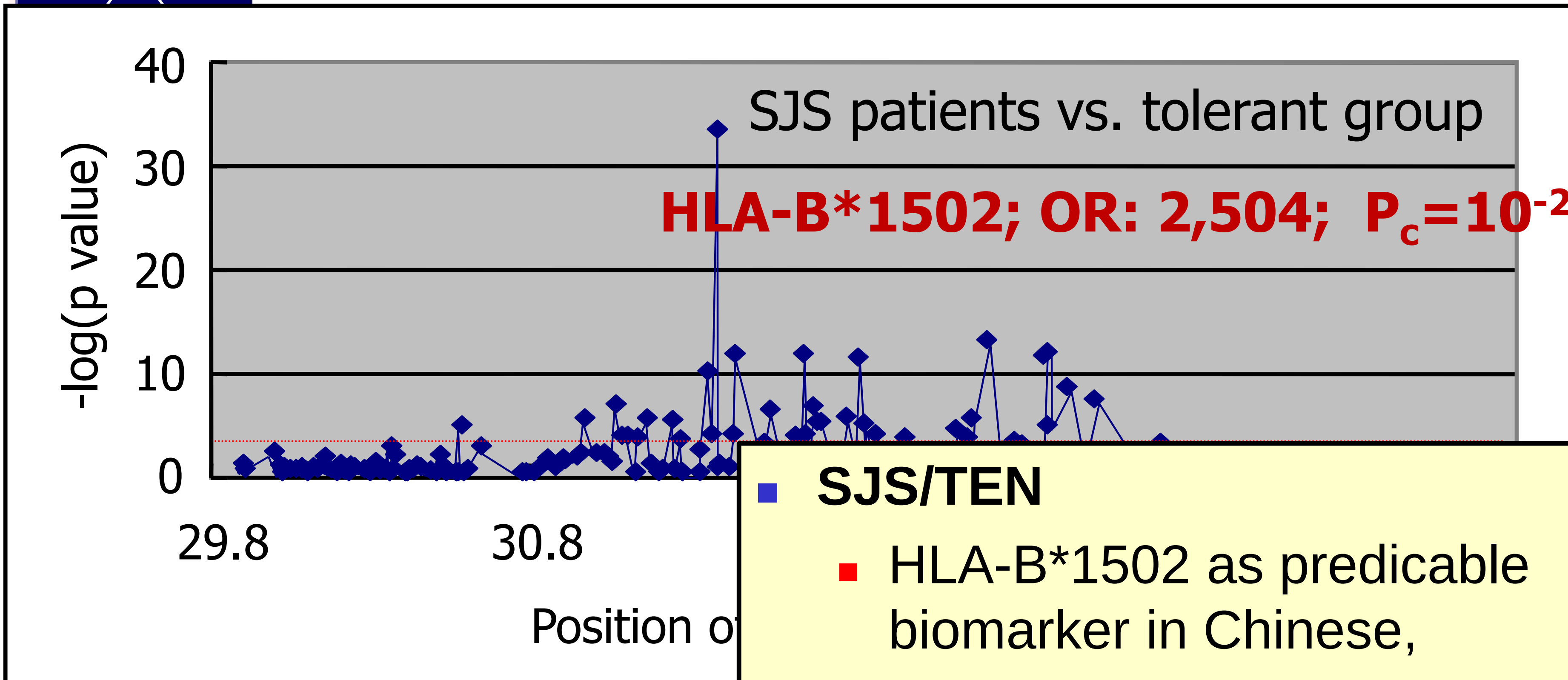
[a]A general statement in the candesartan (Atacand) labeling. [b]http://www.fda.gov/cder/drug/infopage/codeine/default.htm.

Huang S-M and Temple R, Clin Pharmacol & Ther 2008. 84; 287~294

Drug Induced Steven- Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)

- **Idiosyncratic, Type B ADR**
- **Life-threatening skin lesion with high fever and systematic complication**
- **> 100 causative drugs: allopurinol, carbamazepine, phenobarbital, zonisamide, NSAIDs diclofenac, loxoprofen, non-pyrines, acetaminophen etc.**
- **Mortality rate: 5% (SJS) and 30~40% (TEN)**

Carbamazepine induced SJS/TEN



➢ Higher frequency in Chines
(0.25%) than Caucasian
(0.014% in new exposure to
CBZ)

- **SJS/TEN**
  - HLA-B*1502 as predicable biomarker in Chinese, Thai and Indian patients,
  - Not in Caucasians and Japanese (Korean)

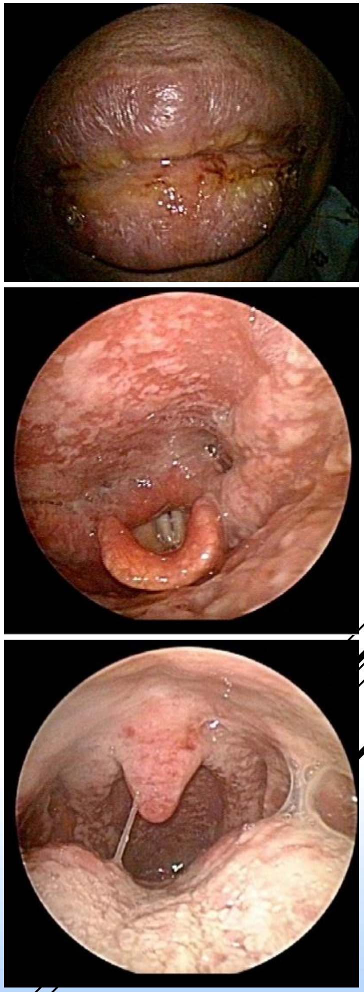
Genotyping of Drug Induced SCAR:

determined by genetic profile of the ethnic population (HLA)

Carbamazepine induced SCAR : F/59

- HLA-B*1502: the only one in our experiences

- Largely *3101, *1511



Antiepileptic Drugs

No	성별	나이	키 (cm)	몸무게 (kg)	Genotype Result	Diagnosis	Induced Drug
1	F	59	150	53	**HLA-B*15:11**, 51:01	SJS	**Carbamazepine**
2	F	48	145	39	HLA-B *35:01, 51:01	SJS	Carbamazepine
4	M	67	177	82	HLA-A *24:02, **31:01** HLA-B *07:02, 58:01	DRESS	Carbamazepine
5	M	22	170	75	HLA-A *02:06, 26:03 HLA-B *15:01, 67:01	R/O SJS	Carbamazepine
6	**F**	**52**	**153**	**52**	**HLA-A *11:01, 24:02** **HLA-B *15:01, 15:02** **HLA-C *01:02, 08:01**	**SJS**	**Carbamazepine**

1	M	57	UK	UK	HLA-B *51:01, 55:04	SJS	Lamotrigine
2	**F**	**26**	**158**	**49**	**HLA-B *58:01, 58:01**	**SJS**	**Lamotrigine**
3	M	16	170	64	HLA-A *31:01 (-) HLA-B *27:05, 40:01	SJS	Lamotrigine
4	M	69	163	53	HLA-B *48:01, 51:01	SJS	Lamotrigine
5	F	39	163	62	HLA-B *07:02, 51:01	SJS	Lamotrigine
6	M	60	160	55	HLA-B *51:01, 51:01	SJS	R/O Phenytoin

Genotype service from PGRC, Inje Univ.

Allopurinol

No	성별	나이	키 (cm)	몸무게 (kg)	Genotype Result	Diagnosis	Induced Drug	Symptom
1	M	63	164	56	HLA-B*13:02, 58:01	SJS	Allopurinol	toxic hepatitis, drug eruption
2	F	72	UK	UK	HLA-B*48:01, 58:01	R/O SJS	Allopurinol	fever, skin rash
3	M	22	181	91	HLA-B*44:03, 58:01	R/O SJS	Allopurinol	skin lesion patch, edema, fever, desquamatio
4	F	31	162	74	HLA-B*58:01, 59:01	SJS	Allopurinol	skin rash, whole body rednes sgeneral edema
5	M	29	170	108	HLA-B*13:02, 58:01	R/O SJS	Allopurinol	skin rash, fever, 안구충혈
6	M	43	155	54	HLA-B*51:01, 58:01	SJS	Allopurinol	전신 피부반응(oral ulcer, fever), 안구/양쪽 손발톱증상
7	F	55	162	62	HLA-B*15:01,58:01	SJS	Allopurinol	전신 erythematous bullaes, patches, itching, pain
8	F	78	156.4	52	HLA-A*30:01, 33:03 HLA-B*13:02, 28:01 HLA-C*03:02, 06:02	SJS	Allopurinol	fever, whole body skin rash

HLA class A and class B allele frequencies in Koreans (vs. Japanese)

(n = 485)

Allele	GF(%)	Allele	GF(%)	Allele	GF(%)	Allele	GF(%)	Allel	GF(%)	Allele	GF(%)
A*0101	1.75	B*0702	3.51	DRB1*0101	6.8	Cw*0102	18.25	B*4002	3.81	DRB1*1403	0.93
A*0201	16.49	B*0705/6a	0.82	DRB1*0301	2.89	Cw*0103	0.21	B*4003	0.31	DRB1*1405	3.51
A*0203	0.52	B*0801	0.41	DRB1*0401	0.72	Cw*0202	0.82	B*4006	3.81	DRB1*1406	0.82
A*0206	7.11	B*1301	2.06	DRB1*0403	3.51	Cw*0302	10.82	B*4402	1.24	DRB1*1407	0.21
A*0207	2.99	B*1302	3.51	[illegible]	[illegible]	[illegible]	[illegible]	B*4403	8.45	DRB1*1410	0.21
A*0210	0.62	B*1401	2.06	[illegible]	[illegible]	[illegible]	[illegible]	B*4601	4.43	DRB1*1412	0.21
A*0301	1.75	**B*1501**	**10.5**	[illegible]	[illegible]	[illegible]	[illegible]	B*4701	0.1	DRB1*1501	7.42
A*0302	0.21	**B*1502**	**0.21**	[illegible]	[illegible]	[illegible]	[illegible]	B*4801	3.4	DRB1*1502	3.3
A*1101	10.82	B*1507	0.62	[illegible]	[illegible]	[illegible]	[illegible]	B*5001	0.1	DRB1*1602	0.62
A*2402	21.65	B*1511	1.96	[illegible]	[illegible]	[illegible]	[illegible]	B*5101	8.35	DQB1*0201/2a	9.38
A*2601	5.98	B*1518	0.93	[illegible]	[illegible]	[illegible]	[illegible]	B*5102	0.62	DQB1*0301	13.51
A*2602	0.62	B*1527	0.21	[illegible]	[illegible]	[illegible]	[illegible]	B*5201	2.78	DQB1*0302	10.31
A*2603	1.03	B*1538	0.1	[illegible]	[illegible]	[illegible]	[illegible]	B*5401	5.88	DQB1*0303	11.44
A*2901	1.03	B*2705	2.47	[illegible]	[illegible]	[illegible]	[illegible]	B*5502	2.68	DQB1*0401	8.76
A*3001	3.51	B*3501	5.67	[illegible]	[illegible]	[illegible]	[illegible]	B*5504	0.1	DQB1*0402	3.71
A*3004	1.86	B*3503	0.41	[illegible]	[illegible]	[illegible]	[illegible]	B*5507	0.21	DQB1*0501	9.28
A*3101	5.36	B*3701	1.44	[illegible]	[illegible]	[illegible]	[illegible]	B*5601	0.72	DQB1*0502	2.16
A*3201	0.31	B*3802	1.13	[illegible]	[illegible]	[illegible]	[illegible]	B*5701	0.21	DQB1*0503	5.05
A*3303	16.29	B*3901	1.03	[illegible]	[illegible]	[illegible]	[illegible]	**B*5801**	**6.49**	DQB1*0601	9.59
A*6801	0.1	B*3904	0.1	[illegible]	[illegible]	[illegible]	[illegible]	B*5901	2.06	DQB1*0603	0.93
		B*4001	4.02	[illegible]	[illegible]	[illegible]	[illegible]	B*6701	0.93	DQB1*0604	5.05
		B*8101	0.1	DRB1*1401	2.99					DQB1*0609	3.71
										DQB1*0602	7.11

Cf) HLA-B*1502: CBZ
Han Chinese 8.6%
vs. no from Japanese

Cf) HLA-B*5801: allopurinol
Han Chinese 9-11%,
Caucasian 1-6%,
Japanese 0.68%,
African 2-4%

cf) HLA-B*5701: Abacavir
Caucasian: 8%

PCR-SSOP analysis   DNA sequence analysis

Tissue Antigens 2005: 65: 437–447

Worldwide Frequencies of HLAs associated with AED induced SCAR

- **HLA-B*1502 was reported genetic biomarkers for anticonvulsants-induced SCAR**
  - Carbamazepine, Phenytoin, Lamotrigine, Oxcarbazepine

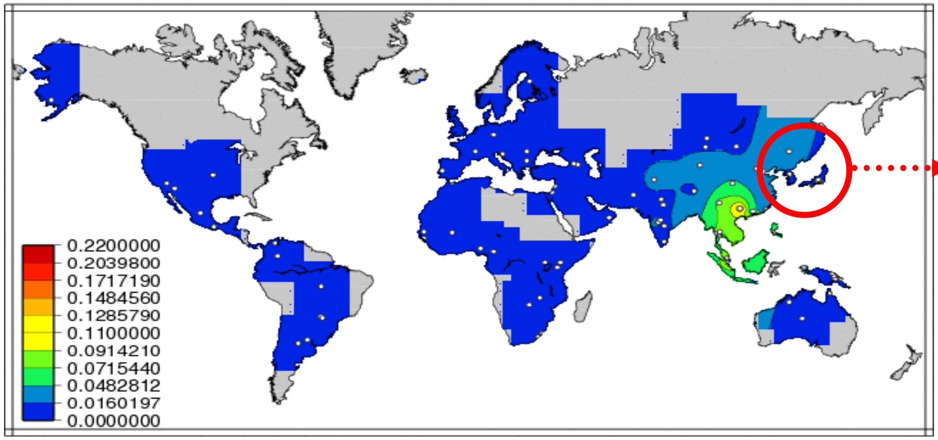


Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.

Rare frequency in Korean population

Same serologic type with HLA-B*1502 serologic type

Causative drug	HLA-B	Race		Selectivity	References
Carbamazepine	*1502	Han Chinese (Taiwan)	SJS/TEN	59/60	16
		Han Chinese (Hong Kong)	SJS/TEN	4/4	11
		Asians in Europe	SJS/TEN	4/4	13
		Thai	SJS	37/42	18
		Indians	SJS	6/8	17
		Caucasians	SJS/TEN	0/8	13
		Japanese	SJS/TEN	0/15	22
		Han Chinese (Taiwan)	DIHS	0/13	16
		Caucasians	DIHS	0/56	29
	*1511	Japanese	SJS/TEN	4/15	22
Phenytoin	*1502	Han Chinese (Taiwan)	SJS/TEN	8/26	28
		Thai	SJS/TEN	4/4	18
Lamotrigine	*1502	Han Chinese (Taiwan)	SJS	2/6	28
Oxcarbazepine		Han Chinese (Taiwan)	SJS	3/3	28

ADR, adverse drug reactions; HLA, human leukocyte antigen; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

http://www.pypop.org/popdata/

Worldwide Frequencies of HLAs associated with AED induced SCAR

- **HLA-B*3101** was also reported genetic biomarkers for **CBZ-induced ADRs**

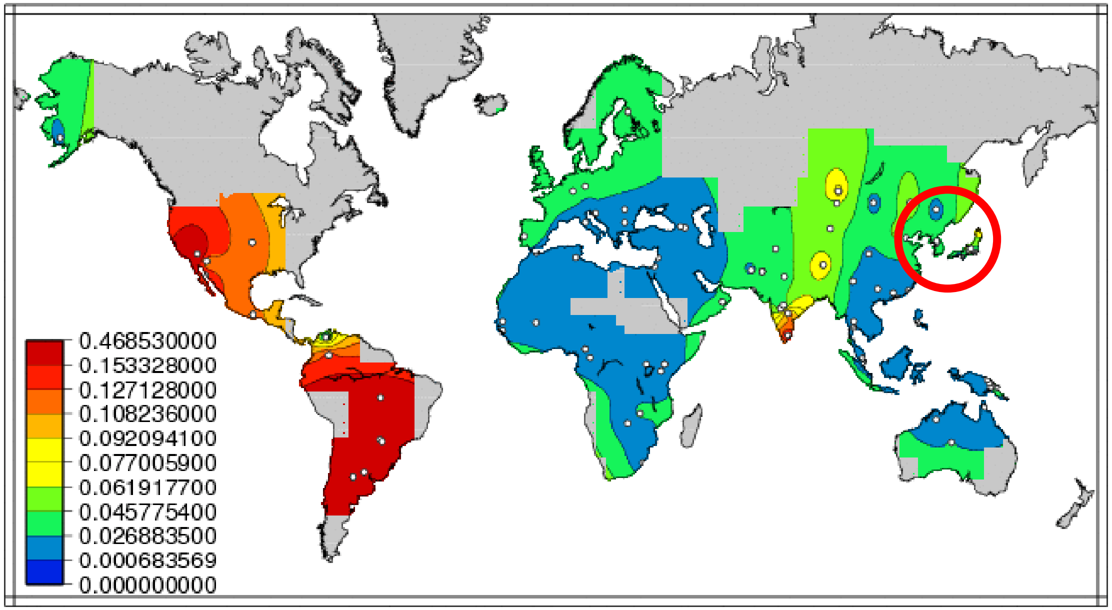


Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.

