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Original Paper

Gene Polymorphisms Affect the Effectiveness of Atorvastatin in Treating Ischemic Stroke Patients

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Key Words
Atorvastatin • Ischemic stroke • Lipid metabolism related gene • SNP • Single nucleotide polymorphism

Abstract
Background/Aims: The aim of the present study is to investigate whether the single nucleotide polymorphism (SNP) in lipid metabolism related genes would affect the effectiveness of atorvastatin in both Han and Uighur populations. ***Methods:*** 200 ischemic stroke patients were treated with atorvastatin. The differences of blood lipid level and their ratios were measured. Six lipid related genes, HMGCR, APOA5, LPL, CETP, LDLR and PCSK9 were selected as candidate genes. And nine SNP loci in these six genes were genotyped by SNaPshot technique. ***Results:*** In all patients treated with atorvastatin, the SNP rs662799 significantly affected the ratio of ΔLDL and ΔLDL/LDL ($p < 0.05$); the SNP rs320 significantly affected the ratio of ΔLDL/LDL and Δ(LDL/HDL)/(LDL/HDL) ($p < 0.01$) and the SNP rs708272 significantly affected the ratio of ΔLDL ($p < 0.05$). In Han population treated with atorvastatin, the SNP rs662799 significantly affected the ratio of ΔTG ($p < 0.05$); the SNP rs320 significantly affected the ratio of ΔLDL/LDL and Δ (LDL/HDL)/(LDL/HDL) ($p < 0.01$). In Uighur population treated with atorvastatin, the SNP rs2266788 significantly affected the ratio of ΔHDL ($p < 0.05$); the SNP rs662799 significantly affected the ratio of ΔLDL/LDL ($p < 0.05$) and the SNP rs708272 significantly affected the ratio of ΔLDL ($p < 0.05$). ***Conclusion:*** Polymorphisms of rs662799 and rs2266788 in APOA5 gene, rs320 in LPL gene and rs708272 in CETP gene had significant association with the effect of the lipid-lowering therapy via atorvastatin calcium on ischemic stroke patients.

Introduction

Stroke is the second most common cause of death in the world with high prevalence, mortality and morbidity [1]. In China, stroke is the leading cause of death, even much higher than coronary heart disease [2]. Nearly 70% of global stroke deaths occur in developing

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countries, and 40% of them in China [2]. Epidemiological studies revealed that ischemic stroke accounts for at least 70% of stroke cases in China, which is significantly higher than the incidence in western countries [1].

Stroke is a heterogeneous syndrome, with more than 150 known causes [3]. Among them, inflammation, atherosclerosis and hyperlipidemia play important roles in the development of stroke [4]. Targeting the dysfunction of lipid metabolism, especially reducing the LDL level, attenuates the atherosclerosis process and reduces the incidence and mortality of ischemic stroke [5, 6]. Atorvastatin is a widely used statin to reduce blood lipid level with better safety and tolerance [7-9]. However, some patients responded to statin treatment very poorly [10].

Genome-wide association study (GWAS) showed that the SNPs (single nucleotide polymorphisms) are related to not only blood lipid level [11], but also the therapeutic effect of statin [12]. Therefore, we investigated the relationship of candidate SNPs and the therapeutic effect of atorvastatin.

We selected 9 SNPs in 6 genes with allele frequency higher than 5%, including: rs662799 and 2266788 in the gene ApoA5 (apolipoprotein A-5); rs328 and rs320 in the gene LPL (lipoprotein lipase); rs12916 and rs3846662 in the gene HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase); rs688 in the gene LDLR (low-density lipoprotein receptor); rs708272 in the gene CETP (cholesteryl ester transfer protein); and rs505151 in the gene PCSK9 (proprotein convertase subtilisin/kexin type 9). They were proven to be associated with blood lipid level [13, 14]. But whether these SNPs affect the therapeutic effect of atorvastatin or not is unclear. Our results here would provide important evidences for precision medication and prevention of ischemic stroke.

