

Association of *CYP3A4*1G* and *CYP3A5*3* With the 1-year Outcome of Acute Ischemic Stroke in the Han Chinese Population

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Background and purpose: Previous studies have shown that common variants within *CYP3A4* and *CYP3A5* are associated with statin pharmacokinetics and the risk of cardiovascular disease. However, the association of variants in *CYP3A4* and *CYP3A5* with the prognosis of ischemic stroke remains undetermined. Therefore, we investigated this herein. *Methods:* Four hundred thirty-three consecutive patients with acute ischemic stroke were recruited. The outcome at the 1-year follow-up was assessed using the modified Rankin Scale (mRS). Two variants, *CYP3A4*1G* and *CYP3A5*3*, were genotyped by the improved Multiple Ligase Detection Reaction platform. *Results:* Binary logistic regression analysis showed that the *CYP3A4*1G/*1G* homozygote was associated with poor outcome at 1 year (mRS score ≥ 2) after adjustment for conventional factors in the additive model (odds ratio [OR] = 2.92; 95% confidence interval, 1.07-7.98; $P = .037$) and recessive model (OR = 3.37; 95% confidence interval, 1.26-9.04; $P = .016$). Subgroup analysis indicated that the *CYP3A4*1G/*1G* homozygote was associated with poor prognosis at 1 year among patients with stable high-intensity atorvastatin therapy (40-80 mg/d) after adjustment for conventional factors in the additive model (OR = 8.16; 95% confidence interval, 1.50-44.44; $P = .015$) and recessive model (OR = 9.06; 95% confidence interval, 1.72-47.64; $P = .009$). No significant association was identified between *CYP3A5*3* and the 1-year outcome of patients with ischemic stroke. *Conclusions:* Our study findings suggest that the *CYP3A4*1G/CYP3A4*1G* genotype may be associated with poor prognosis at 1 year after acute ischemic stroke in the Han Chinese population.

Key Words: Ischemic stroke—*CYP3A4*1G*—*CYP3A5*3*—single nucleotide polymorphism

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Introduction

Statins are widely prescribed to lower the low-density lipoprotein cholesterol level in patients with cardiovascular diseases, such as stroke. Inpatient statin use was shown to effectively reduce short-term mortality in

patients with acute ischemic stroke.¹ The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial provided strong evidence that atorvastatin use can effectively reduce the stroke recurrence risk in patients with recent ischemic stroke or transient ischemic attack.²

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However, responses to the statin varied interindividually, which may lead to therapeutic inefficiency or statin-related adverse effects. Previous studies indicated that genetic variants involved in statin pharmacokinetics contributed to this variation.^{3–6} The Heart Protection Study 2-Treatment of High-density Lipoprotein Cholesterol to Reduce the Incidence of Vascular Events trial showed that Chinese patients with atherosclerotic cardiovascular disease had a 10-fold higher risk of developing myopathy than European patients who were given the same statin therapy.⁷ A pharmacokinetic study reported that plasma exposure to a statin was significantly higher in Chinese individuals than in Caucasian individuals residing in the same environment.⁸ The reason for this finding may be partly due to a difference in statin pharmacogenetics between Chinese and Caucasian populations.

