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Original Article

Interactions Among *CYP2C8*, *EPHX2*, and *CYP4A11* Variants and CYP Plasma Metabolite Levels in Ischemic Stroke

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***Aim*: To better understand the relationship between the interactions among rs17110453, rs751141, and rs9333025 variants and plasma levels of cytochrome P450 (CYP) metabolites, i.e.,20-hydroxyeicosatetraenoic acid (20-HETE), epoxyeicosatrienoic acids (EETs), and dihydroxyeicosatrienoic acids (DiHETEs) in ischemia stroke (IS).**

***Methods*: We measured plasma CYP metabolite levels in 218 acute IS cases and 126 controls, and a subset of samples were assessed to further understand the association between relevant variants and IS risk in our previous study. We assessed the associations between variant interactions and levels of 20-HETE, EETs, and DiHETEs as well as the associations between levels of 20-HETE, EETs, and DiHETEs and IS risk after adjusting for other potential confounders. Furthermore, the association between variant interactions and IS risk after adjusting for other covariates, including CYP metabolites levels, was evaluated.**

***Results*: The interactions among variants rs17110453, rs751141, and rs9333025 were significantly associated with high 20-HETE, high DiHETEs, and low EETs after adjusting for the status of diabetes mellitus and hypertension. High 20-HETE, high DiHETEs, and low EETs were independent risk factors for IS after adjusting for hypertension, diabetes mellitus, and the interactions among rs17110453, rs751141, and rs9333025. Furthermore, the interactions among rs17110453, rs751141, and rs9333025 were significantly associated with a higher risk of IS after adjusting for CYP metabolites (OR=2.02, 95% CI: 1.28−5.27, *P*=0.007).**

***Conclusion*: The association between the interactions among rs17110453, rs751141, and rs9333025 and IS risk in Chinese population may be partly but not exclusively mediated by plasma levels of 20-HETE, EETs, and DHETs. Further well-designed studies are warranted to replicate this finding.**

Key words: Ischemia Stroke, Cytochrome P450, *CYP* genes, Polymorphism, CYP metabolites

Introduction

Ischemic stroke (IS) is a severe complex disease, which causes a huge public health burden globally[1]. It is critical to better understand its etiology for the better management with regard to prevention and treatment of this disease. Besidesthe risk factors of hypertension, smoking, diabetes mellitus, and other chronic and inflammatory diseases, genetic factors have also been suggested to explain a proportion of the etiology of IS[2, 3].

Arachidonicacid, a membrane fatty acid, canbe metabolized to a variety of bioactive compoundsby the cytochrome P450 (CYP) enzymes[4], including epoxyeicosatrienoic acids (EETs) and 20-hydroxyeicosatetraenoic acid (20-HETE)[5]. EETs can be further metabolized to dihydroxyeicosatrienoic acids (DiHETEs)[6]. EETs can relax vessels and play protective roles in the cardiovascular system[4]. 20-HETE has also been detected in the cerebral vasculature of the stroke-prone sponta-

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neously hypertensive rat and contributes to stroke severity[7]. Pharmacological inhibition of 20-HETE synthesis also reduces infarct size in rats following transient occlusion of the middle cerebralartery[8, 9]. Despite these preclinical links between CYP metabolites and IS, little is known about the role of 20-HETE, EETs, and DiHETEs in the development of human IS. Although research has shown that plasma CYP metabolite levels are potentially associated with IS[10], the exact relationship, particularly whether variants of CYP pathway genes play roles in the relationship, remains insufficiently understood.

Several studies have shown that individual genetic variants of CYP pathway may be associated with a risk of IS[11-14]. In a previous study, we demonstrated that the gene−gene interactions among variants rs17110453, rs751141, and rs9333025 conferred a higher risk of IS[15]. However, the underlying mechanism for such an association is not well understood.