Table 4. Subgroup analysis of association of the *HLA-A*3101* allele with carbamazepine-induced cutaneous adverse drug reactions

Subgroup	Number of patients Positive for *HLA-A*3101*	Negative for *HLA-A*3101*	Total	*P*-value	OR (95% CI)
All CBZ-induced cADRs	45	32	77	[a]1.09×10^{-16}	9.5 (5.6–16.3)
DIHS	21	15	36	[a]2.06×10^{-9}	9.5 (4.6–19.5)
SJS/TEN	5	1	6	[a]2.35×10^{-4}	33.9 (3.9–295.6)
Others	19	16	35	[a]4.74×10^{-8}	8.0 (3.9–16.6)
CBZ-tolerant controls	54	366	420	–	–

cADRs, cutaneous adverse drug reactions; CBZ, carbamazepine; CI, confidence interval; DIHS, drug-induced hypersensitivity syndrome; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.
[a]Significant after Bonferroni's correction.

http://www.pypop.org/popdata/

Worldwide Distribution of HLAs Associated with Other Drug-Induced SCARs

- **HLA-B*5801** was reported genetic biomarkers for Allopurinol-induced cutaneous ADRs

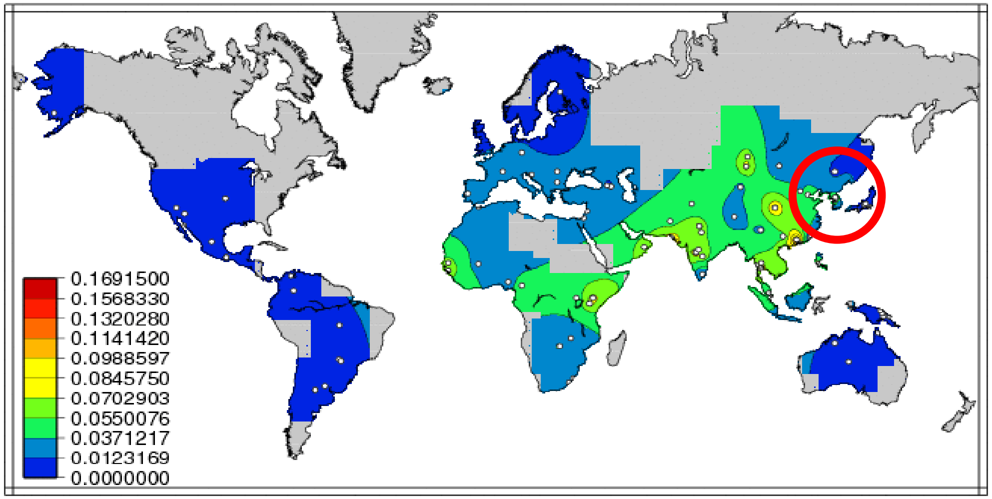
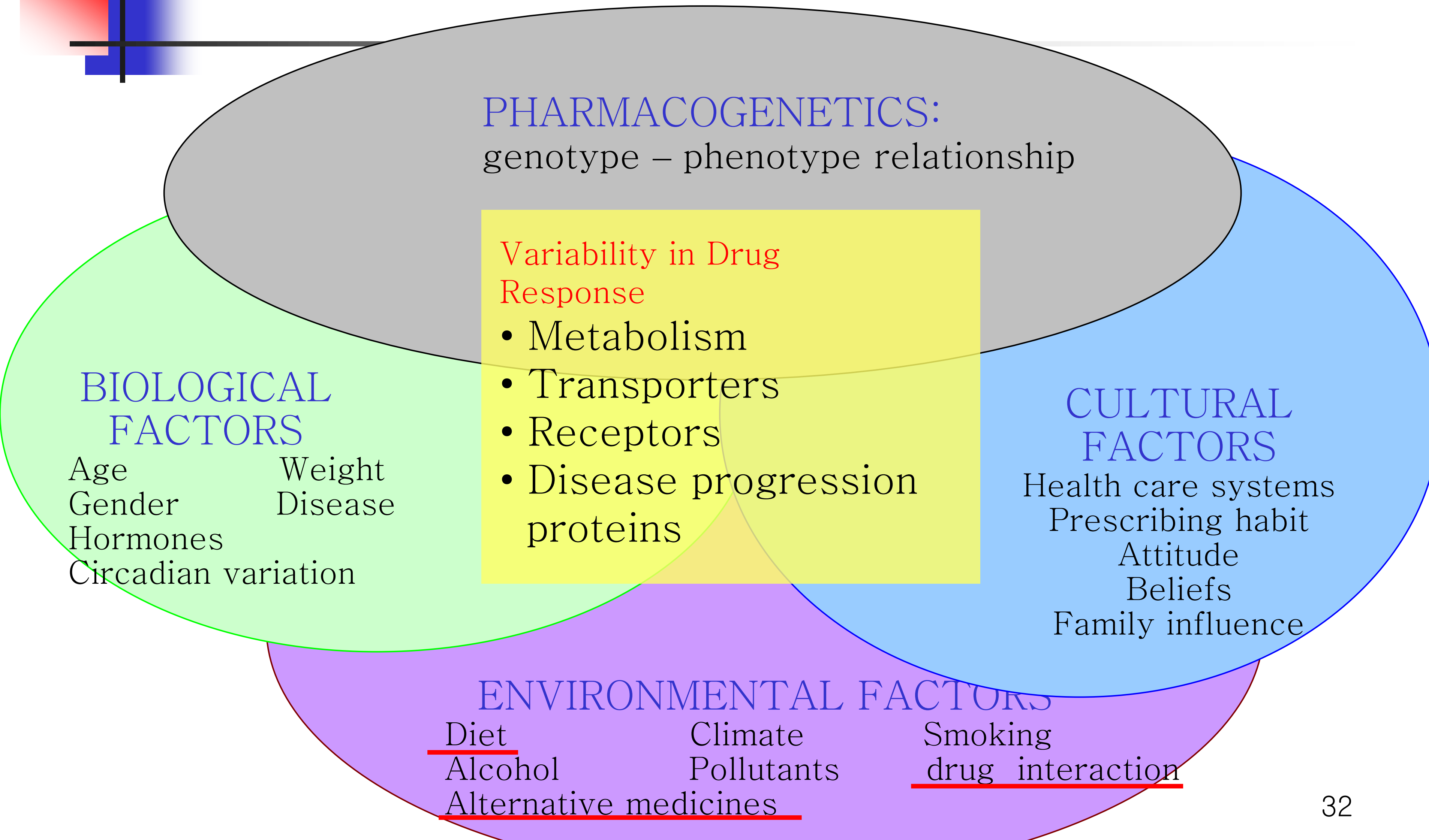


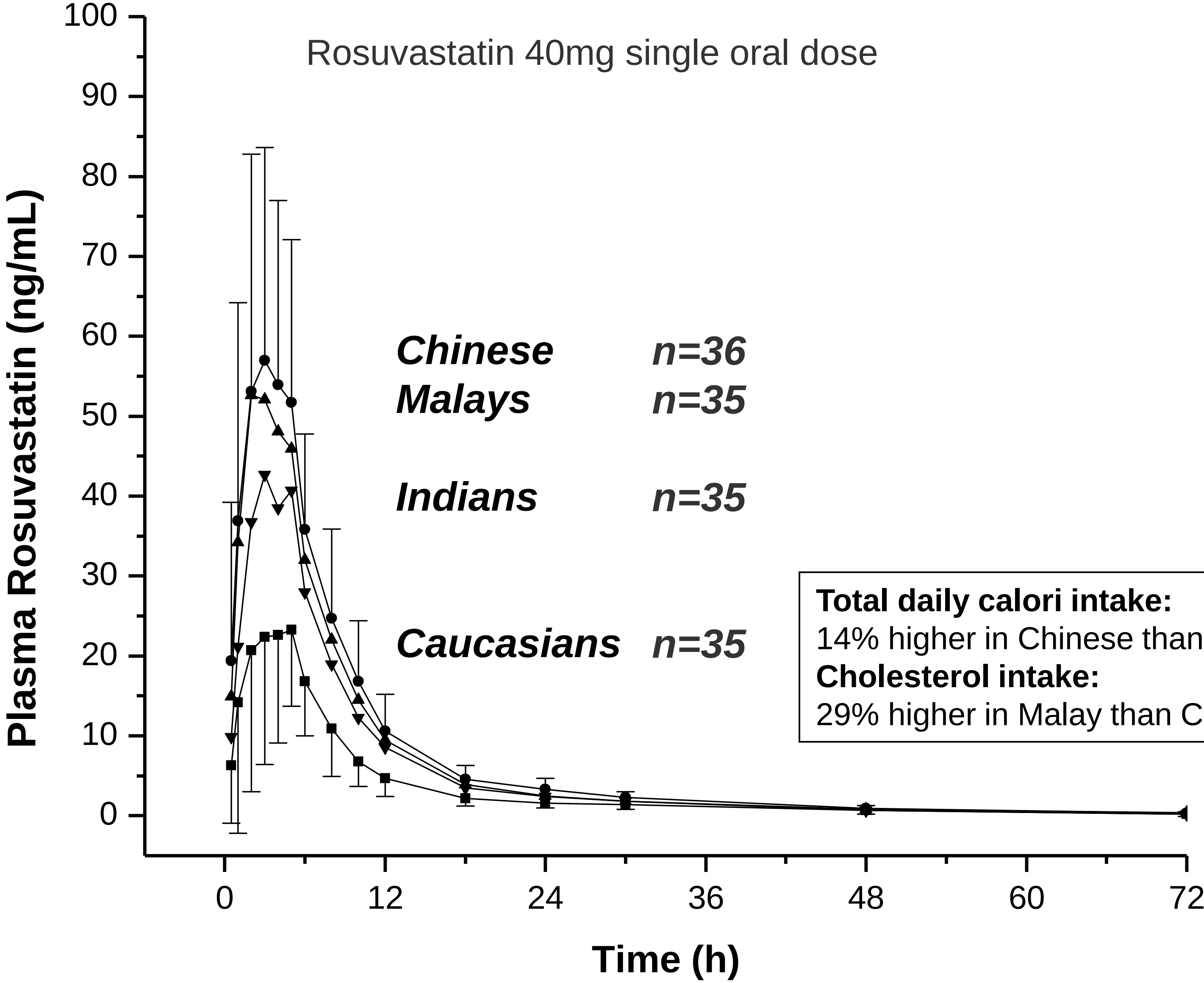
Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.

Ethnicity	Study design	Types of SCARs[a]	Frequency of HLA-B*5801 (%)		P-value	OR (95% CI)	Sensitivity (%)	Specificity (%)	Ref.
			Patients	Controls					
Han Chinese	Case–control	SJS/TEN/HSS	51/51 (100)	20/135 (15.0)[d]	4.7×10^{-24} [d]	580.3 (34.4–9780.9)	100	85.2	[11]
European	Case–control	SJS/TEN	14/27 (55)	28/1822 (1.5)[c]	$<1.0 \times 10^{-6}$ [d]	80 (34–187)	55.6	98.5	[9]
Japanese[e]	Case–control	SJS/TEN	2/10 (20)	6/986 (0.61)[c]	$<1.0 \times 10^{-4}$	40.83 (10.5–158.9)	40	99.4	[21]
Thai	Case–control	SJS/TEN	27/27 (100)	7/54 (13.0)[d]	1.6×10^{-13}	348.3 (19.2–6336.9)	100	87	[8]
Korean	Case–control	SJS/TEN/DIHS	23/25 (92.0)	6/57 (10.5)[d]	2.45×10^{-11} [d]	97.8 (18.3–521.5)	92.0	89.5	[20]

Factors can confound the genotype-phenotype relationship of drug response



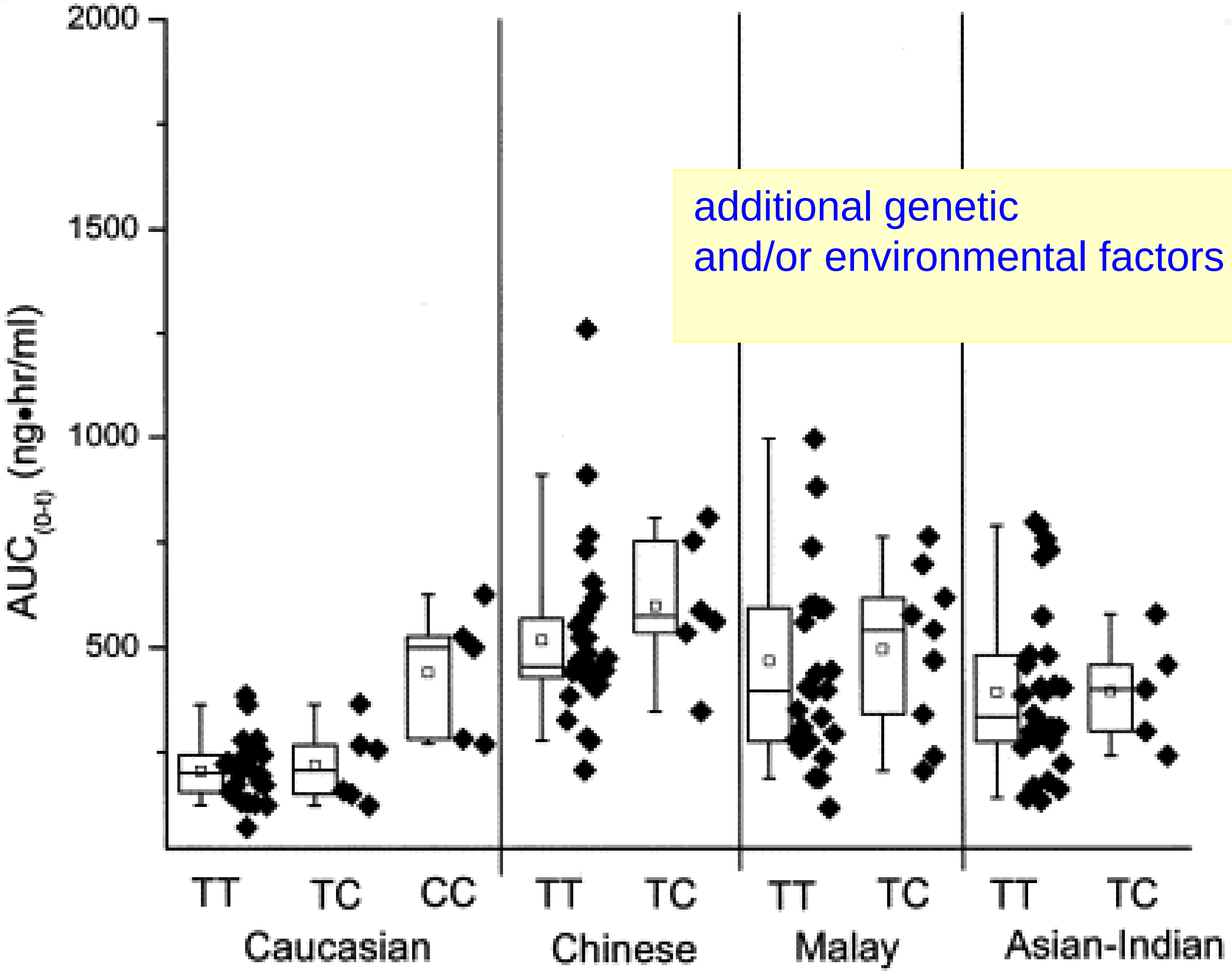
Ethnic Difference of Rosuvastatin PKs between White and Asian Subjects Residing in the Same Environment



Total daily calori intake:
14% higher in Chinese than Caucasian subjects
Cholesterol intake:
29% higher in Malay than Caucasian subjects

Lee et al. CP&T 2005;78(4):330-41

Comparison of Rosuvastatin pharmacokinetics among Caucasian and Asian subjects in relation to SLCO1B1 genetic polymorphism



additional genetic
and/or environmental factors ??