Cytochrome P450 3A4 (CYP3A4) and cytochrome 3A5 (CYP3A5) enzymes were crucial in oxidative metabolism in approximately 60% of clinically prescribed drugs.^{9,10} Atorvastatin, simvastatin, and lovastatin were mainly metabolized by CYP3A4 and CYP3A5, whereas rosuvastatin and pitavastatin were not affected by CYP3A4 and CYP3A5.^{11,12} The interindividual enzyme activities of CYP3A4 and CYP3A5 varied substantially, which were highly influenced by genetic variations.^{9,13} Among currently identified variants within *CYP3A4*, *CYP3A4*1G* (rs2242480, IVS10+12G>A) was the most prevalent in the Han Chinese population.¹⁴ Pharmacokinetic studies identified *CYP3A4*1G* as being associated with elevated *CYP3A4* messenger RNA (mRNA) transcription and increased catalytic activity of the enzyme.^{4,15,16} *CYP3A5*3* is the most studied among common variants of *CYP3A5*. The variant frequency of *CYP3A5*3* varied among populations: it was highest in Caucasians (82%), lower in Mexicans (75%) and Chinese individuals (65%), and the lowest in Africans (33%).¹⁷ A cohort study indicated that the *CYP3A5*3*/**3* homozygote was associated with a greater lipid-lowering response to a statin than *CYP3A5*1*/**1* and *CYP3A5*1*/**3* genotypes.⁶ The influence of *CYP3A4*1G* and *CYP3A5*3* on statin pharmacokinetics and the risk of cardiovascular disease have been studied. However, the association of these variants with the prognosis of ischemic stroke has not been elucidated.

The present study aimed to investigate the association of *CYP3A4*1G* and *CYP3A5*3* with the 1-year prognosis of acute ischemic stroke in a Han Chinese population, in an attempt to provide evidence for individualized secondary prevention treatment in ischemic stroke.

Materials and Methods

Ethical Statements

The present study was approved by the ethics review board of the university. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before

their information and blood samples were collected. All procedures were performed under relevant guidance.

Study Population

From January 2014 to December 2016, consecutive patients diagnosed with acute ischemic stroke in the Department of Neurology of the First Affiliated Hospital of Zhengzhou University were registered in this prospective hospital-based cohort study. According to the World Health Organization criteria, stroke was defined as focal or whole neurological deficits persisting for more than 24 hours due to vascular origin. Trained residents in the Department of Neurology used a standard case report form to record information. The recorded information included age, sex, medical history, clinical manifestations, National Institutes of Health Stroke Scale score on admission, results of neuroimaging examinations, laboratory test results, and therapy. All the patients were followed up at 1 month, 6 months, and 12 months after the index stroke by trained neurologists who were blinded to patient registration. The follow-up information included medication adherence, blood pressures, laboratory test results, modified Rankin scale (mRS) score, stroke recurrence, and death. Medication adherence was measured by the percentage of days covered (PDC). PDC more than equal to 80% was considered as fully adherent.¹⁸ The mRS was used to assess outcome; good outcome was defined as an mRS score less than equal to 1, and poor outcome as an mRS score more than equal to 2.

In the present study, the inclusion criteria were as follows: (1) stroke diagnosed in accordance with World Health Organization criteria; (2) acute ischemic lesions confirmed by CT or magnetic resonance imaging (MRI); (3) age more than equal to 18 years; (4) Han Chinese descent; (5) admission within 3 days after onset; (6) mRS score less than equal to 1 before stroke onset; and (7) PDC more than equal to 80% for statin adherence during the 1-year follow-up. The exclusion criteria were as follows: (1) fatal stroke; (2) hemorrhagic stroke; (3) severe systemic diseases, such as heart, liver, and kidney failure; (3) malignancies, autoimmune diseases, and hematologic diseases; (4) statin pretreatment before the index stroke; (5) statin intolerance or incontinence during hospitalization or follow-up; (6) individuals taking statins that were not metabolized by *CYP3A4* and *CYP3A5*, such as rosuvastatin and pitavastatin; and (7) individuals who were lost to follow-up or died during the follow-up. Hemorrhagic stroke was excluded based on results of neuroimaging examinations, such as computed tomography (CT) and magnetic resonance imaging.

Genotyping

Extraction of genomic DNA and quality control were performed as previously described.¹⁹ Two variants, *CYP3A4*1G* (rs2242480) and *CYP3A5*3* (rs776746), were genotyped by the improved Multiple Ligase Detection Reaction platform (Table 1).

Table 1. Information of CYP3A4*1G and CYP3A5*3

	SNP	Chr	Location	Allele	MAF (CHB) ^a
CYP3A4*1G	rs2242480	7	99361466	G/A	0.243
CYP3A5*3	rs776746	7	99270539	A/G	0.291

SNP single nucleotide polymorphism, Chr chromosome, MAF minor allele frequency, CHB Chinese Han, Beijing.