Considering that the assessed variants are predicted to be functional, and the proteins encoded by the corresponding genes are potentially important in the development of stroke[10], we hypothesize that the potential effect of the identified variant interactions on IS risk is at least partially mediated by the influence on plasma levels of relevant CYP metabolites (20-HETE, EETs, and DiHETEs). The aim of the current study is to test this hypothesis to better understand the relationship between interactions among rs17110453, rs751141, and rs9333025, relevant CYP metabolite levels, and IS risk.

Materials and Methods

Ethics Statement

This study was approved by the Ethics Committee of The People's Hospital of Deyang City. All patients provided written informed consent before their enrollment into this study.

Study Populations

The detailed procedures for the recruitment of acute IS cases and controls were described in a previous study[15]. Briefly, 396 acute IS patients who suffered their first IS related to atherothrombosis (n=270) or small artery disease (n=126) according to theTrial of ORG 10172 in the Acute Stroke Treatment classification system[16] and who were admitted to The People's Hospital of Deyang City within 72 hours of their index stroke were consecutively recruited between August 2010 and March 2013. The exclusion criteria were as follows: (1) any clinically relevant arrhythmia (including atrial fibrillation), cerebral embolism, or other determined or undetermined etiological syndromes of IS; (2) a family history of apoplexy or a previous history of stroke; and (3) cerebral hemorrhage. A total of 378 controls were selected from outpatients with no history of stroke, as confirmed by medical history combined with physical and laboratory examinations at the hospital. Controls had no family history of stroke and were genetically unrelated to the included IS patients. Relevant characteristics and clinical variables of involved subjects, including data regarding age, sex, blood pressure/hypertension, body mass index (BMI), diabetes mellitus, cigarette smoking, alcohol intake, total plasma cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), were collected. The genotypes of 10 variants, including *CYP2J2* rs10889160, *CYP2C8* rs17110453, *CYP2C8* rs1934980, *CYP2C9* rs1799853, *CYP2C9* rs1057910, *CYP3A5* rs776746, epoxide hydrolase 2 (*EPHX2*) rs751141, *CYP4A1l* rs2269231, *CYP4A1l* rs9333025, and *CYP4F2* rs3093135, were examined using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) method. According to our previous analyses[15], IS patients have a higher prevalence of history of hypertension and diabetes as well as an older age. The frequency of the GG genotype for rs9333025 was significantly higher in the IS patients than in the controls (P<0.001). There was a significant influence of gene−gene interactions among rs17110453, rs751141, and rs9333025 on IS risk. Individuals with a combination of rs17110453CC, rs751141GG, and rs9333025GG had a significantly higher risk of IS than those with a combination of rs17110453AA, rs751141AA, and rs9333025AA (OR=2.86, 95% CI: 1.24−7.26, P=0.004).

Measurement of Plasma 20-HETE, EETs, and DiHETEs Levels

Among the original 396 IS patients and 378 controls, we measured the plasma CYP metabolite levels in a randomly selected subset of 218 cases and 126 controls. Based on previous studies, including one conducted by us[10, 17], such a sample size should be sufficient to support our research. Thus, we used such a sample size in the current study and will expand the study size in future. A blood sample (4 ml) was collected intoEDTA/butylated hydroxytoluene (BHT)/glutathione at the second day after admission. Plasma was isolated following centrifugation, and samples were stored at −80°C until analysis. Specifically, plasma 20-HETE level was measured using a stable isotope dilution gas chromatography/mass spectrometer (GC/MS). Total plasma EETs and DiHETEs levels were measured using a stable isotope dilution GC/MS following base hydrolysis and separation on high per-

Table 1. Clinical characteristics of the 218 ischemia stroke patients and 126 controls in this study