Lee et al. CP&T 2005;78(4):330-41

Ethnic difference of transporter activity, as well as profile of genetic variants

was estimated to be only 1.01. On the other hand, assuming that only the ethnicity-related difference in the allele frequency of *ABCG2* 421C<A affects the difference in the averaged pharmacokinetics parameters between the two ethnic groups, the $AUCR_{J/C}$ value was estimated to be 1.18. Therefore, even when the ethnicity-related differences in the frequencies of mutations in *SLCO1B1* and *ABCG2* are considered with an assumption of mutual independence of these mutations, one can explain only a small part ($AUCR_{J/C}$: 1.19 (=1.01 × 1.18)) of the overall variability in the pharmacokinetics of rosuvastatin observed in the clinical studies ($AUCR_{J/C}$: 2.13) (**Figure 1b**). Given that the ratio of F_aF_g in Japanese subjects to that in Caucasians was calculated to be 1.05 (**Figure 1e**), the ethnicity-related difference in hepatic availability should explain the variability in rosuvastatin exposure between Asians and Caucasians. Ethnic variability has been observed in the pharmacokinetics of other statins as well. (**Figure 2**) Therefore, the smaller protein expression and/or transport activity (V_{max}/K_m), and the consequently smaller transport clearance of OATP1B1 in Asians as compared with Caucasians is considered a possible cause of the variability in the pharmacokinetics of these statins between the two ethnic groups.

osure of

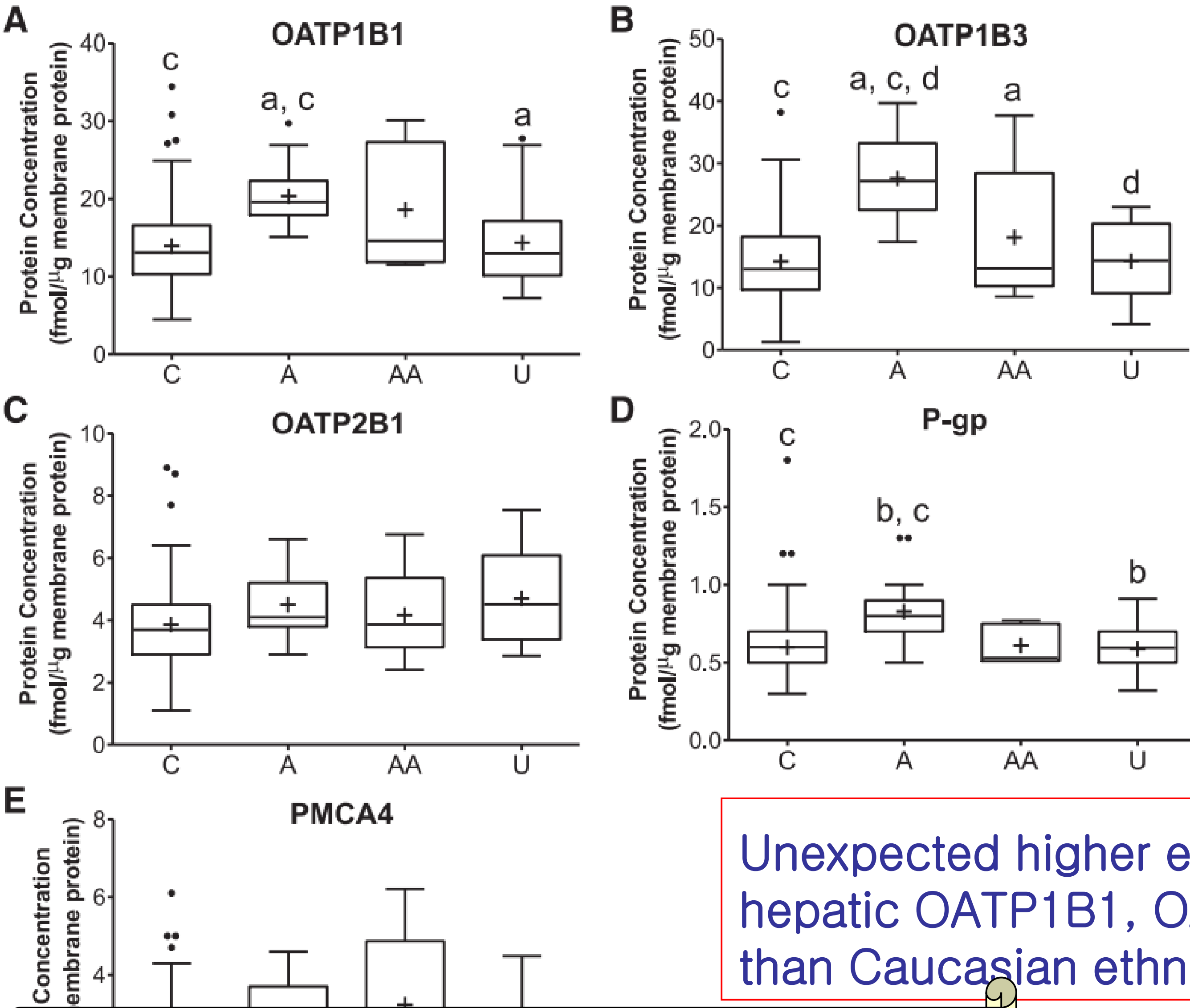
type		
(421C>A)		
	Frequency	
	aucasian	Japanese
	0.74	0.423
	0.241	0.455
	0.0196	0.123
	3.37	3.98
	1.18	

astatin in plasma than

erence in hepatic

ty in Asian subjects

her. 2013 Jul;94(1):37-51.

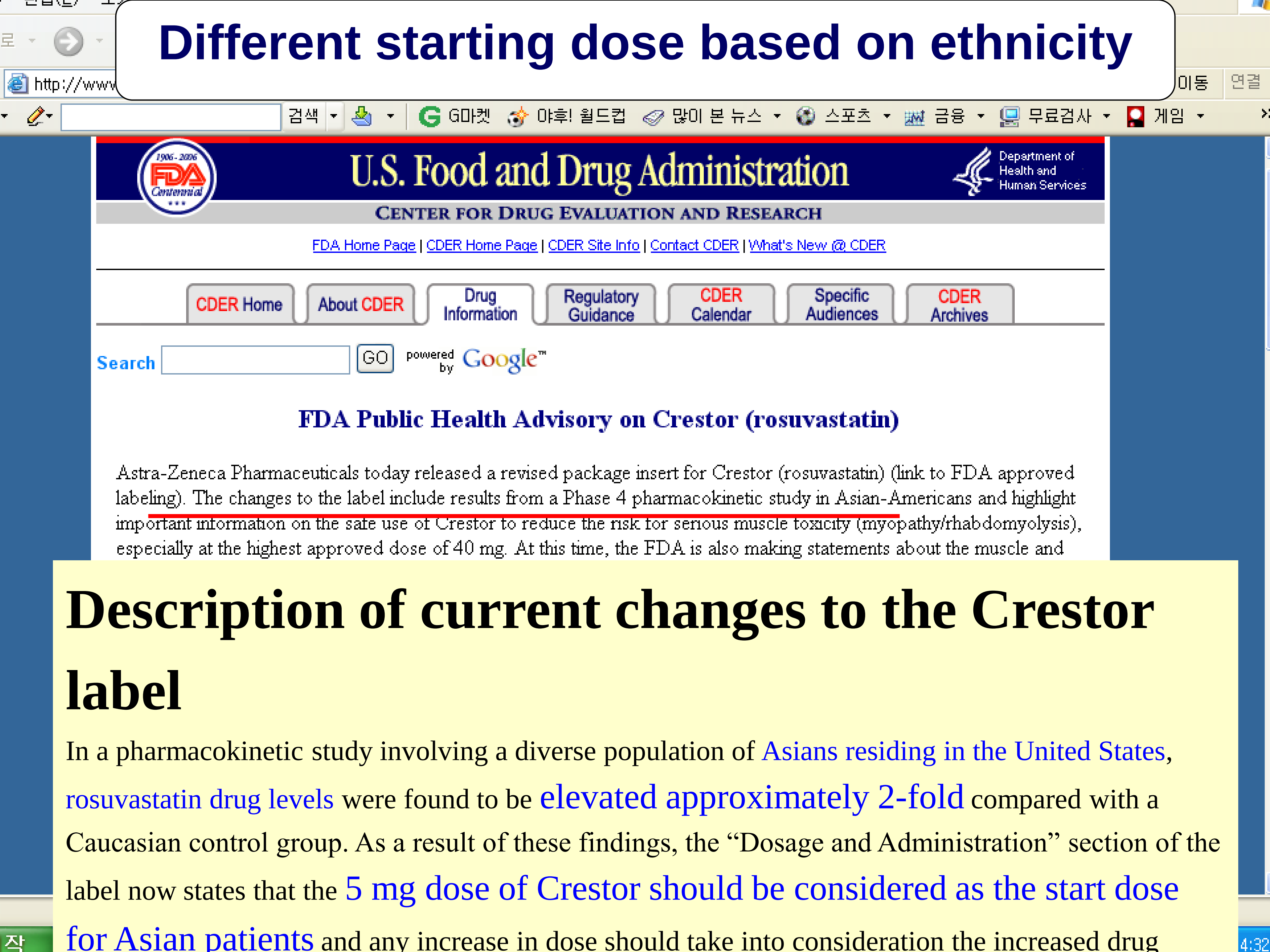


Liver tissues from
- 102 Caucasian
- 18 Asian
- 5 African American
- 16 Unidentified ethnic

Unexpected higher expression of hepatic OATP1B1, OATP1B3 in Asian than Caucasian ethnic subjects

It seems to have ethnic difference
in the expression of PK related genes

Different starting dose based on ethnicity

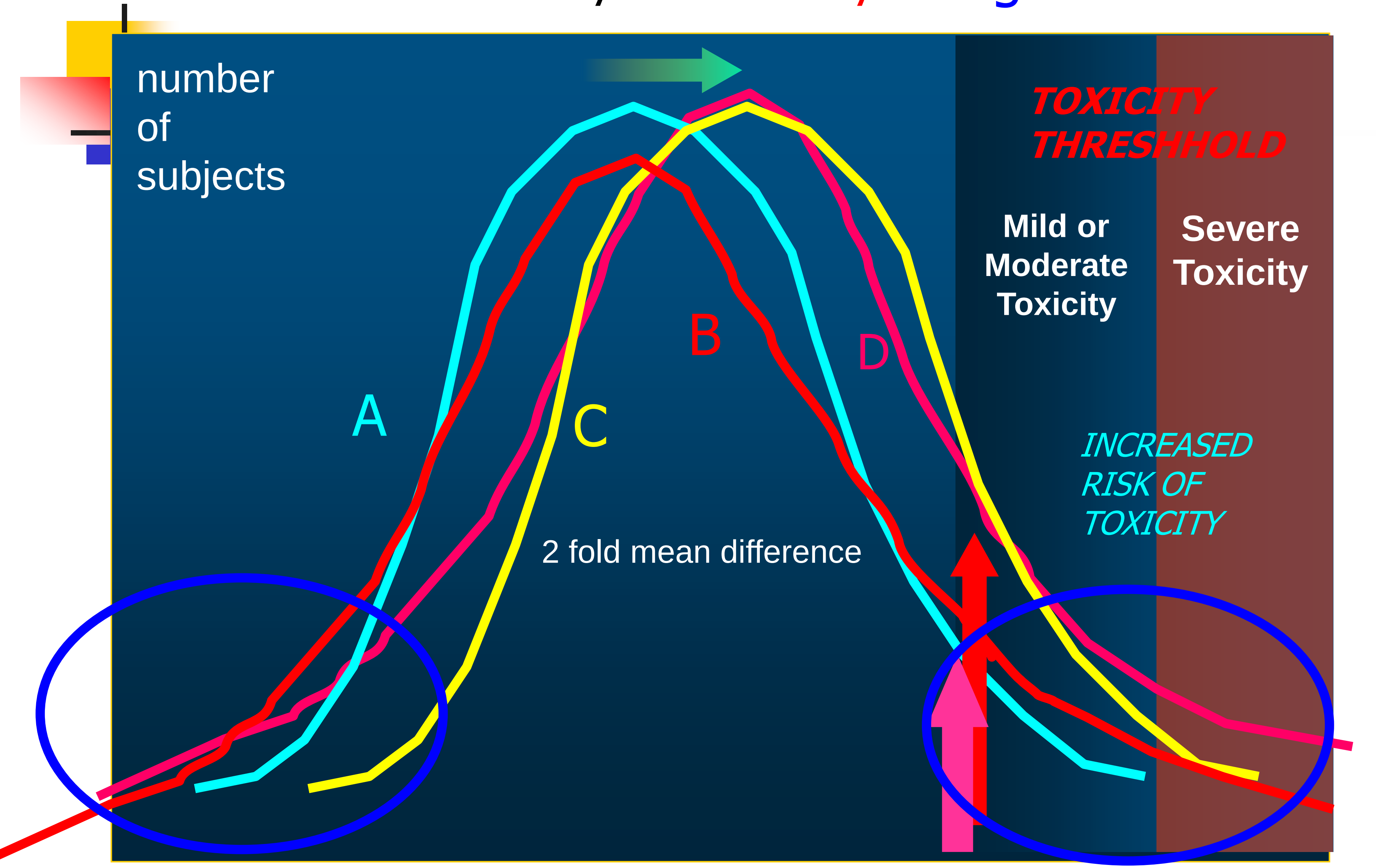


Description of current changes to the Crestor label

In a pharmacokinetic study involving a diverse population of Asians residing in the United States, rosuvastatin drug levels were found to be elevated approximately 2-fold compared with a Caucasian control group. As a result of these findings, the "Dosage and Administration" section of the label now states that the 5 mg dose of Crestor should be considered as the start dose for Asian patients and any increase in dose should take into consideration the increased drug

An Issue of Ethnic Difference of Drug Disposition

– AUC vs. efficacy and toxicity: "Edge effect"



Phenotype (AUC) "Edge Population"

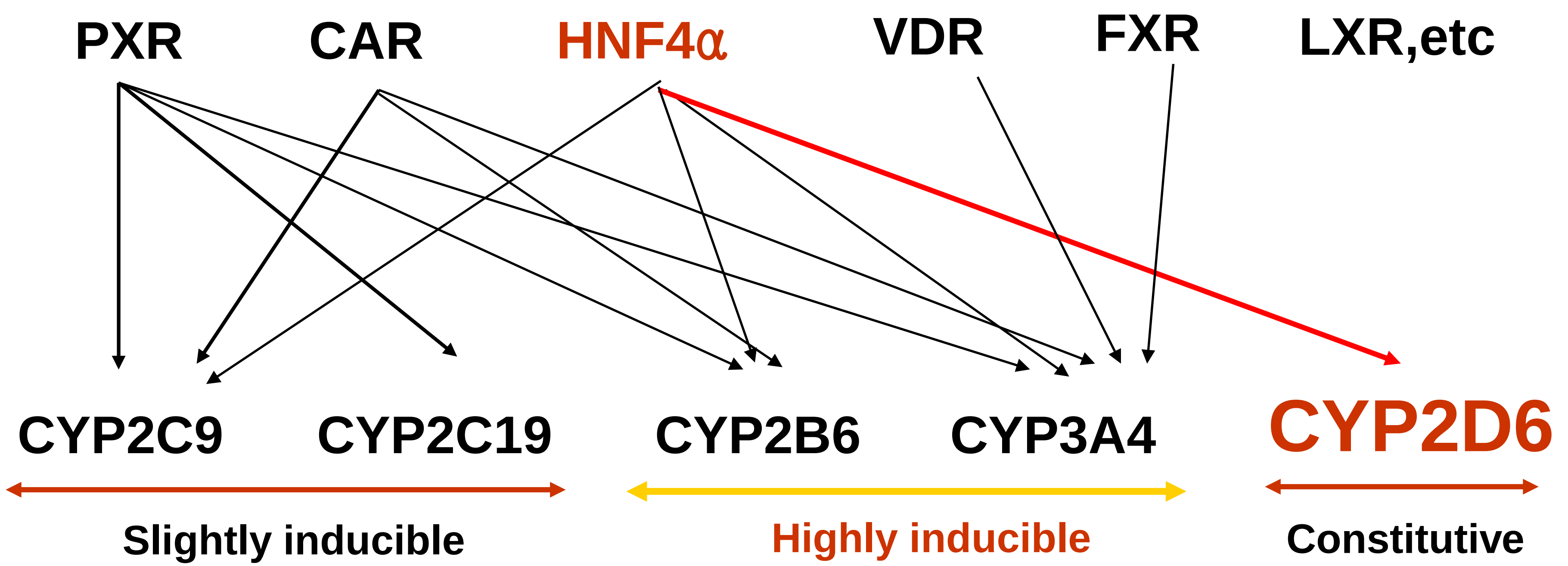
Pharmacogenomics of Expression Regulation

- possible additional factor to confound the genotype-phenotype prediction in an ethnic population?