^aFrom the 1000 Genomes Project.

Statistical Analysis

Univariate logistic regression analysis was conducted to evaluate the association of CYP3A4*1G and CYP3A5*3 with poor outcome at 1 year after ischemic stroke in additive, dominant, and recessive models. The chi-square test and Student's *t* test were used to compare categorical and continuous variables, respectively, between the good and poor outcome groups. Binary logistic regression analysis was used to assess the association of CYP3A4*1G and CYP3A5*3 with poor outcome at 1 year following ischemic stroke after adjusting for conventional vascular factors in the additive, dominant, and recessive models. The level of significance was set at *P* less than .05 (2-tailed). SPSS 22.0 software (SPSS, Inc., Chicago, IL) was used to analyze the data.

Results

Baseline Characteristics

Four hundred thirty-three patients were enrolled and analyzed in this study. The mean age (mean \pm standard deviation) of patients was 62.34 \pm 11.03 years, and 302

(69.7%) were men. The average levels (mean \pm standard deviation) of total cholesterol and low-density lipoprotein cholesterol at admission were 4.38 \pm 0.96 mmol/L and 2.80 \pm 0.80 mmol/L, respectively. During the 1-year follow-up, 308 patients had a good outcome (mRS \leq 1), and 125 patients had a poor outcome (mRS \geq 2). The demographic characteristics of the 433 patients are shown in Table 2.

Associations of CYP3A4*1G and CYP3A5*3 With 1-year Outcome of Acute Ischemic Stroke

Among 433 patients, the distribution frequencies of CYP3A4*1*1, CYP3A4*1*1G, and CYP3A4*1G/*1G genotypes were 242 (55.9%), 169 (39.0%), and 22 (5.1%), respectively. The distribution frequencies of CYP3A5*1*1, CYP3A5*1*3, and CYP3A5*3*3 genotypes were 32 (7.39%), 187 (43.2%), and 214 (49.4%), respectively. The conventional factors included age, sex, smoking history, drinking history, hypertension, dyslipidemia, hyperhomocysteinemia, intracranial artery stenosis (>50%), and the National Institutes of Health Stroke Scale score at admission. Binary logistic regression analysis indicated that CYP3A4*1G/*1G was associated with a poor

Table 2. Demographic characteristics of the 433 patients with ischemic stroke

Variable	mRS score \leq 1 (n = 308)	mRS score \geq 2 (n = 125)	<i>P</i> value
Age (\geq 60 y)	147 (47.7%)	70 (56.0%)	0.119
Male sex	218 (70.8%)	84 (67.2%)	0.463
Hypertension	205 (66.6%)	95 (76.0%)	0.054
Diabetes mellitus	102 (33.1%)	40 (32.0%)	0.822
Hyperlipidemia	125 (40.6%)	52 (41.6%)	0.846
Smoking history	83 (26.9%)	37 (29.6%)	0.576
Drinking history	66 (21.4%)	35 (28.0%)	0.146
Hyperhomocysteinemia	192 (42.8%)	70 (40.5%)	0.603
Coronary artery disease	22 (7.1%)	8 (6.4%)	0.783
ICAS (>50%)	79 (26.8%)	50 (42.4%)	0.002
NIHSS score >3 on admission	108 (35.1%)	96 (76.8%)	<0.001
SBP (mmHg)	144.22 (19.38)	143.34 (24.83)	0.695
DBP (mmHg)	84.71 (13.89)	81.61 (21.20)	0.075
TC level (mmol/L)	4.36 (0.96)	4.42 (0.96)	0.546
TG level (mmol/L)	1.69 (1.03)	1.45 (0.68)	0.021
HDL-C level (mmol/L)	1.09 (0.28)	1.13 (0.28)	0.195
Hcy level (mmol/L)	18.72 (13.32)	18.15 (9.99)	0.664
FG level (mmol/L)	6.18 (2.31)	6.05 (2.24)	0.577

Categorical variables are shown as counts (percentage, %), and continuous variables as the mean (standard deviation).