Characteristic	Stroke patients (n=218)	Controls (n=126)	P value
Age (years)	67.58 ± 10.86	65.92 ± 10.14	0.151
Men (n, %)	129 (59.17)	74 (58.73)	0.968
Diabetes mellitus (n, %)	76 (34.86)	31 (24.60)	0.042
Hypertension (n, %)	170 (77.98)	52 (41.27)	<0.001
Previous myocardial infarction (n, %)	0	0	–
Cigarette smoking (n, %)	89 (40.83)	52 (41.27)	0.999
Alcohol intake (n, %)	92 (42.20)	53 (42.06)	0.999
Body mass index (kg/m^2)	24.62 ± 2.41	24.12 ± 2.26	0.063
Total cholesterol (mM)	5.52 ± 1.37	5.41 ± 1.23	0.348
Low density lipoprotein-cholesterol (mM)	3.23 ± 1.31	3.11 ± 1.22	0.392
Triglycerides (mM)	1.92 ± 1.14	1.86 ± 1.11	0.672
Previous treatment (n, %)			
Antihypertensive drugs	95 (43.58)	51 (40.48)	0.572
Hypoglycemic drugs	50 (22.94)	25 (19.84)	0.516
Statins	28 (12.84)	14 (11.11)	0.663
Aspirin	58 (26.61)	35 (27.78)	0.835

formance liquid chromatography (HPLC), as described previously[10, 17, 18]. The measurement of CYP plasma metabolite levels was established to be highly valid and reproducible[17, 18].

Statistical Analysis

Continuous variables were compared using the Student's t-test or one-way analysis of variance (ANOVA) if normally distributed;otherwise rank test was used. The χ^2 test was used to assess Hardy–Weinberg equilibrium for genotype frequencies. For gene–gene interaction analyses, the generalized multifactor dimensionality reduction (GMDR) method[15, 19] was applied. We compared the plasma CYP metabolite levels across evaluated cases and controls according to their genotype categorization for the variants rs17110453, rs751141, and rs9333025 based on our previous findings[15]. Cases with genotype combination of rs17110453CC, rs751141GG, and rs9333025GG were categorized as a subgroup, and cases with other genotype combinations were categorized as another subgroup. Similarly, controls were categorized into two subgroups. Multivariable logistic regression analyses were then performed to assess the association between the interactions among rs17110453, rs751141, and rs9333025 and CYP metabolites levels after adjusting for other relevant covariates as well as to assess the association between CYP metabolites levels and IS risk after controlling for other relevant covariates. Furthermore, multivariable analysis evaluating the relationship between variant interactions, CYP metabolite levels, and other covariates with IS risk was performed. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

Clinical Characteristics

Continuous variables, including plasma CYP metabolite levels, age, BMI, TC, TG, and LDL-C, were all normally distributed as suggested by the Shapiro–Wilk test (all $P>0.05$). The main characteristics of the 218 IS cases and 126 controls in whom the CYP metabolite levels were measured are shown in **Table 1**. Generally, there were no significant differences between cases and controls regarding age, gender, myocardial infarction history, cigarette smoking, alcohol intake, BMI, previous drug treatment as well as TC, LDL-C, and TG concentrations (all $P>0.05$). Furthermore, these characteristics did not differ significantly between subgroups of cases according to subtypes of stroke (atherothrombotic stroke or small artery disease stroke) (all $P>0.05$). On the other hand, the proportions of cases with diabetes mellitus or hypertension are higher than those of controls ($P=0.042$ and $P<0.001$, respectively).

Plasma CYP Metabolite Levels

Plasma levels of 20-HETE and DiHETEs were significantly higher in IS cases than in controls, and EETs levels were significantly lower in cases (all $P<0.001$, **Table 2**). Adjustment for diabetes mellitus or

Table 2. CYP plasma metabolite levels in ischemia stroke patients and controls

Characteristics	Stroke patients (n=218)	Controls (n=126)	P value
20-HETE (pmol/L)	1711±162	1465±123	<0.001
DiHETEs (nmol/l)	83.16±5.24	69.73±4.22	<0.001
EETs (nmol/l)	61.76±4.52	73.68±4.88	<0.001

CYP, cytochrome P450; HETE, hydroxyeicosatetraenoic acid; DiHETEs, dihydroxyeicosatrienoic acids; EET, epoxyeicosatrienoic acids.

hypertension did not alter results for plasma 20-HETE, DiHETEs, and EETs.