- Genomics of gene regulation
  - SNPs in nuclear receptor, e.g. PXR, CAR, HNF4α
  - Alternative Splicing Variants
  - Allelic imbalance
  - Copy Number Variation
- Epigenomics
  - microRNA
  - DNA methylation
  - Histone modification

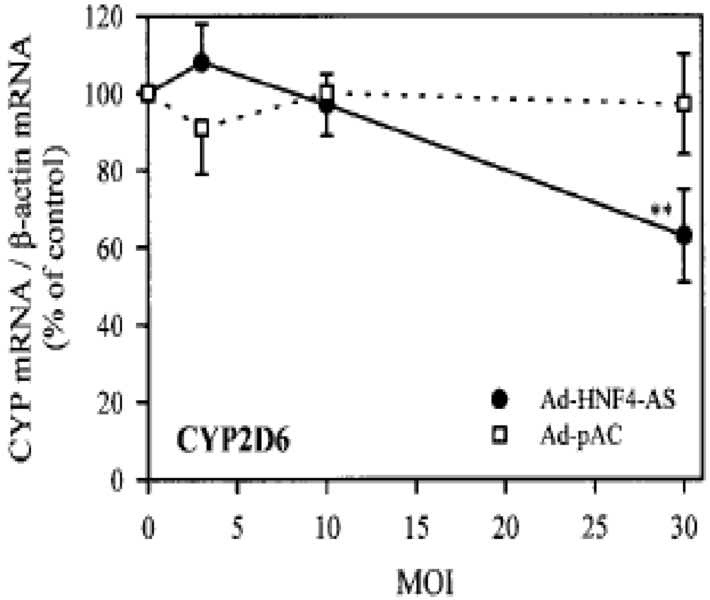
Gene-Gene Interaction between CYP2D6 and HNF4A

Regulation of CYP Expression by Nuclear Receptors



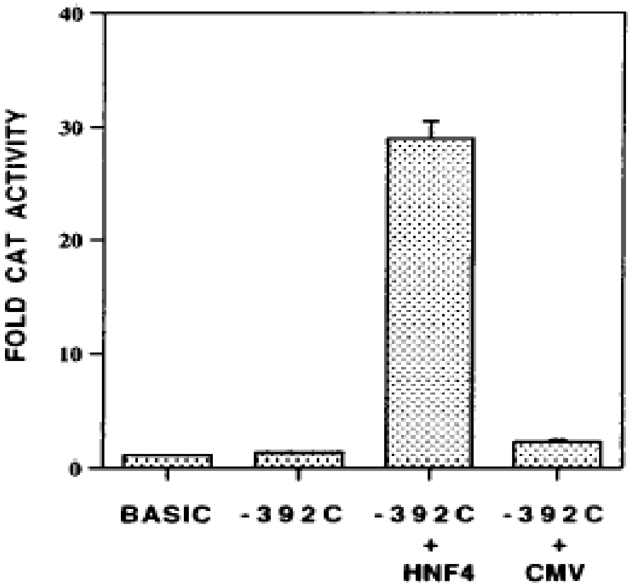
Constitutional expression of CYP2D6 is regulated by HNF4α

Anti-mRNA of HNF4α



Jover et al. (2001) Hepatology

CYP2D6 promoter



Cairns et al. (1996) J Biol Chem

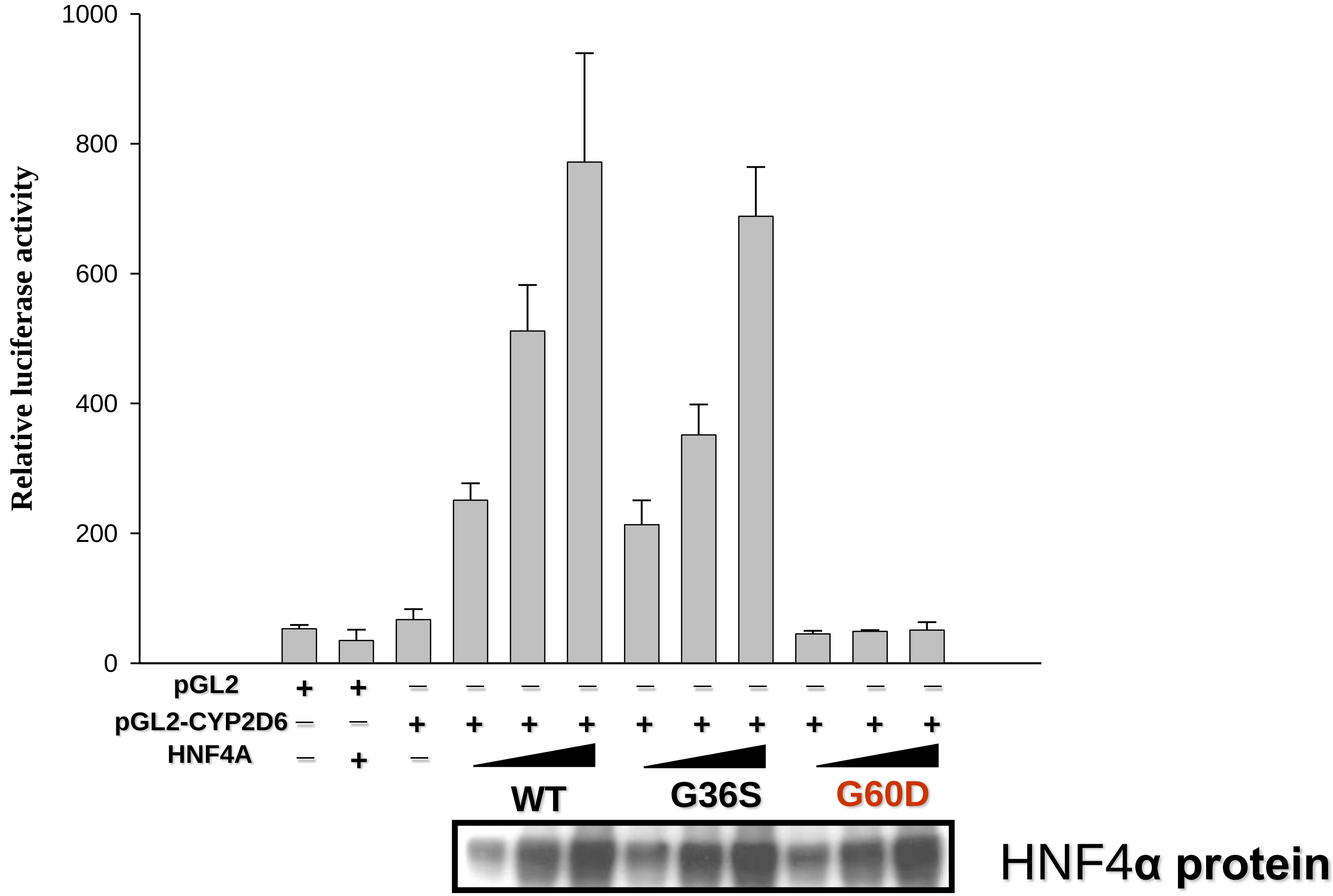
HNF4α SNPs identified in a Korean population

Position	Location	Effect	Frequency(%)
-2130A>C	Promoter		1
-2003G>A	Promoter		19
-2002T>C	Promoter		2
-1650A>G	Promoter		25
-1461C>T	Promoter		2
-1072C>G	Promoter		1
-1048GGG>delGGG	Promoter		37
-755A>C	Promoter		19
4654C>T	IVS2-5		2
4676G>A	Exon2+18	G36S	3.8
4749G>A	Exon2+91	G60D	1.3
4768G>C	Exon2+110	S66S	3
28152G>T	Exon10+1189	P428P	1
28278G>A	IVS10+1315		1
28421G>A	IVS10+1343		4
28658T>G	IVS10+1695		2
28693G>T	IVS10+1730		1
29031G>A	IVS10+2068		1
29172A>T	IVS10+2209		2
29172A>C	IVS10+2209		51

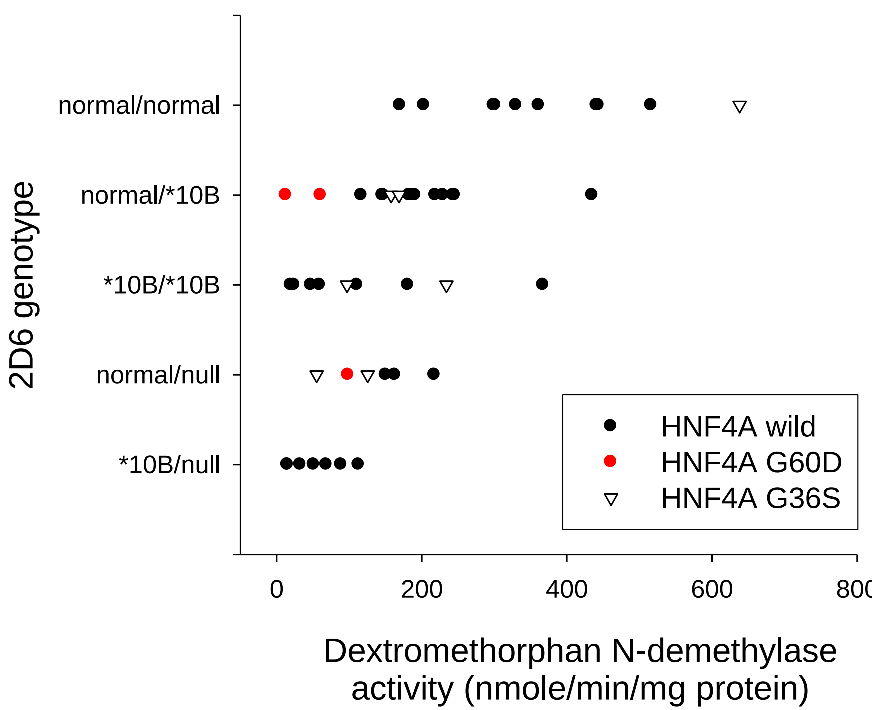
- 22 SNPs in HNF4α genes
  (exon: 4, intron: 8, promoter: 8)
- HNF4α G36S and G60D are novel
  HNF4α variants
  G36S (3.8% in 612 subjects)
  G60D (1.3% in 612 subjects)

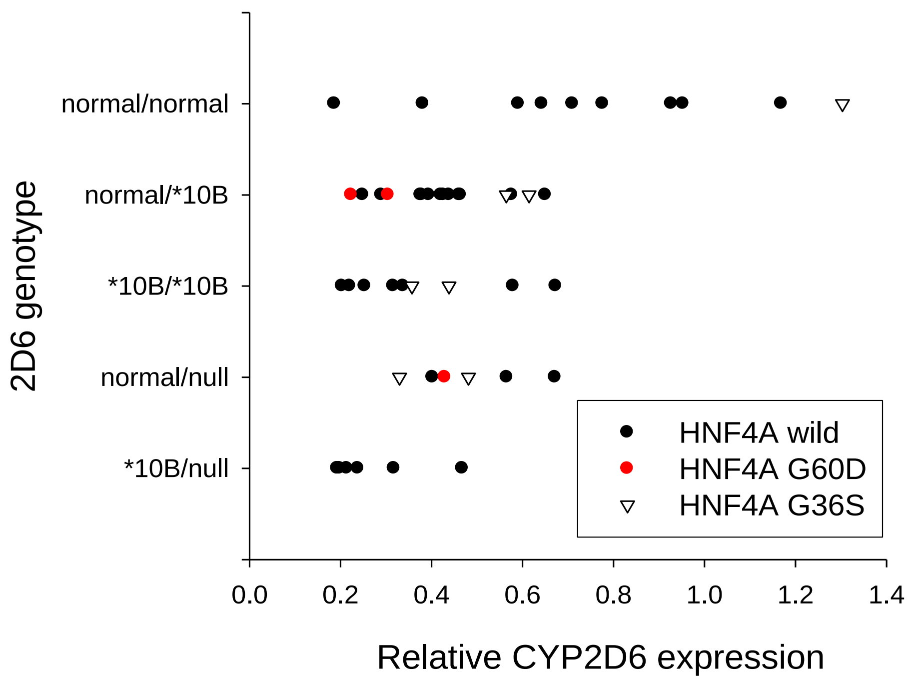
Lee SS, Shin JG et al. Hepatology, 2008

No Transactivation activity of HNF4α variants from the CYP2D6 promoter assay



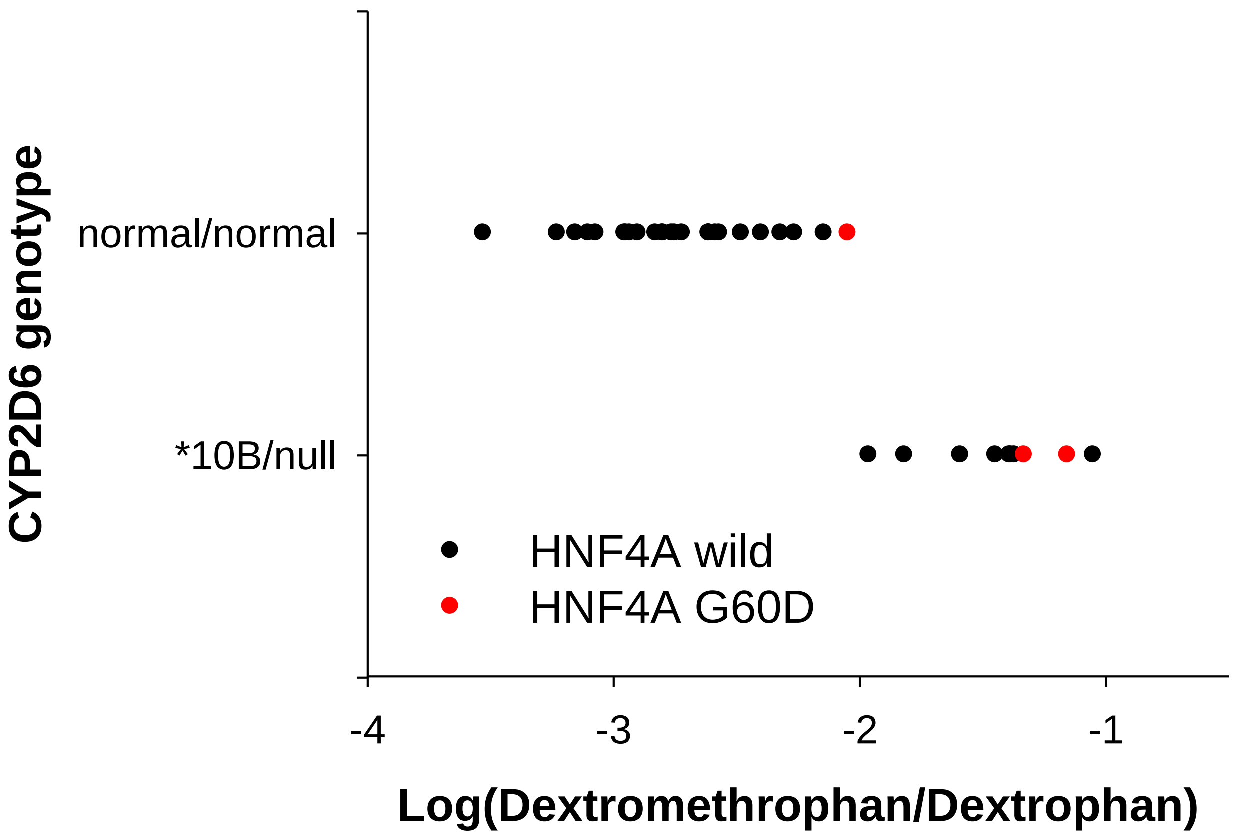
Effect of HNF4a G60D variant on CYP2D6 function in human liver tissues