DBP, diastolic blood pressure; FG, fasting glucose; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; mRS, modified Rankin scale, ICAS, intracranial artery stenosis; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 3. Association of CYP3A4*1G and CYP3A5*3 with the 1-year outcome of ischemic stroke

Variant		mRS score ≤1 (n = 308)	mRS score ≥2 (n = 125)	OR(95%CI)	P-value	O ^a (95%CI)	P value ^a
<i>CYP3A4*1G</i>							
Additive	*1/*1	170 (55.2%)	72 (57.6%)				
	*1/*1G	127 (41.2%)	42 (33.6%)	0.78 (0.50-1.22)	0.275	0.68 (0.41-1.13)	0.137
	*1G/*1G	11 (3.6%)	11 (8.8%)	2.36 (0.98-5.69)	0.056	2.92 (1.07-7.98)	0.037
Dominant	*1/*1G+*1G/*1G	138 (44.8%)	53 (42.4%)	0.91 (0.60-1.38)	0.648	0.84 (0.52-1.35)	0.461
Recessive	*1G/*1G	11 (3.6%)	11 (3.6%)	2.61 (1.10-6.18)	0.025	3.37 (1.26-9.04)	0.016
<i>CYP3A5*3</i>							
Additive	*1/*1	20 (6.5%)	12 (9.6%)				
	*1/*3	141 (45.8%)	46 (36.8%)	0.54 (0.25-1.20)	0.130	0.52 (0.21-1.26)	0.146
	*3/*3	147 (47.7%)	67 (53.6%)	0.76 (0.35-1.64)	0.485	0.67 (0.28-1.58)	0.355
Dominant	*1/*3+*3/*3	288 (93.5%)	113 (90.4%)	0.65 (0.31-1.38)	0.263	0.60 (0.26-1.38)	0.226
Recessive	*3/*3	147 (47.7%)	67 (53.6%)	1.23 (0.81-1.87)	0.325	1.10 (0.68-1.77)	0.704

CI, confidence interval; mRS, modified Rankin scale; OR, odds ratio.

^aAdjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, intracranial artery stenosis (>50%), smoking history, drinking history, and National Institutes of Health Stroke Scale score at admission.

prognosis at 1 year after adjusting for conventional factors in the additive model (odds ratio [OR]=2.92; 95% CI, 1.07-7.98, P = .037) and recessive model (OR = 3.37; 95% CI: 1.26-9.04, P = .016) (Table 3). The associations of CYP3A5*3 with the 1-year outcome did not achieve statistical significance in binary logistic analysis (Table 3).

During the follow-up, 261 patients were taking stable moderate-intensity atorvastatin (10-20 mg/d), and 172 patients were taking stable high-intensity atorvastatin (40-80 mg/d). For patients with high-intensity atorvastatin therapy, binary logistic regression analysis revealed that the CYP3A4*1G/*1G homozygote was associated with poor outcome at 1 year after adjusting for conventional factors in the additive model (OR = 8.16; 95% CI: 1.50-44.44, P = .015) and recessive model (OR = 9.06; 95% CI: 1.72-47.64, P = .009) (Table 4). No significant

association was identified between CYP3A5*3 and the 1-year outcome of ischemic stroke in patients receiving high-intensity atorvastatin therapy (Table 4). For patients with moderate-intensity atorvastatin therapy, the association of CYP3A4*1G and CYP3A5*3 with the 1-year outcome did not achieve statistical significance in binary logistic regression analysis (Table 5).