Association between Plasma CYP Metabolite Levels and CYP Genetic Variants

We did not detect associations between CYP metabolite levels and 10 assessed variants of CYP pathway genes (all $P>0.05$, **Supplementary Table**). However, stratified analyses based on different genotype combinations of the three relevant variants revealed differences in CYP metabolite levels between subgroups of variant genotype combinations. Specifically, IS patients carrying the genotype combination of rs17110453CC, rs751141GG, and rs9333025GG tended to have higher 20-HETE and DiHETEs levels and lower EETs level than controls who carried the same genotype combination (all $P<0.001$, **Table 3**). When focusing on IS patients, individuals with the genotype combination of rs17110453CC, rs751141GG, and rs9333025GG tended to have higher 20-HETE and DiHETEs levels and lower EETs level than individuals with other genotype combinations of these variants (all $P<0.001$, **Table 3**).

Logistic Regression Analyses for Assessing the Relationship between Variant Interactions, CYP Metabolite Levels, and IS Risk

Our previous analysis suggested thatthe interactions among rs17110453, rs751141, and rs9333025 were significantly associated with an increased risk of IS (OR=2.36, 95% CI 1.23−5.30, P=0.005)[15]. In the current study, we found that the genotype combination of rs17110453CC, rs751141GG, and rs9333025GG was significantly associated with 20-HETE (OR=2.01, 95%CI 1.32−5.62, P=0.004), DiHETEs (OR=1.93, 95%CI 1.22−4.28, P=0.006), and EETs (OR=1.88, 95%CI 1.17−3.34, P=0.018) after adjusting for status of diabetes mellitus and hypertension. The 20-HETEs and DiHETEs as well as EETs were significantly associated with a risk of IS after adjusting for hypertension, diabetes mellitus, and the genotype combination of rs17110453CC, rs751141GG, and rs9333025GG (**Table 4**). Furthermore, the interactions among rs17110453CC, rs751141GG, and rs9333025GG were identified to be independently associated with a higher risk of IS after adjusting for covariates, including CYP metabolites (OR=2.11, 95% CI: 1.27−5.53, P=0.006).

Discussion

In the present study, we detected that the interactions among variants rs17110453, rs751141, and rs9333025 were significantly associated with CYP metabolite levels; these levels were significantly associated with IS risk, suggesting that our previous finding of the association between the interactions among rs17110453, rs751141, and rs9333025 and IS risk may be mediated by CYP metabolites levels. On the other hand, it was detected that the interactions among rs17110453CC, rs751141GG, and rs9333025GG was independently associated with a higher risk of IS after adjusting for other covariates, including CYP metabolites, suggesting that such an association was not exclusively mediated by CYP metabolite levels. Our findings generate new knowledge for the relationship between rs17110453, rs751141, and rs9333025 interactions, CYP metabolite levels, and stroke risk.

In our study, we found that the plasma levels of 20-HETE and DiHETEs were significantly higher in IS cases than in controls and that EETs levels were significantly lower in these cases. The adjustment for diabetes mellitus or hypertension did not alter the results. Ward *et al.*[10] and Lee *et al.*[20] also observed elevated levels of total plasma and urinary DiHETEs in IS patients compared with controls, which is in accordance with our findings. 20-HETE is a potent vasoconstrictor[4] and is involved in endothelial dysfunction[21]; it also helps in the formation of oxygen radicals[22]. The inhibition of 20-HETE synthesis reduces both cerebral 20-HETE levels and total infarction volume following transient occlusion of the middle cerebral artery[8, 9]. In contrast to the effect of 20-HETE, which is a vasoconstrictor, is that of EETs, which are vasodilators[5]. The vascular actions of EETs are modulated by their metabolism to the inactive DiHETEs[4].