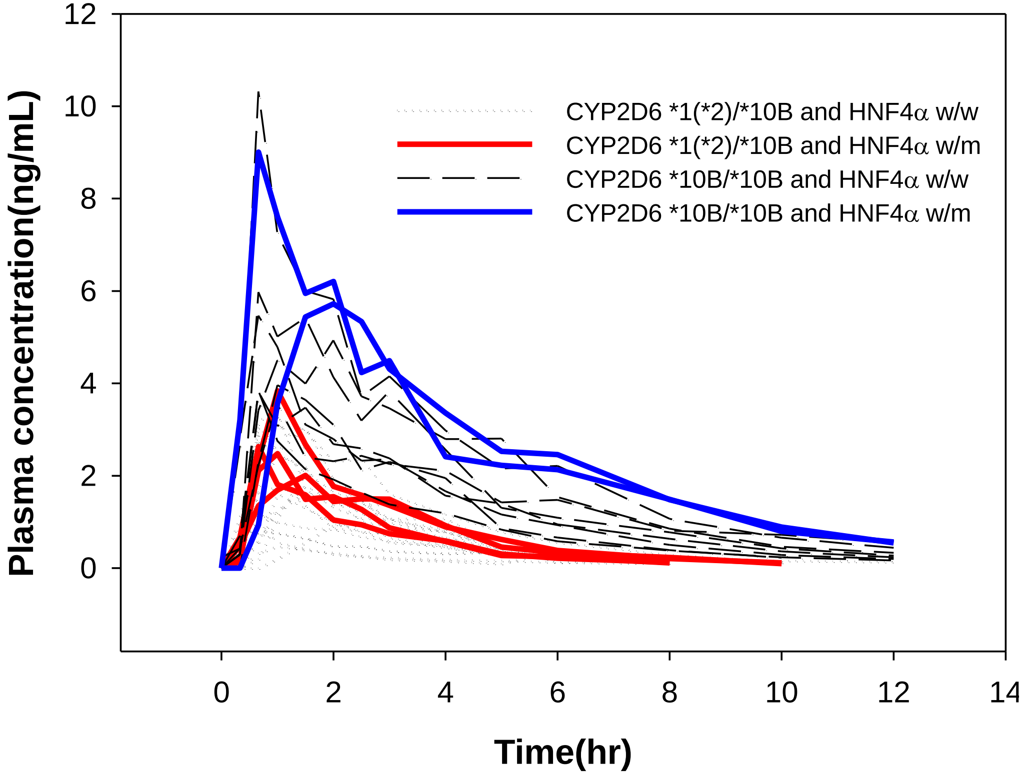
tendency of decreased activity and reduced expression of CYP2D6 of liver tissue with HNF4α G60D variant

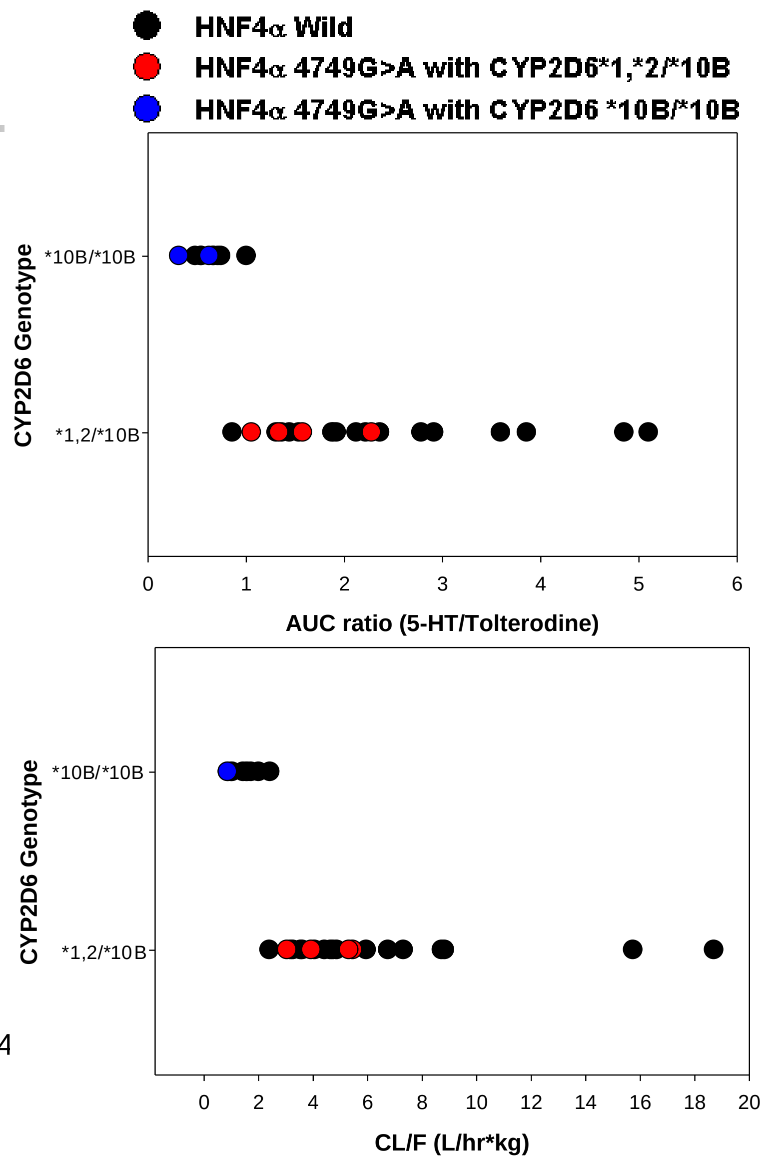
Effect of HNF4a G60D variant on CYP2D6 activity *in vivo*



Decreased tendency of CYP2D6 activity *in vivo* in subjects with HNF4α G60D

Effect of HNF4α G60D variant on the disposition of tolterodine, a CYP2D6 substrate





Ethnic difference of HNF4α G36S and G60D Variants

Population	n	Allelic Frequency (%)	
		G36S	G60D
Korean	612	3.8	1.3
Chinese	94	1.1	0.5
Vietnamese	139	3.6	0.7
[illegible]	[illegible]	[illegible]	[illegible]

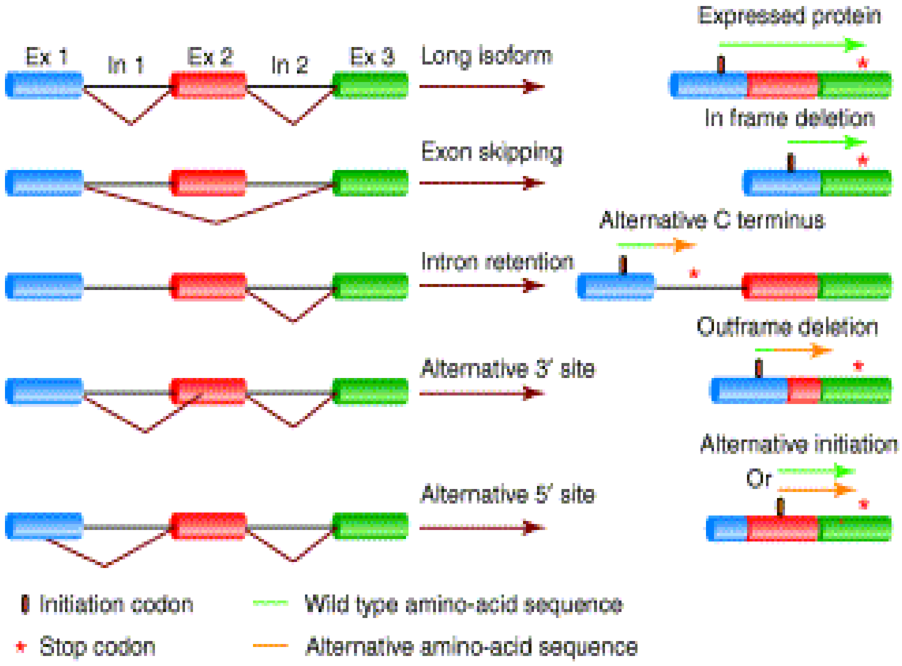
Minor allelic variant, but a nuclear receptor HNF4α genetic variant may cause the altered transcription of downstream gene CYP2D6.

☞ may contribute in part to the ethnic difference in genotype to phenotype prediction

Alternative splicing variant:

another potential of being confounder for genotype-phenotype prediction

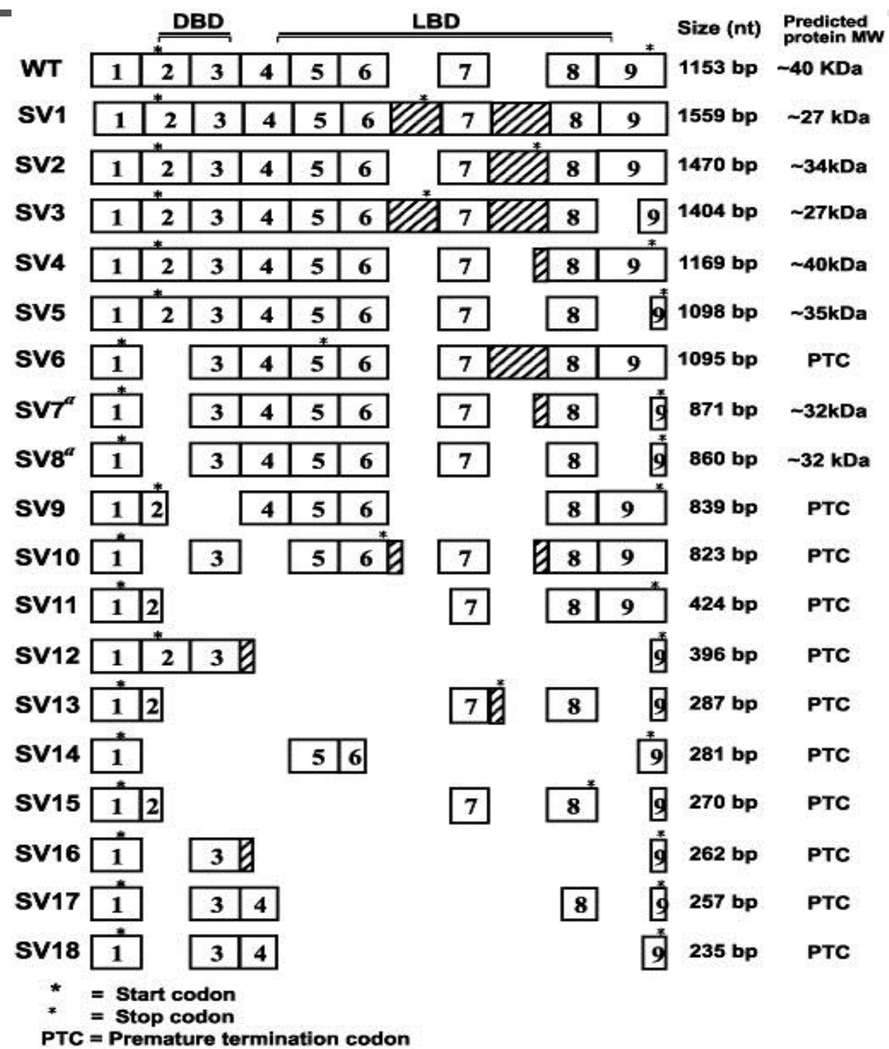
- A major factor of post transcriptional regulation
- increase complexity (mutiple protein isoforms from a single gene)
- 30–65% of human genes are alternatively spliced
- can lead to qualitative changes in protein sequence
- can lead to quantitative changes of functional protein
- the types of alternative splicing that have been observed include ①exon skipping, ②intron retention and ③use of alternative splice donor or acceptor site



TRENDS in Biotechnology

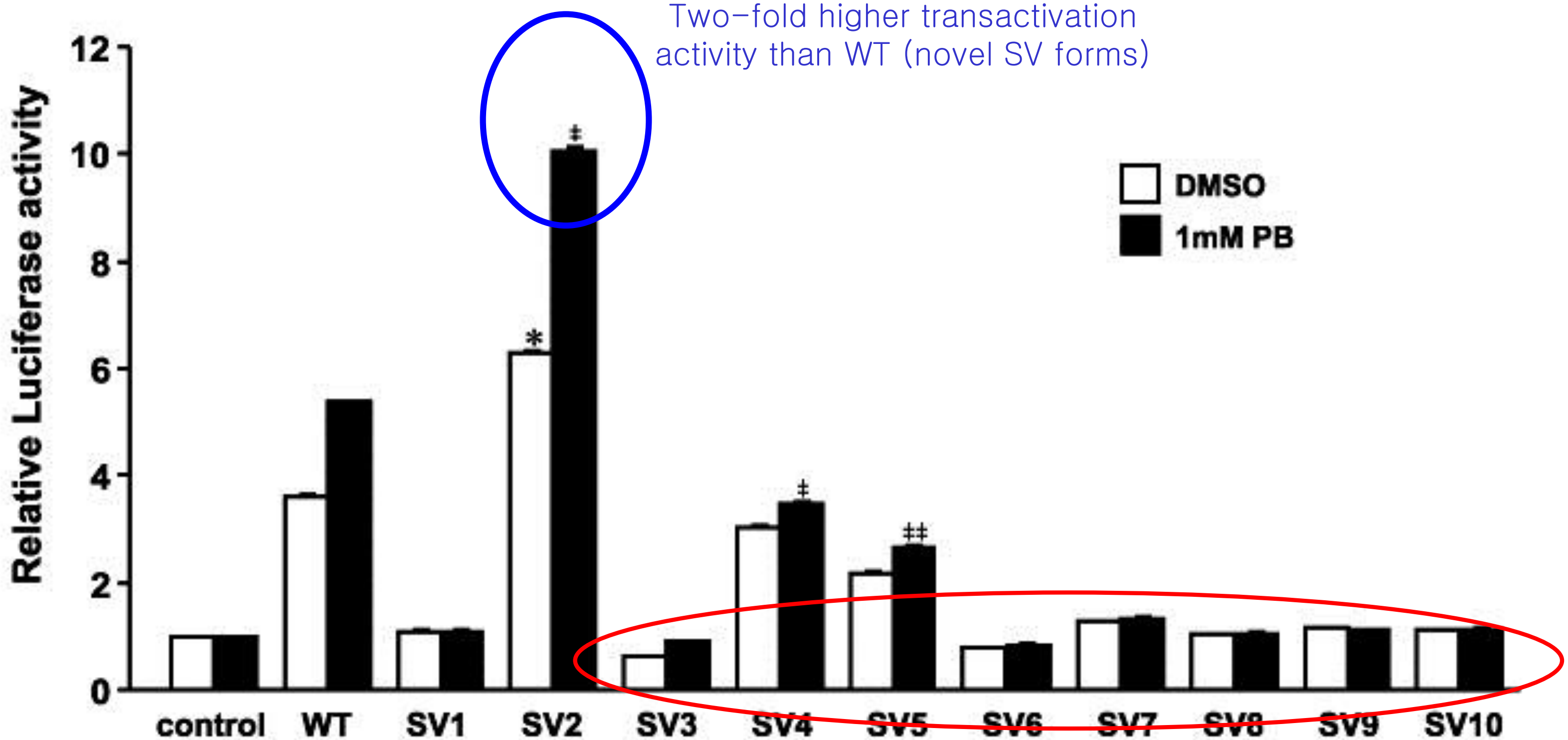
ASV of Constitutive Androstane Receptor (CAR) : identification from Korean liver tissues

Novel ASVs



- ✓ 18 hCAR splicing variants (SVs)
- ✓ including 4 novel
- ✓ identified from 30 Korean human liver tissues

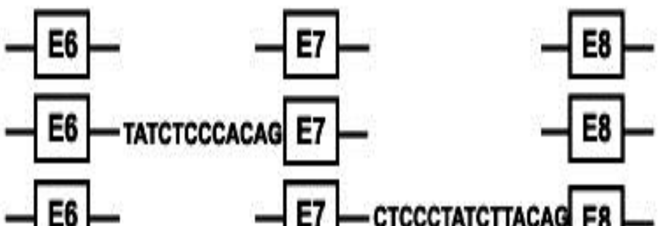
hCAR splice variants cause altered Transactivation of downstream CYP2B6 gene



***, $p < 0.05$; p is the level statistical difference from the untreated CAR WT- transfected cells by t-test.,**
‡, $p < 0.05$, ‡‡ $p < 0.01$; p is the level statistical different from the PB treated CAR WT- transfected cells by t- test.