Discussion

To our knowledge, this is the first study to evaluate the association of CYP3A4*1G and CYP3A5*3 with the outcome of acute ischemic stroke in the Han Chinese population. Our study indicated that the CYP3A4*1G/*1G homozygote is associated with poor outcome (mRS score ≥2) at 1 year in the Han Chinese population with acute

Table 4. Association of tested single nucleotide polymorphisms with outcome in patients receiving high-intensity atorvastatin therapy

Variant		mRS score ≤1 (n = 125)	mRS score ≥2 (n = 47)	OR(95% CI)	P-value	OR ^a (95% CI)	P value ^a
<i>CYP3A4*1G</i>							
Additive	*1/*1	67 (53.6%)	27 (57.4%)				
	*1/*1G	53 (42.4%)	14 (29.8%)	0.66 (0.31-1.37)	0.263	0.79 (0.32-1.91)	0.596
	*1G/*1G	5 (4.0%)	6 (12.8%)	2.98 (0.84-10.58)	0.092	8.16 (1.50-44.44)	0.015
Dominant	*1/*1G+*1G/*1G	58 (46.4%)	20 (42.6%)	0.86 (0.44-1.68)	0.652	1.13 (0.50-2.53)	0.770
Recessive	*1G/*1G	5 (4.0%)	6 (12.8%)	3.51 (1.02-12.12)	0.036	9.06 (1.72-47.64)	0.009
<i>CYP3A5*3</i>							
Additive	*1/*1	11 (8.8%)	5 (10.6%)				
	*1/*3	57 (45.6%)	15 (31.9%)	0.58 (0.17-1.92)	0.372	0.42 (0.10-1.72)	0.226
	*3/*3	57 (45.6%)	27 (57.4%)	1.04 (0.32-3.30)	0.944	0.58 (0.15-2.27)	0.432
Dominant	*1/*3+*3/*3	114 (91.2%)	42 (89.4%)	0.81 (0.27-2.47)	0.711	0.50 (0.13-1.91)	0.312
Recessive	*3/*3	57 (45.6%)	27 (57.4%)	1.51 (0.77-2.97)	0.231	1.07 (0.48-2.40)	0.871

CI, confidence interval; mRS, modified Rankin scale; OR, odds ratio.

^aAdjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, intracranial artery stenosis (>50%), smoking history, drinking history, and National Institutes of Health Stroke Scale score at admission.

Table 5. Association of tested single nucleotide polymorphisms with outcome in patients receiving moderate-intensity atorvastatin therapy

Variant		mRS score ≤ 1 (n = 183)	mRS score ≥ 2 (n = 78)	OR(95% CI)	P-value	O*(95% CI)	P-value*
<i>CYP3A4*1G</i>							
Additive	<i>*1/*1</i>	103 (56.3%)	45 (57.7%)				
	<i>*1/*1G</i>	74 (40.4%)	28 (35.9%)	0.87 (0.50-1.51)	0.614	0.59 (0.30-1.16)	0.130
	<i>*1G/*1G</i>	6 (3.3%)	5 (6.4%)	1.91 (0.55-6.57)	0.306	1.83 (0.45-7.50)	0.399
Dominant	<i>*1/*1G+*1G/*1G</i>	80 (43.7%)	33 (42.3%)	0.94 (0.55-1.61)	0.834	0.68 (0.36-1.30)	0.245
Recessive	<i>*1G/*1G</i>	6 (3.3%)	5 (6.4%)	2.02 (0.60-6.83)	0.249	2.24 (0.57-8.84)	0.252
<i>CYP3A5*3</i>							
Additive	<i>*1/*1</i>	9 (4.9%)	7 (9.0%)				
	<i>*1/*3</i>	84 (45.6%)	31 (40.0%)	0.47 (0.16-1.38)	0.172	0.56 (0.17-1.90)	0.356
	<i>*3/*3</i>	90 (47.7%)	40 (53.6%)	0.57 (0.35-1.64)	0.299	0.71 (0.22-2.35)	0.578
Dominant	<i>*1/*3+*3/*3</i>	174 (95.1%)	71 (91.0%)	0.53 (0.19-1.46)	0.211	0.64 (0.20-2.04)	0.454
Recessive	<i>*3/*3</i>	90 (49.2%)	40 (51.3%)	1.09 (0.64-1.85)	0.756	1.16 (0.62-2.15)	0.651

CI, confidence interval; mRS, modified Rankin scale; OR, odds ratio.

*Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, intracranial artery stenosis (>50%), smoking history, drinking history, and National Institutes of Health Stroke Scale score at admission.

ischemic stroke in additive and recessive models, especially in those receiving high-intensity atorvastatin therapy. We did not identify a significant association between *CYP3A5*3* and the 1-year prognosis of acute ischemic stroke in the studied population.

Among currently identified variants within *CYP3A4*, *CYP3A4*1G* (24.01%) was the most prevalent in the Han Chinese population; other variants were relatively rare (minor allele frequency <5%).¹⁴ A previous study evaluated the influence of *CYP3A4*1G* on atorvastatin pharmacokinetics in Han Chinese patients with coronary disease. It showed that the mean areas under the plasma concentration-time curve from 0 to infinity of atorvastatin and its metabolite were significantly lower in *CYP3A4*1G/*1G* homozygote carriers than in individuals with the *CYP3A4*1/*1* homozygote and *CYP3A4*1/*1G* heterozygote, respectively.⁴ A case-control study indicated that *CYP3A4*1G* was associated with an increased risk of severe carotid artery disease in the Han Chinese population.¹⁶ A recent pharmacokinetic study demonstrated that compared with *CYP3A4*1/*1* and *CYP3A4*1/*1G* genotypes, the *CYP3A4*1G/*1G* homozygote was associated with a significantly decreased plasma concentration of diltiazem in patients after renal transplantation.¹⁵ These studies implied that the *CYP3A4*1G/*1G* homozygote was associated with decreased efficiency of substrates metabolized by *CYP3A4*. Our data were consistent with those reported in these studies. We suspect that the association between *CYP3A4*1G/*1G* and poor outcome of ischemic stroke was mediated by the impact of *CYP3A4*1G* on atorvastatin pharmacokinetics. We did not obtain statin pharmacokinetic data in the present study. Further cohort studies including statin pharmacokinetic data with a larger sample size are needed to validate the association.

The present study did not identify a significant association between *CYP3A5*3* and the 1-year outcome of patients with acute ischemic stroke. *CYP3A5*3* altered the reading frame by creating a cryptic splice site in intron 3, which resulted in a premature termination codon.¹⁷ Therefore, *CYP3A5*3* was associated with decreased mRNA expression; individuals carrying the *CYP3A5*3/*3* homozygote were considered as not expressive of *CYP3A5*.⁹ The impact of *CYP3A5*3* on the lipid response of statin therapy has remained inconsistent in published studies.^{5,6,20} The reason for this finding may lie in the study design and studied population. Another reason is that this result may be due to the lesser extent contribution of *CYP3A5* to statin metabolism compared to *CYP3A4*. It was estimated that *CYP3A5* contributed to approximately 15% of atorvastatin metabolism, whereas *CYP3A4* accounted for 85% of atorvastatin metabolism.²¹ Therefore, assessment of the influence of *CYP3A5*3* may be confounded by other variables. More studies are needed to further explore the influence of *CYP3A5*3* on statin efficiency.

The present study was a retrospective analysis based on a prospective observational cohort. Therefore, we did not influence clinical activities such as determining the statin type or dose on prescription. Although simvastatin and lovastatin were metabolized by *CYP3A4* and *CYP3A5*, only atorvastatin was prescribed in the enrolled patients. Our data provide evidence for potential individualized statin treatment for patients with ischemic stroke. We suspect that genotyping of *CYP3A4*1G* may be of clinical significance in the clinical decision to use statin therapy.