Table 3. 20-HETE, DiHETE and EETs levels according to different genotype combinations in patients and controls

	Stroke patients combination of rs17110453CC, rs751141GG, and rs9333025GG ($n=36$)	Stroke patients other genotype combination ($n=187$)	Controls combination of rs17110453CC, rs751141GG, and rs9333025GG ($n=16$)	Controls other genotype combination ($n=110$)
20-HETE (pmol/L)	1756 ± 172 †‡	1452 ± 161	1521 ± 126	1396 ± 111
DiHETEs (nmol/l)	84.23 ± 5.21 †‡	71.72 ± 4.56	72.62 ± 4.73	68.98 ± 4.54
EETs (nmol/l)	60.65 ± 4.27 †‡	73.72 ± 5.13	70.87 ± 4.56	75.55 ± 5.01

HETE, hydroxyeicosatetraenoic acid; DiHETEs, dihydroxyeicosatrienoic acids; EET, epoxyeicosatrienoic acids. †, $P<0.001$, compared with controls with the genotype combination of rs17110453CC, rs751141GG, and rs9333025GG. ‡, $P<0.001$, compared with stroke patients with other genotype combination.

In the current study, we detected that DiHETEs are significantly higher and EETs are significantly lower in IS cases than in controls, suggesting that there may be increased soluble epoxide hydrolase (sEH) activity in IS patients. In a mouse model of stroke, inhibiting sEH results in reduced ischemic damage and elevated cortical blood flow during vascular occlusion[23]. Our study and those conducted by others indicate that CYP metabolites might play a role in the pathophysiology of acute IS.

CYP genes encode for enzymes responsible for arachidonic acid metabolism. Numerous studies have indicated that genetic variants of CYP pathway genes may be associated with a risk of IS[11, 24-26]. We have previously demonstrated that the gene−gene interaction of the variants rs17110453 (*CYP2C8*), rs751141 (*EPHX2*), and rs9333025 (*CYP4A11*) predispose patients to IS risk[15]. *CYP2C8* encodes for a major epoxygenase enzyme, and its functional variants may decrease circulating EET metabolite level. *EPHX2* encodes for sEH, which can metabolize EETs to less biologically active DHET[6]. The dysregulation of sEH has been implicated in IS development[24]. *CYP4A11* encodes for CYP ω-hydroxylase, which can metabolize AA into 20-HETE. Functional variants within this gene may be associated with IS by regulating 20-HETE[26]. In the current study, it was suggested that the interaction effect of the variants rs17110453, rs751141, and rs9333025 on IS risk was partially but not exclusively mediated by CYP450 metabolite levels. We speculate that the interactions among rs17110453CC, rs751141GG, and rs9333025GG could potentially confer individuals with this specific genotype combination to have lower circulating EET levels and higher 20-HETE levels than those with other genotype combinations, thereby increasing the risk of IS. Our findings warrant further investigations to clarify the underlying mechanism.

Our study has several strengths. We explored the research question using a subset of subjects evaluated in our previous study, ensuring assessing the relationship of genotype information, metabolite levels, and disease status in the same group of subjects. Our study helps to better understand the relationship between the identified variant interactions, CYP metabolites levels, and IS risk. The findings of the current study will lead further research to better understand the genetic basis for the complex pathogenesis of IS.

Potential limitations of our study need to be acknowledged. First, we detected significant differences between the evaluated cases and controls with regard to diabetes mellitus and hypertension status. One previous study demonstrated that 20-HETE excretion might be associated with hypertension[26]. However, our regression analyses for the research question of interest adjusted for these potential covariates and provided adjusted estimates. In our study sample there were no significant differences between IS cases and controls with regard to age and cigarette smoking, which were suggested to be IS risk factors in previous research. Selection bias might exist in the current study, and our findings need to be replicated in further studies. Second, subjects in the current study are only a subset of individuals involved in the previous analysis, precluding a more comprehensive evaluation of the research question with all previously involved subjects. However, such a subset of individuals was randomly selected, and there were no significant differences of the main characteristics (age, gender, myocardial infarction history, cigarette smoking, alcohol intake, BMI, diabetes mellitus, and hypertension as well as TC, LDL-C, and TG concentrations) between the subset of individuals included in the current study and those that were not included. Third, CYP450 metabolite levels may be affected by acute cerebral ischemia itself[27]. In the present study, plasma CYP450 metabolite levels were measured in acute phase, and we did not eliminate potential effect of acute cerebral ischemia on CYP450 metabolite levels. Further studies are needed to evaluate CYP450 metabolite levels in