Ethnic Difference :

Quantitative expression level of the hCAR ASVs in Livers of Koreans and Caucasians

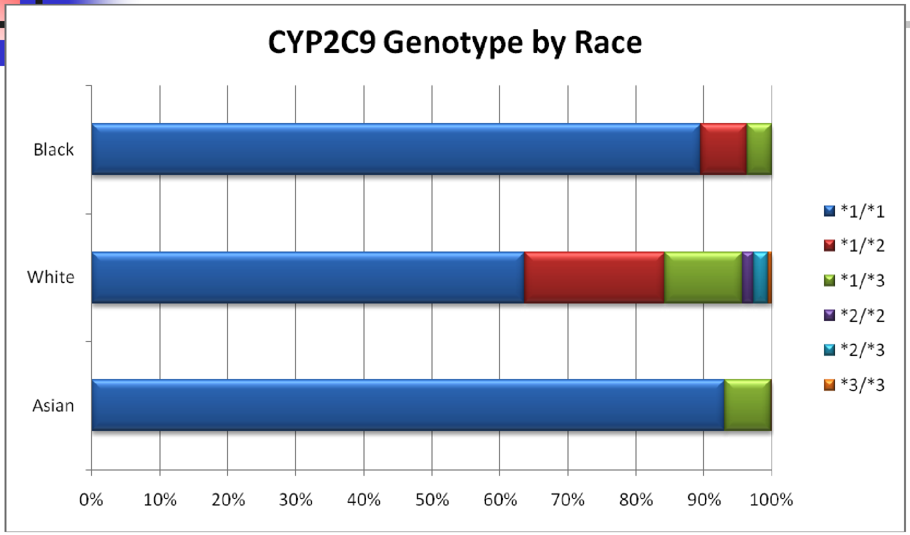


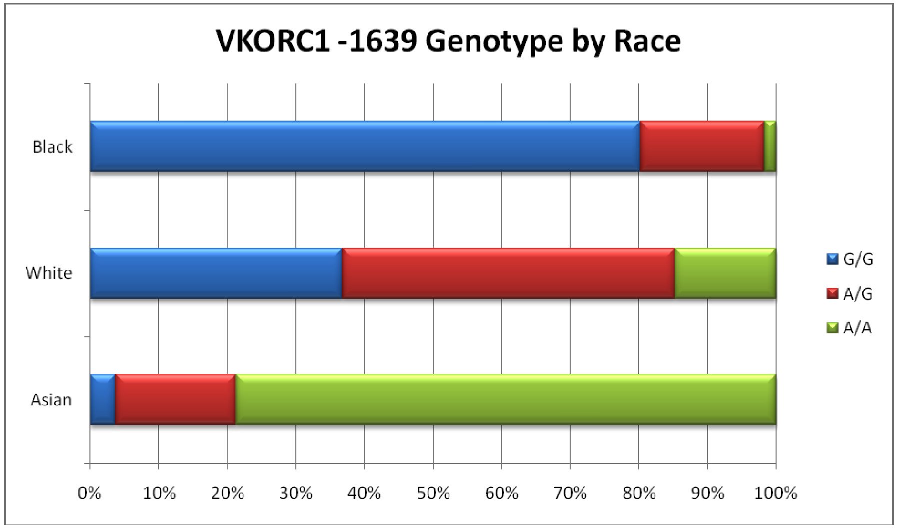
Activity	% of total transcripts	
	Korean	Caucasian
WT, SV5+SV8 (Normal)	10.5 ± 3.1	21.4 ± 2.1*
SV1 (Low)	-	-
SV4 + SV7	45.1 ± 4.4	53.5 ± 6.1

- Ethnic difference in nuclear receptor ASV profile may cause the different regulation of downstream enzyme activity, such as CYP2B6.
- May contribute in part to confound the genotype to phenotype prediction of CYP2B6 genetic polymorphism in different ethnic subjects.

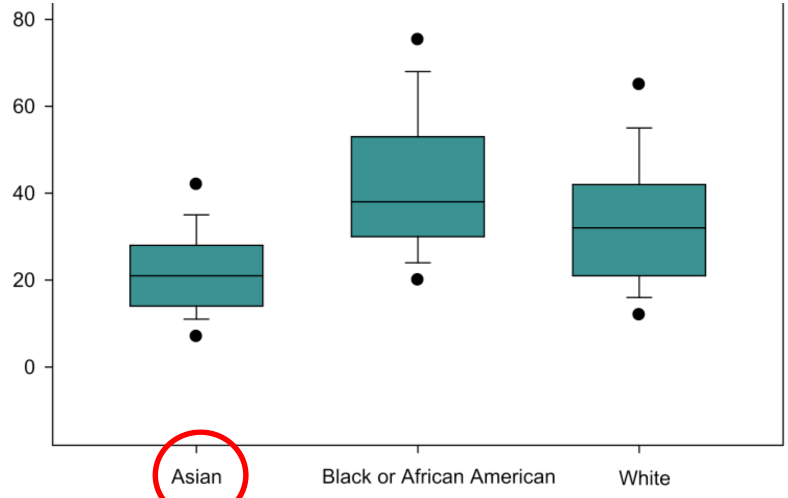
Combined effect of genetic and environmental factors: "Warfarin drug response"

Ethnic difference in allele frequency of CYP2C9 PM and VKORC1





In Asian,
Lower CYP2C9 PM (need low warfarin dose)
Higher VKORC1 A allele (need low warfarin dose) ⇒ lower dose in Asian



Distribution of Therapeutic Warfarin Dose by Race
Boxes show median, 25th and 75th percentile; whiskers show 10th and 90th percentile, and points show 5th and 95th percentile.

IWPC. NEJM. 2009

Global effort for the development of Warfarin dose prediction algorithm for global clinical utility in diverse ethnic populations

IWPC – 21 teams involved from the world

4 continents and 9 countries

- Asia
  - Israel, Japan, Korea, Taiwan, Singapore
- Europe
  - Sweden, United Kingdom
- North America
  - USA (11 states: Alabama, California, Florida, Illinois, Missouri, North Carolina, Pennsylvania, Tennessee, Utah, Washington, Wisconsin)
- South America
  - Brazil

Development of Warfarin dose prediction algorithm for global clinical utility in diverse ethnic populations

IWPC pharmacogenetic guided dosing algorithm

- Collected 5700 data set
- 5052 patients within target INR of 2-3
- 4043 patients for model development
- 1009 patients for validation cohort

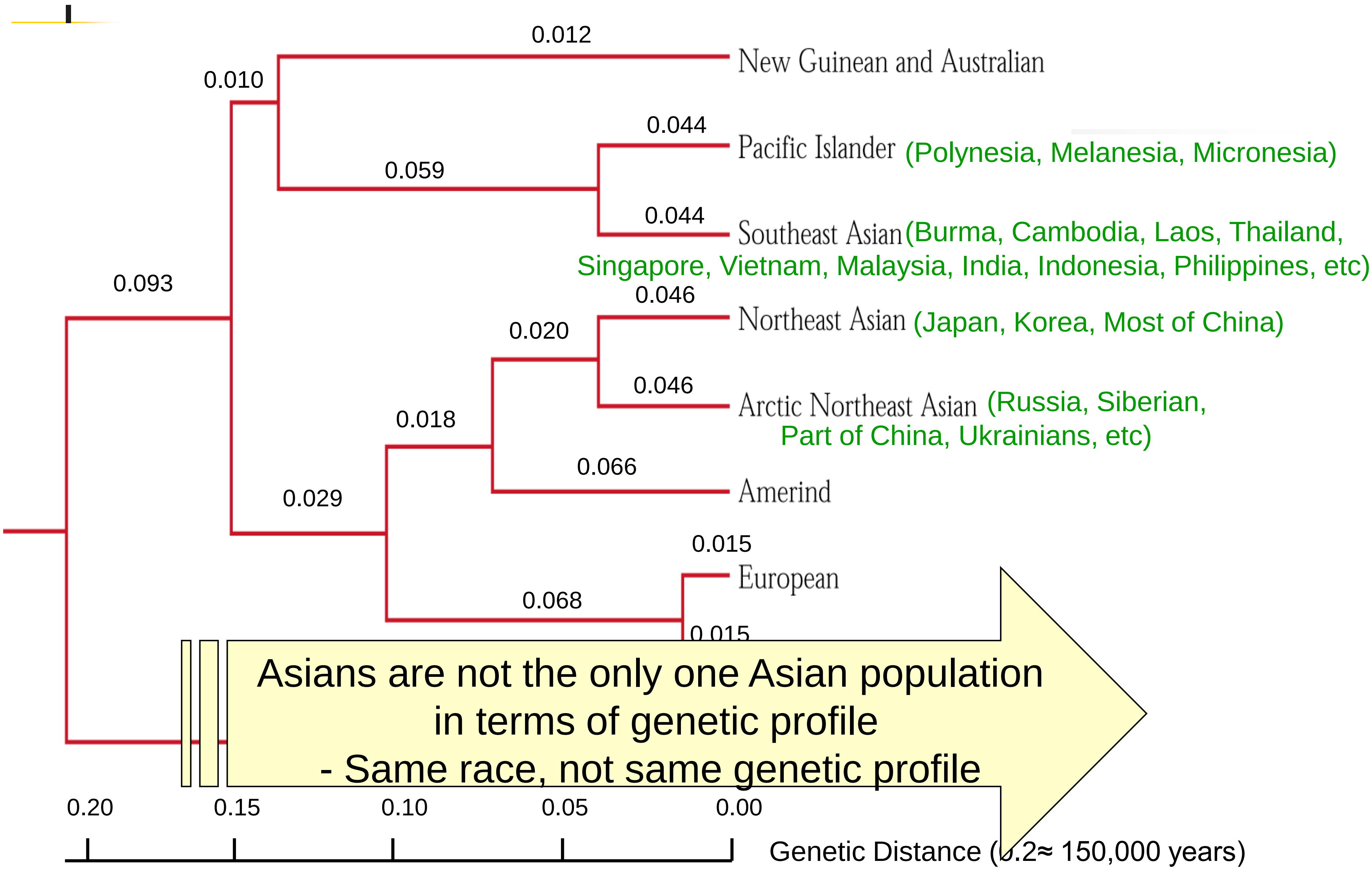
		5.6044	
-		0.2614 x	Age in decades
+		0.0087 x	Height in cm
+		0.0128 x	Weight in kg
-		0.8677 x	*VKORC1*^ A/G
-		1.6974 x	*VKORC1* A/A
-		0.4854 x	*VKORC1* genotype unknown
-		0.5211 x	*CYP2C9* *1/*2
-		0.9357 x	*CYP2C9* *1/*3
-		1.0616 x	*CYP2C9* *2/*2
-		1.9206 x	*CYP2C9* *2/*3
-		2.3312 x	*CYP2C9* *3/*3
-		0.2188 x	*CYP2C9* genotype unknown
-		0.1092 x	Asian race
-		0.2760 x	Black or African American
-		0.1032 x	Missing or Mixed race
+		1.1816 x	Enzyme inducer status
		0.5503 x	Amiodarone status
	Square root of weekly warfarin dose**		

Is this last model of wafarin dose estimation based on PGx information for global use?
In each of Asian countries?

IWPC, NEJM 2009

Linkage Tree: Analysis of Nine Population Clusters

(used 120 genes in 42 populations, Cavalli-Sforza LL, et al., Princeton Univ. Press 1994)



Different Warfarin dosing among different Asian ethnic populations

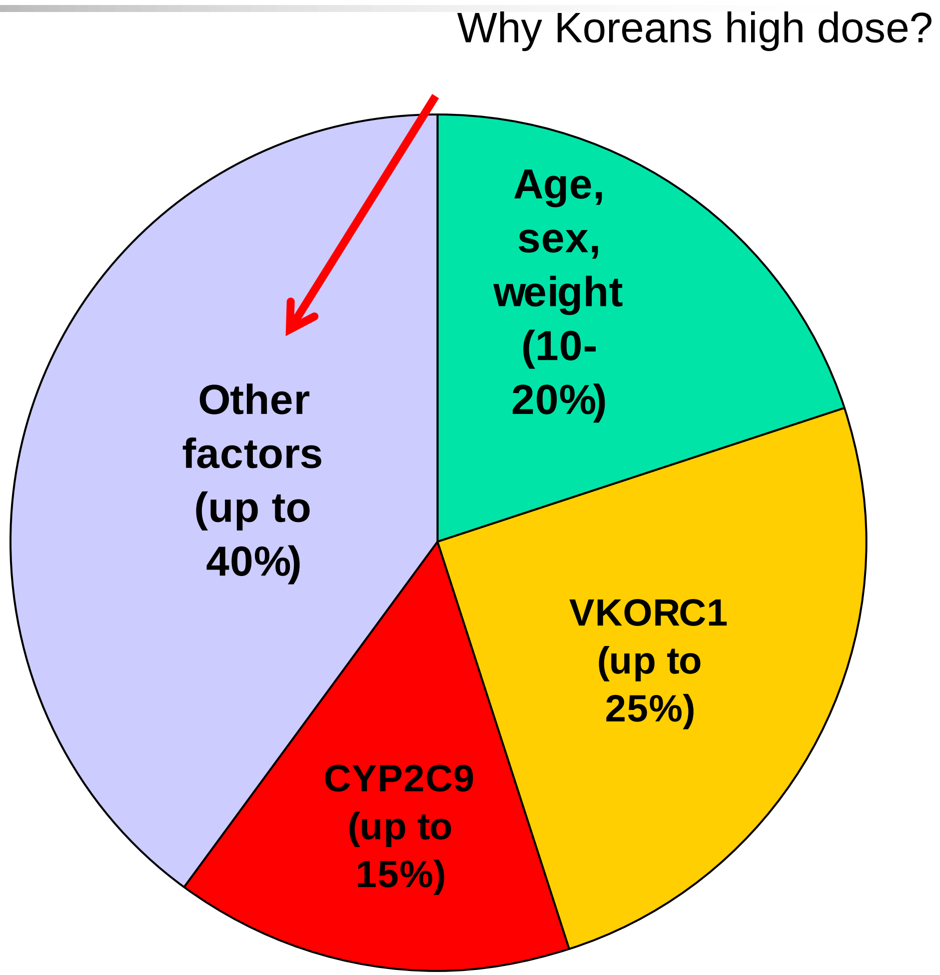
Should we consider the ethnic difference among Asian populations for the dose prediction?
What factor may influence on the such ethnic difference among Asian population?
Fine tuning of global predictive model for warfarin dose in Asian population?