There are several limitations in the present study. First, it was based on a single center; therefore, it may have sampling bias. Second, we did not obtain statin pharmacokinetic data in our recruited population. In the future,

the statin pharmacokinetic data of patients with stroke are needed to better understand the efficiency of statin therapy on stroke prognosis. Lastly, reexamination of the plasma lipid level at regular intervals was suggested to patients who were prescribed a statin; however, these tests were not performed at strict time points after discharge. Therefore, we did not analyze the association of CYP3A4*1G and CYP3A5*3 with the lipid-lowering response of atorvastatin. Further cohort studies with a larger sample size from multiple centers are needed to validate this association.

In conclusion, the present study indicated that CYP3A4*1G is associated with poor outcome at 1 year after acute ischemic stroke in the Han Chinese population. Further studies that assess the statin pharmacokinetic data and lipid-lowering response in patients with stroke are needed to validate this association.

References

- Song B, Wang Y, Zhao X, et al. Inpatient statin use is associated with decreased mortality of acute stroke patients with very low low-density lipoprotein cholesterol. *J Stroke Cerebrovasc Dis* 2015;24:2369-2374.
- Amarenco P, Bogousslavsky J, Callahan 3rd A, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549-559.
- Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther* 2005;78:330-341.
- He BX, Shi L, Qiu J, et al. The effect of CYP3A4*1G allele on the pharmacokinetics of atorvastatin in Chinese Han patients with coronary heart disease. *J Clin Pharmacol* 2014;54:462-467.
- Kadam P, Ashavaid TF, Ponde CK, et al. Genetic determinants of lipid-lowering response to atorvastatin therapy in an Indian population. *J Clin Pharm Ther* 2016;41:329-333.
- Kivist KT, Niemi M, Schaeffeler E, et al. Lipid-lowering response to statins is affected by CYP3A5 polymorphism. *Pharmacogenetics* 2004;14:523-525.
- HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013;34:1279-1291.
- Birmingham BK, Bujac SR, Elsby R, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. *Eur J Clin Pharmacol* 2015;71:329-340.
- Lamba J, Hebert JM, Schuetz EG, et al. PharmGKB summary: very important pharmacogene information for CYP3A5. *Pharmacogenet Genom* 2012;22:555-558.
- Danielson PB. The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. *Curr Drug Metab* 2002;3:561.
- Corsini A, Bellosta S, Baetta R, et al. New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther* 1999;84:413-428.
- White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J Clin Pharmacol* 2002;42:963-970.
- Willrich MA, Rodrigues AC, Cerda A, et al. Effects of atorvastatin on CYP3A4 and CYP3A5 mRNA expression in mononuclear cells and CYP3A activity in hypercholesterolemic patients. *Clin Chim Acta* 2013;421:157-163.
- Hu GX, Dai DP, Wang H, et al. Systematic screening for CYP3A4 genetic polymorphisms in a Han Chinese population. *Pharmacogenomics* 2017;18:369-379.
- Zhou LY, Zuo XC, Chen K, et al. Significant impacts of CYP3A4*1G and CYP3A5*3 genetic polymorphisms on the pharmacokinetics of diltiazem and its main metabolites in Chinese adult kidney transplant patients. *J Clin Pharm Ther* 2016;41:341-347.
- He BX, Shi L, Qiu J, et al. A functional polymorphism in the CYP3A4 gene is associated with increased risk of coronary heart disease in the Chinese Han population. *Basic Clin Pharmacol Toxicol* 2011;108:208-213.
- Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet* 2001;27:383-391.
- Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol* 2016;68:789-801.
- Li SH, Shi CH, Li YS, et al. Association of GWAS-reported variant rs11196288 near HABP2 with ischemic stroke in Chinese Han population. *J Mol Neurosci* 2017;62:209-214.
- Willrich MA, Hirata MH, Genvigir FD, et al. CYP3A53A allele is associated with reduced lowering-lipid response to atorvastatin in individuals with hypercholesterolemia. *Clin Chim Acta* 2008;398:15-20.
- Willrich MA, Hirata MH, Hirata RD. Statin regulation of CYP3A4 and CYP3A5 expression. *Pharmacogenomics* 2009;10:1017-1024.