Table 4. Multiple regression analysis of the major risk factors for ischemia stroke

Risk factor	Odds ratio	95% confidence intervals	*P* value
Hypertension	3.23	2.23−10.86	<0.001
Diabetes mellitus	1.76	1.04−3.75	0.037
20- hydroxyeicosatetraenoic acid (pmol/L)	2.16	1.24−5.43	0.006
Dihydroxyeicosatrienoic acids (nmol/l)	1.99	1.18−5.23	0.011
Epoxyeicosatrienoic acids (nmol/l)	1.84	1.16−4.59	0.042
Combination of rs17110453CC, rs751141GG, and rs9333025GG	2.11	1.27−5.53	0.006
CYP4A11 rs9333025	0.84	0.75−1.38	0.353
Age (>68 yr)	0.68	0.82−1.67	0.212
Cigarette smoking	0.89	0.84−1.38	0.371
Low density lipoprotein-cholesterol (mM)	1.01	0.91−2.26	0.091
Total cholesterol (mM)	0.85	0.77−1.54	0.264

Other input variables including: body mass index, alcohol intake, *CYP2J2* rs10889160, *CYP2C8* rs17110453, *CYP2C8* rs1934980, *CYP2C9* rs1799853, *CYP2C9* rs1057910, *CYP3A5* rs776746, *EPHX2* rs751141, *CYP4A1l* rs2269231, and *CYP4F2* rs3093135.
OR for continuous variables means per 1-unit increase.

chronic phase and clarify the effect of acute cerebral ischemia on CYP450 metabolite levels. Fourth, due to the nature ofthe limited sample size and single-center study, findings of the current study need to be validated in larger, multi-center studies. Studies focusing on populations beyond Chinese are warranted todetermine whether our findings can be generalized to other populations. It is also meaningful to extend our study to include follow-up data to better understand the research question of interest. We are in the process of collecting follow-up information to conduct more comprehensive analyses.

In conclusion, our study suggests that the association between the identified interactions among rs17110453, rs751141, and rs9333025 and IS risk in Chinese population is partially but not exclusively mediated by CYP450 metabolite levels. Further studies are warranted to better understand the relationship.

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Conflict of Interest

The authors declare no conflicts of interest.

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Supplementary Table. Association of 20-HETE, DiHETEs and EET levels with genotype distribution ischemia stroke patients and controls