Ethnic	Warfarin dose (mg/day)	Indication	INR	N	Allele frequency (%)			Ref
					CYP2C9*2	CYP2C9*3	VKORC1	
Korean	4.07±1.22	MHVR	1.7-2.8	265	-	5.3 (2-6)	1173C>T: 93.8	(1)
	4.1±1.6	A Fib	1.8-2.7	108	-	5.5	1173C>T: 90.3	(2)
Japanese	2.89±0.75	MHVR	1-2.6	31	-	-	1173C>T: 90.3	(3)
	2.5 (median)	-	1.6-2.5	828	-	2.4	1173C>T: 91.3	(4)
	3.2±1.26	MHVR, A Fib, DVT, PE	1.1-3.5	125	-	2.8	1173C>T: 89.2	(5)
Chinese	3.53±1.6	A Fib, DVT	1.8-3.2	69	0	2.9	H1: 86.2	(6)
	3.68±1.68	MHVR, A Fib, DVT	2-3	139	0	7	H1: 87	(7)
Malays	3.28±1.39	MHVR, A Fib, DVT	2-3	82	1	9	H1: 67	(7)
Indians	6.21±2.94	MHVR, A Fib, DVT	2-3	35	4	18	H1: 14	(7)

(1) Pharmacogenet Genomics 2009, 103–12 ; (2) Pharmacogenomics 2007, 329-37 ; (3) Pharmacogenomics 2007, 713-19 ; (4) J Hum Genet 2006, 249–53 ; (5) Clin Pharmacol Ther 2006, 169-78 ; (6) Pharmacogenetics and Genomics 2005, 687–691 ; (7) Clin Pharmacol Ther 2006, 197–205

Many factors influencing on Warfarin Dose
: genetic and **nongenetic factors**

- Age
- BSA or weight
- Amiodarone & drug-drug interaction
- Target INR
- Race
- Sex
- Plasma vitamin K level / diet containing high ingredient of Vit K
- Decompensated CHF or post-operative state
- The patient's genetic status



Major Korean diet composed of vit K1 rich food . Japanese diet?


Spinach 324 ug


Turnip greens 324 ug


Shrimp <0.01 ug


Soy beans / Tobu 386 ug


Beef 85 ug


asparagus 72 ug


Lettuce 68 ug


Scallions 103 ug


Broccoli 88 ug


Fish 5.8 ug


Fried egg 3.2 ug

As phylloquinone (vit K1) contents per one serving

Plasma concentration of vit K in Chinese and UK

Table 1. Subject characteristics and plasma biochemical markers of vitamin K status in older individuals in Shenyang and Cambridge

(Mean values and standard deviations)

	Chinese				British			
	Men (*n* 86)		Women (*n* 92)		Men (*n* 67)		Women (*n* 67)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	66·9	4·7	64·4*	4·4	68·8	6·0	67·9††	6·5
Weight (kg)	68·8	9·5	59·9**	10·5	78·8††	9·6	69·5** ††	12·2
Height (m)	1·669	0·062	1·551**	0·053	1·734††	0·063	1·597** ††	0·071
Phylloquinone (nmol/l)								
Geometric mean	1·88		2·48*		0·66††		0·73††	
95 % CI	1·61	2·19	2·14	2·88	0·57	0·75	0·64	0·84
Triacylglycerol (mmol/l)	1·25	0·70	1·63**	0·80	1·12	0·51	1·31* †	0·59
tOC (μg/l)	13·9	5·9	19·0**	6·1	18·2††	7·3	24·5** ††	10·8
ucOC (% of tOC)	13·3	9·1	22·8**	9·9	31·6††	12·9	32·7††	9·5

tOC, total osteocalcin; ucOC, undercarboxylated osteocalcin.
Mean value was significantly different from that for men in the same population: *$P<0·05$, **$P<0·01$.
Mean value was significantly different from that for the Chinese counterparts: †$P<0·05$, ††$P<0·01$.

British Journal of Nutrition 2004.939-945

Comparison of serum vit K concentrations between in Japanese and Korean

Japanese

Table 1. Subject characteristics

n	379
Age (years)	63.0 (10.8)
Body weight (kg)	52.1 (7.3)
Body height (cm)	151.6 (6.0)
BMI (kg/m^2)	22.6 (2.8)
K_1 (nmol/l)	3.51 (2.70)
MK-4 (nmol/l)	0.20 (0.31)
MK-7 (nmol/l)	10.0 (15.1)
ucOC (ng/ml)	4.68 (3.15)
iOC (ng/ml)	8.69 (7.13)
25-OH-D (nmol/l)	51.8 (16.3)
iPTH (pmol/l)	4.9 (1.8)
Ca (mmol/l)	2.30 (0.10)
P (mmol/l)	1.12 (0.15)
BAP (U/l)	31.4 (11.2)
NTX (pmol BCE/μmol Cr)	57.3 (25.5)
$L_{2\text{-}4}$ BMD (g/cm^2)	0.970 (0.186)
$L_{2\text{-}4}$ Z-score	0.178 (1.405)
FN BMD (g/cm^2)[a]	0.750 (0.128)
FN BMD Z-score[a]	0.398 (0.857)

J Bone Miner Metab 2008. 79-85

Korean

Table 2. Dietary vitamin K intake and serum vitamin K concentration of the subjects N=24

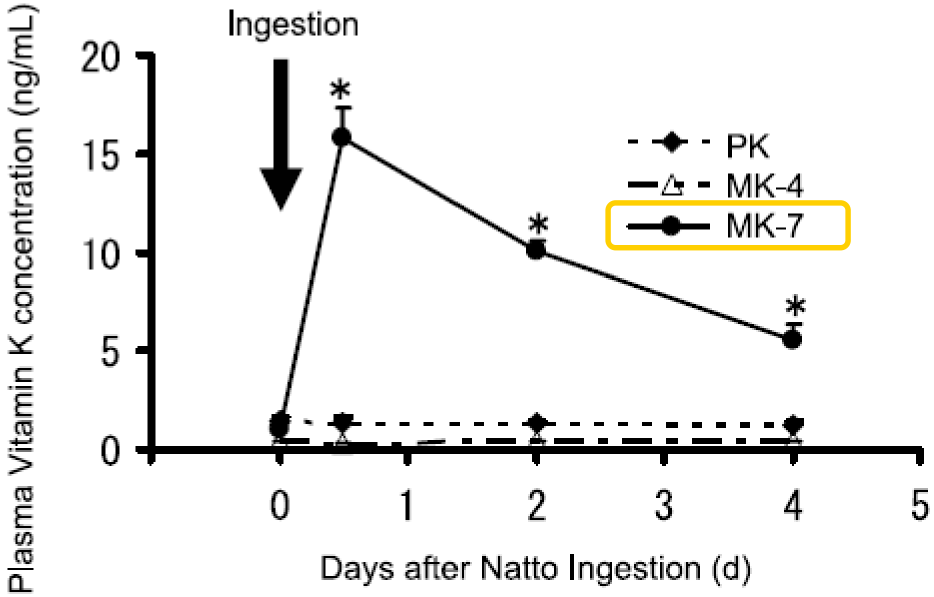
Variables	Mean±SD(range)
Dietary vitamin K(μg/day)	690.9±422.0(172.2－1331.3)
Serum vitamin K (ng/ml)	3.3± 2.0(0.6－ 6.7)

Values are mean±SD

7.32±4.44 nmol/L

Korean Journal of Nutrition 1999. 287-295

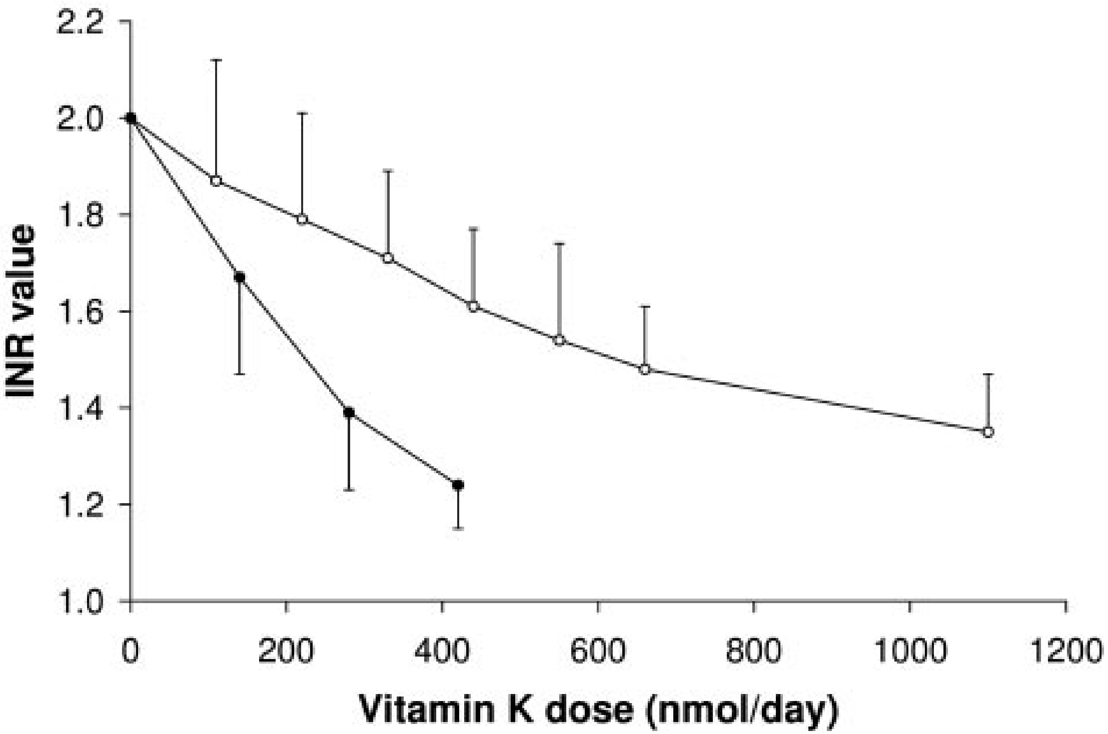
Effect of Dietary Supplment Natto on the plasma concentrations of Vitamin K2 isoforms



Plasma concentrations of PK (phylloquinone), MK-4 (menaquinone-4), and MK-7 (menaquinone-7) before and after the ingestion of natto (50g). **After natto intake, the plasma concentration of MK-7 was significantly increased** at 12h (15.80 ± 1.57 ng/mL) and that of PK and MK-4 were not affected by natto intake.

Kazuhiro H et al., 2006. J nutr sci vitaminol, 52, 297-301.

Effect of vit-K containing dietary supplements on acenocoumarol induced INR value in subjects taking daily dose of vit-K for 1 week



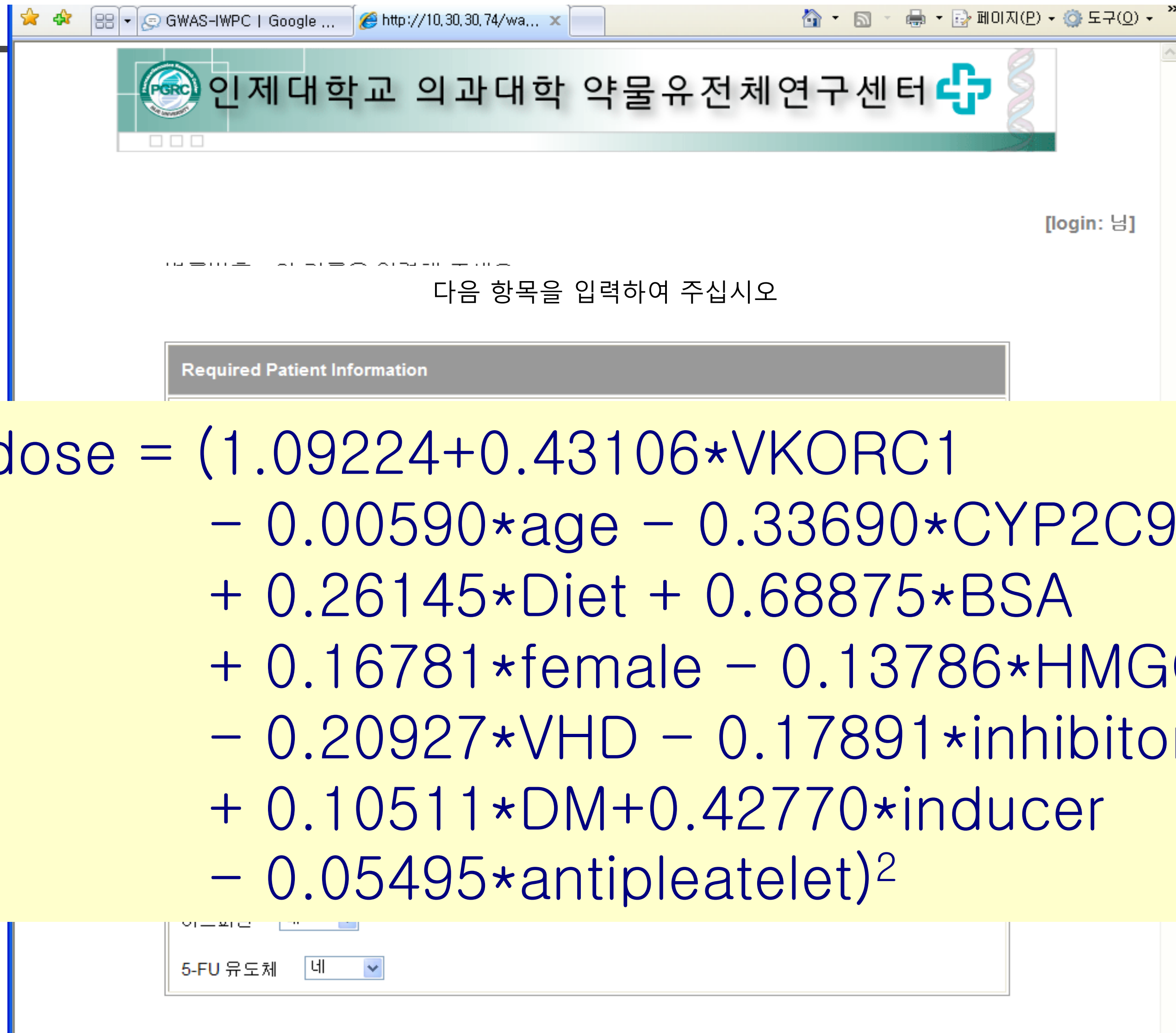
Interference of K vitamins with oral anticoagulants. Participants were

treated with acenocoumarol until they reached a stable target INR level of 2.0.

Subsequently they received a daily dose of vitamin K (as indicated) for 1 week. At the end of the week blood was taken by venipuncture, and the vitamin K dose was increased during the next week. Points are means of 12 values; error bars represent SD. E indicates K1; and F, MK-7.