Assay	EETs (nmol/l)		20-HETE (pmol/L)		DiHETEs (nmol/l)	
	Stroke patients (n=218)	Controls (n=126)	Stroke patients (n=218)	Control (n=126)	Stroke patients (n=218)	Control (n=126)
rs17110453						
AA	61.76 ± 6.25	73.11 ± 5.64	1712 ± 182	1539 ± 173	83.13 ± 6.04	69.18 ± 7.14
AC	60.62 ± 5.02	74.23 ± 6.36	1694 ± 184	1511 ± 182	83.35 ± 10.72	70.68 ± 7.22
CC	62.72 ± 5.63	72.45 ± 6.64	1687 ± 188	1436 ± 191	82.98 ± 10.24	71.87 ± 6.13
rs776746						
AA	61.26 ± 6.71	73.89 ± 6.76	1666 ± 168	1489 ± 175	84.04 ± 6.74	70.96 ± 6.25
AG	60.87 ± 4.88	74.02 ± 6.52	1728 ± 177	1423 ± 164	83.95 ± 6.32	70.24 ± 5.46
GG	61.96 ± 5.23	73.24 ± 6.97	1706 ± 186	1498 ± 185	82.87 ± 8.92	69.66 ± 7.33
rs751141						
GG	61.75 ± 6.64	74.26 ± 6.72	1746 ± 194	1479 ± 182	84.24 ± 7.22	68.24 ± 6.37
AG	61.46 ± 6.58	72.42 ± 6.35	1708 ± 166	1536 ± 172	82.86 ± 6.15	69.16 ± 6.13
AA	61.68 ± 5.66	74.77 ± 6.44	1657 ± 182	1542 ± 175	83.01 ± 4.66	70.78 ± 5.22
rs10889160						
AA	61.18 ± 5.19	72.27 ± 6.24	1686 ± 167	1523 ± 179	82.12 ± 8.51	69.36 ± 9.28
AG	61.76 ± 6.34	73.15 ± 6.76	1747 ± 187	1489 ± 164	85.89 ± 9.12	69.86 ± 8.76
GG	61.37 ± 5.75	72.98 ± 6.81	1695 ± 189	1452 ± 161	83.87 ± 8.02	68.98 ± 7.01
rs 9333025						
AA	61.11 ± 5.67	72.96 ± 6.82	1756 ± 197	1479 ± 182	83.72 ± 6.36	69.36 ± 6.28
AG	61.56 ± 6.12	73.25 ± 6.26	1717 ± 184	1436 ± 176	84.23 ± 7.16	70.62 ± 7.76
GG	61.78 ± 5.87	73.25 ± 6.97	1686 ± 188	1486 ± 176	83.87 ± 6.02	71.01 ± 7.22
rs1934980						
CC	61.76 ± 6.45	74.01 ± 7.82	1699 ± 168	1523 ± 189	84.12 ± 8.42	70.36 ± 6.31
CT	61.89 ± 6.47	73.85 ± 6.63	1756 ± 178	1493 ± 181	83.89 ± 7.12	69.35 ± 7.46
TT	60.99 ± 4.66	72.98 ± 5.98	1701 ± 198	1445 ± 164	82.87 ± 8.02	71.02 ± 8.23
rs1799853						
CC	61.76 ± 4.52	73.68 ± 4.88	1711 ± 162	1465 ± 123	83.16 ± 5.24	69.73 ± 4.22
rs1057910						
AA	61.59 ± 8.61	74.18 ± 6.36	1699 ± 162	1467 ± 182	82.68 ± 7.52	69.27 ± 5.28
AC	60.87 ± 6.15	73.14 ± 6.86	1747 ± 162	1429 ± 173	83.89 ± 6.12	69.56 ± 8.27
CC	61.78 ± 7.66	72.21 ± 6.89	1702 ± 188	1494 ± 162	82.88 ± 7.44	70.24 ± 6.68
rs2269231						
AA	61.86 ± 6.23	74.15 ± 7.21	1659 ± 167	1467 ± 179	83.56 ± 7.35	69.97 ± 8.55
AT	61.06 ± 7.12	73.14 ± 6.74	1707 ± 165	1419 ± 174	82.45 ± 8.81	69.23 ± 7.34
TT	61.96 ± 6.66	73.36 ± 6.87	1732 ± 184	1485 ± 166	83.11 ± 7.53	69.58 ± 647
rs3093135						
TT	61.78 ± 6.34	73.32 ± 6.57	1706 ± 172	1567 ± 156	83.25 ± 7.96	69.36 ± 8.28
AT	61.56 ± 6.05	73.36 ± 6.38	1747 ± 171	1619 ± 149	82.89 ± 6.68	70.07 ± 8.35
AA	60.98 ± 7.66	74.51 ± 7.27	1732 ± 176	1645 ± 161	83.07 ± 8.11	69.82 ± 7.14

HETE, hydroxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acids; DiHETE, dihydroxyeicosatrienoic acid.