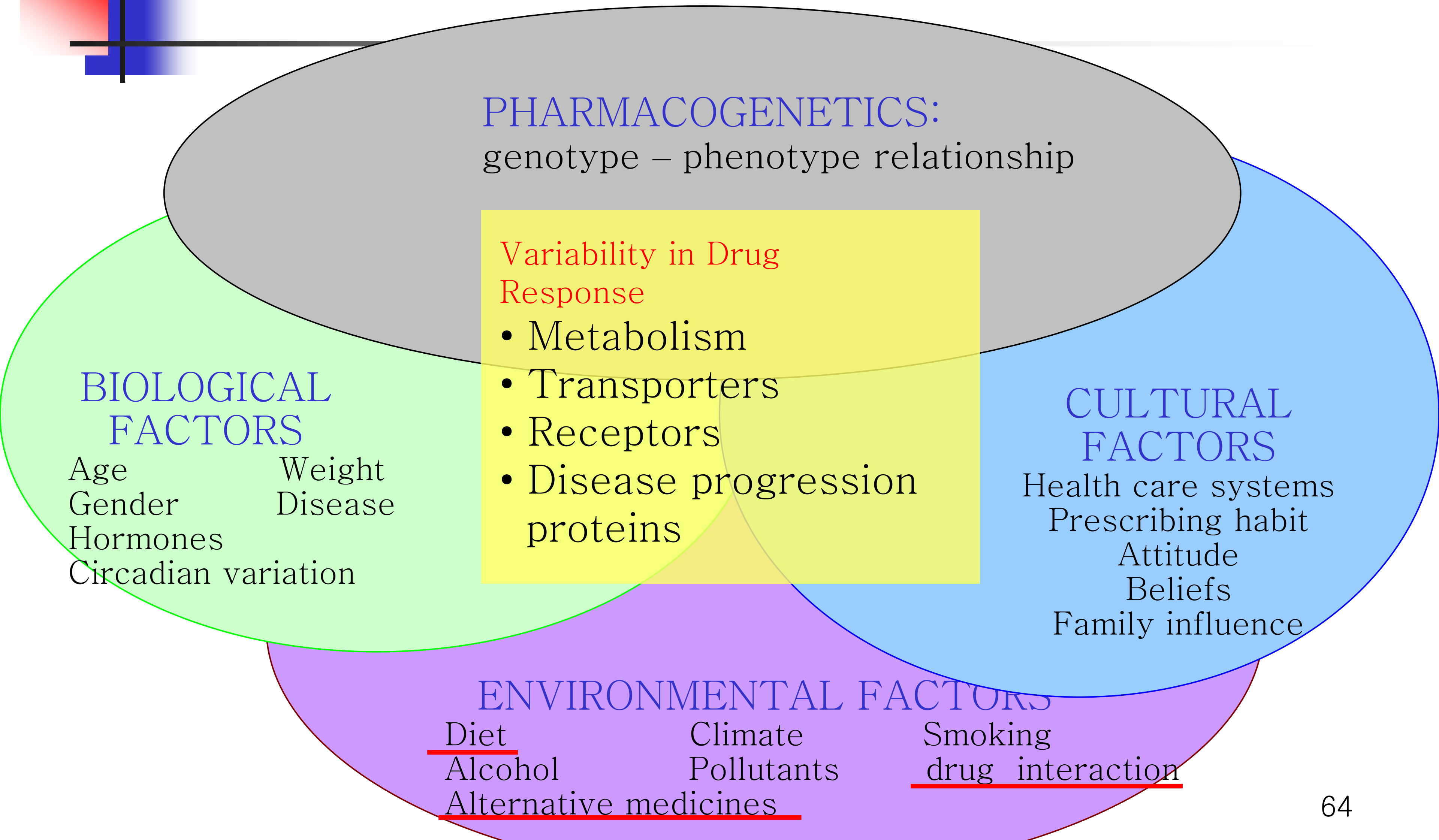
Schurgers LJ et al. Blood 2007; 3279

Web-based Warfarin Dose Prediction Algorithm for the Development of Genotype Guided Pharmacotherapy of Warfarin in Korea



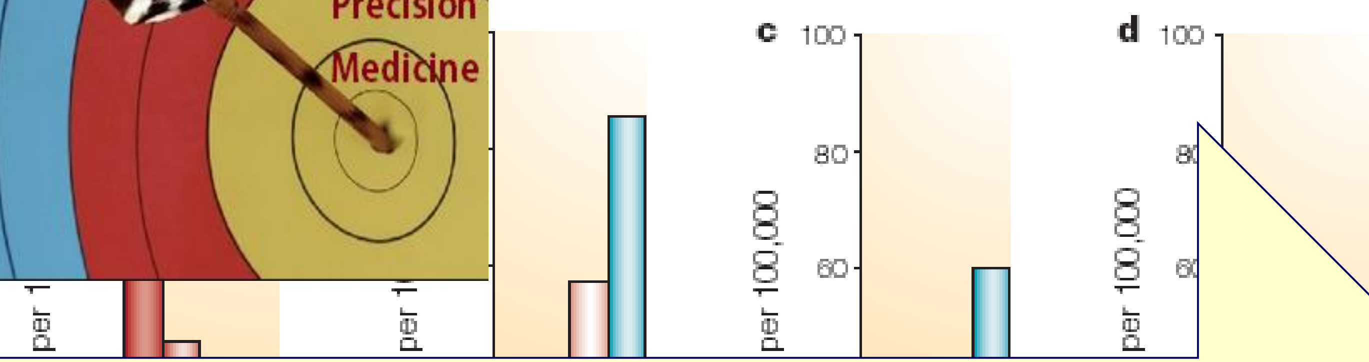
$$\text{Warfarin dose} = (1.09224+0.43106*\text{VKORC1} - 0.00590*\text{age} - 0.33690*\text{CYP2C9} + 0.26145*\text{Diet} + 0.68875*\text{BSA} + 0.16781*\text{female} - 0.13786*\text{HMGCoA} - 0.20927*\text{VHD} - 0.17891*\text{inhibitor} + 0.10511*\text{DM}+0.42770*\text{inducer} - 0.05495*\text{antipleatelet})^2$$

Factors influencing on the ethnic difference of drug response or dose: multiple interactions



Dilution or Augmentation of genetic factors by ... factors

...etic and Environmental Factors on Cancer Risk ...n different ethnics



Ethnicity, same to all situation ?
Japanese reside in Hawaii, Korea, Africa – same ?
1st generation, 2nd generation, 3rd generation in that country
Grouping / categorization of an ethnic population, which level?
Admixed population? In Korea…

Culture is going to be changed… Koreans, yesterday, today, tomorrow

Cancer incidence in Japanese migrant to Hawaii

K... et al. Nature Rev 2004

Thank you for your attention !
감사 합니다.
聞いていただいてありがとうございます
非常謝謝

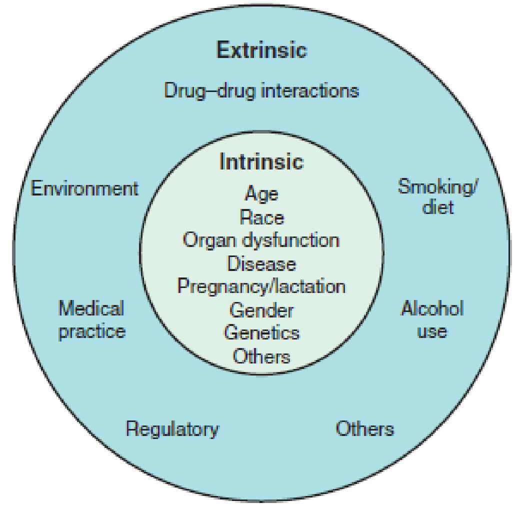
Foundation Meeting of KSCPT, Jan 25, 1992

Korean Society of Clinical Pharmacology and Therapeutics (KSCPT)

- 24 years since established at 1992.
- President: Dr. Il-Seop Lee (GSK, Korea)
- Chair, Board of Directors: Prof. Jae-Gook Shin (Inje Univ.)
- Total No. of Members: 506 (2015)
- No. of Institute having clinical pharmacology program (dept./div.) : 22 institutes (2015)

Impact and Consideration of Ethnic Factors in Global Drug Development

Intrinsic and extrinsic ethnic factors affecting exposure and drug response and risk–benefit assessment in different populations and regions

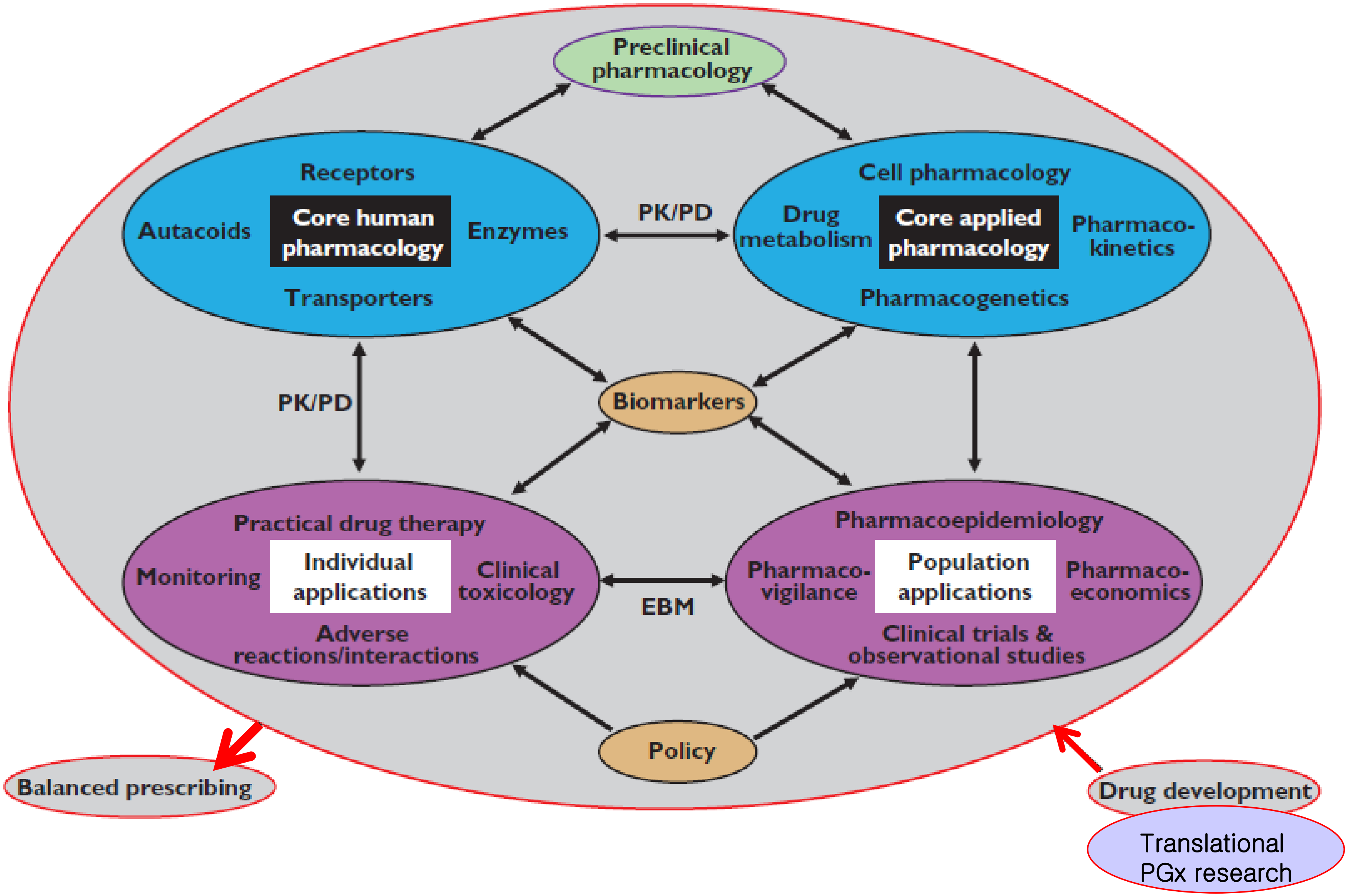


Group	Ethnic factor	Fold change in exposure (AUC)	Initial dose (mg)	Daily dose (mg)
1	Control	1-fold	10–20	5–40
2	Hepatic impairment	1.1-fold (mild) 1.2-fold (moderate)	10–20 10–20	5–40 5–40
3	Renal impairment	1-fold (mild) 1-fold (moderate) 3-fold (severe)	10–20 10–20 5	5–40 5–40 ≤10
4	Race	2-fold (Asians)	5	5–20
5	Cyclosporine	7-fold		5
6	Gemfibrozil	1.9-fold		10
7	Lopinavir/ ritonavir	5-fold		10

Comparative systemic exposure and corresponding starting (and maintenance) dose recommendation in subgroups with various patient factors: young healthy male subjects (control); patients

Clinical pharmacology & Therapeutics | VOLUME 84 NUMBER 3 | SEPTEMBER 2008

All of the factors influencing ethnic differences are …
Biomarkers influencing the drug response



"Operational Definition of Clinical Pharmacology"

Modified from Aronson JK, BJCP 2010

Higher Toxicity with lower dose of docetaxel in Japanese

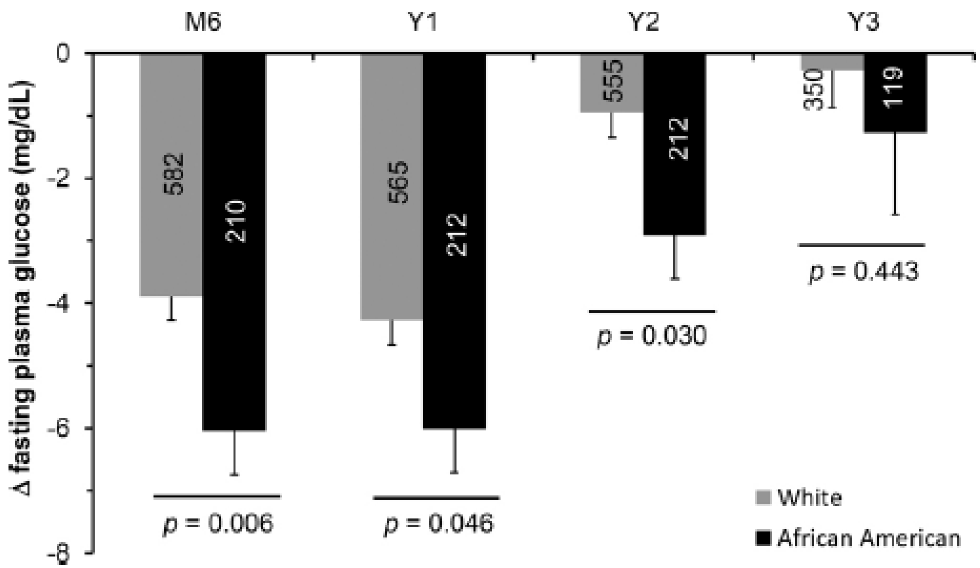
Table 3. Efficacies and toxicities of docetaxel monotherapy (phase III for previously treated non-small cell lung cancer patients)

Authors	Dose (mg/m^2)	N	Gr3-4 ANC (%)	Gr4 ANC (%)	Gr3–4 WBC (%)	Gr4 WBC (%)	Gr3–4 FN (%)	ORR (%)	Median PFS (mo)	Median OS (mo)	Ethnicity
Shepherd *et al.* 2000[55]	75	55	67.3				1.8	5.5		7.5	NA
	100	49	85.7				22.4	6.3		5.9	
Fossella *et al.* 2000[56]	75	121		54			8	6.7	TTP 8.5w	5.8	NA
	100	121		77			12	10.8	TTP 8.4w	6.0	
Hanna *et al.* 2004[57]	75	276	40.2				12.7	8.8	2.9	7.9	NA
Gridelli *et al.* 2004[58]	75	110	18	11	10	3	5	2.7		7.3	NA
Schuette *et al.* 2005[59]	75	103	20.6		27.5		2	12.6	TTP 3.4	6.3	NA
Camps *et al.* 2006[60]	75	129	9.3		10.1		7.8	9.3	TTP 2.7	6.6	NA
Ramlau *et al.* 2006[68]	75	415	60	36	41	11	3	5	TTP 13w	7.8	White/Oriental/Black
Kim *et al.* 2008[61]	75	733		58.2			10.1	7.6	2.7	8.0	White/Asian/Black
Maruyama *et al.* 2008[62]	60	239	73.6		39.3		7.1	12.8	2.0	14.0	Japanese
Paz-Ares *et al.* 2008[63]	75	416	37		2		6	12	TTP 2.6	6.9	Caucasian/Black/Asian/Hispanic
Takeda *et al.* 2009[64]	60	65	85.9		64.1		25.0	6.8	2.1	10.1	Japanese
Krzakowski *et al.* 2010[65]	75	277	29.5	18.8	21.3	4.8	4.7	5.5	2.3	7.2	NA
Lee *et al.* 2010[66]	75	79						7.6	3.4	12.2	Korean
Herbst *et al.* 2010[67]	75	697	24		11		6	10	4.2	10.0	Caucasian/East Asian
Ramlau *et al.* 2012[69]	75	457	21.1				4.2	8.9	4.1	10.4	NA
Garassino *et al.* 2013[70]	75	110	21	12			4	15.5	2.9	8.2	White/Asian
Kawaguchi *et al.* 2014[71]	60	151	80.0		64.0		15.3	17.9	3.2	12.2	Japanese
Reck *et al.* 2014[72]	75	659	29.9	21.2	2.4	0.6	4.7	3.3	2.7	9.1	White/Asian/Black/Indian

ANC, absolute neutrophil count; FN, febrile neutropenia; Gr, grade; NA, not available; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression; w, weeks; WBC, white blood cell.

Kenmotsu H, Cancer Sci 106 (2015) 497–504

Drop in glucose level is higher in African Americans than Whites after metrformin treatment



African Americans shows higher drop of glucose than Whites on metformin treatment

- 582 Whites, 210 AAs
- 850 mg metformin twice daily up to 3 years
- Drop of glucose level:

6 month

- Whites (3.89 ± 0.39 mg/dl)
- AAs (6.04 ± 0.72, *P = 0.006)*

1 year

- Whites (4.45 ± 0.39 mg/dl)
- AAs (6.01 ± 0.76, *P = 0.046)*

2 year

- Whites (0.95 ± 0.47 mg/dl)
- AAs (2.91 ± 0.79, *P = 0.030*

Zhang C, Diabetes & Metabolism 41 (2015) 173–175