Materials and Methods

Patients

A total of 408 ischemic stroke patients were recruited from Department of Neurology of the Youyi Hospital of Wulumuqi. Cases were recruited from those for treatment from July 2010 to July 2012. 200 of them were selected for this study, including Han population (n = 112, 64.0 ± 11.8 years old) and Uighur population (n = 88, 61.9 ± 12.4 years old). The inclusion criteria were: (1) patients were diagnosed as ischemic stroke with clinical manifestation and brain MRI (magnetic resonance imaging) and/or head CT(computed tomography); (2) new onset less than 72 hours and no medical history of antiplatelet, anticoagulant and thrombolytic treatment in the past 2 weeks; (3) carotid duplex ultrasonography and transcranial Doppler study were conducted. The exclusion criteria were: history of intracranial hemorrhage/stroke, hypertension, intracranial hemorrhage, subarachnoid hemorrhage, arteriovenous malformation, neoplasm, aneurysm, post operation or post trauma, infection diseases, autoimmune diseases, severe cardiac, renal and hepatic diseases and women during pregnancy and breastfeeding. Furthermore, the patients with any signs of an allergic reaction to atorvastatin were excluded. All patients underwent systemic investigations including assessment of ischemic cerebral events, medication history, MR imaging with MR angiography, carotid duplex ultrasonography, and transthoracic echocardiography. All subjects agreed by the hospital ethics committee and signed informed consent. All the patients were treated with 20mg atorvastatin (Pfizer, USA) daily for 3 months.

Genotyping

DNA was extracted from the whole blood with Qiagen genomic DNA from whole blood extraction kit. The selected SNPs (9 SNPs in 6 genes, Table 1) were genotyped by SnaP shot genotyping technologies. Nine pairs of PCR primers and multiple SNP single base extension primers were designed using Primer3 online (Table 2). Obtained by multiplex PCR using HotStarTaq of Qiagen, PCR products were purified shrimp alkaline enzyme (SAP) (Promega) and exonuclease I (EXO I) (Epicentre), and then extension reaction was carried out using SnaP shot Multiplex kit (ABI). Extension products were loaded in ABI3130xl after purification. SNP genotyping were analyzed using GeneMapper4.0.

Table 1. Candidate genes and SNP Information

Gene	SNP	Position	Genotype	
HMGCR	rs12916	3'-utr_exon20	C	T
	rs3846662	Intron	C	T
APOA5	rs2266788	3'-utr_exon4	T	C
	rs662799	5'-flanking	A	G
LPL	rs320	Intron	T	G
	rs328	Ser474Ter	C	G
CETP	rs708272	Intron	C	T
LDLR	rs688	Asn591Asn	C	T
PCSK9	rs505151	Gly670Glu	A	G

Table 2. Primers

SNP	Forward Primer	Reverse Primer	Extension Primer
rs17238540	CAGGCATAGAGTCCACAAGCCTAGTT	TTCACAGCCTGACTGGCAGTACC	TTTTTTTTTTTTTTTTTATTTTAATTGGTCTTTTCMAAACTCTTT
rs320	GGGAACAAACCTCCGAGATGCT	GTTTGCAAAATCCCAGCACATTT	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTCACAGAGATCGCTATAGGATTTAAAGC
rs328	TTCACATCCATTTTCTTCCACAGG	TGCATGAAGCTGCCTCCCTTAG	TTTTTTTTTTTTTTTTTTTTTTTTTTTTGCCATGACAAGTCTCTGAATAAGAAGT
rs3846662	TCAGGTTCCAATGGCAACAACA	GGCACCTCCACCAAGCTACACA	TCCTTAAAACTCTTCTCATTGCCTTAC
rs5883	GAGCCCAGTAGGGACACACAGG	CCCCACCCACTCACCTTGAACT	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTCTTCTGGTTCTCTGAGCGAGTCTT
rs662799	AAGCCAGGCAGGGTGAAGATG	AGCATTTGGGCTTGCTCTCCTC	TTTTTTTTTTTTTCCCCAGGAACTGGAGCGAAAGT
rs688	GCATCAGCACGTGACCTCTCCT	GCATCTCGTACGTAAGCCACACC	TTTTTTTTTTTTTTTTTTTTTTTTACTCCATCTCAAGCATCGATGTCAA
rs708272	GCTGCCACACTAGCCCAGAGAG	CTCAACCCCCTAACCTGGCTCA	TTTTTTTTTTAACCTGGCTCAGATCTGAACCCTAACT
rs505151	GAGGAGGGCTGGACCCTGACT	CCTTGACCCTCCCCAGACACC	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGCAACGGCTGTCACGGCC

Statistical Analysis

Clinical data about continuous variables expressed as mean ± SD, and differences between groups were assessed by one way ANOVA test with SPSS 20.0 (IBM). p values under 0.05 were considered statistically significant.

Results

Blood lipid level has been demonstrated to be related to ischemic stroke. But whether the blood lipid level alone could be used as independent prognostic risk factor for ischemic stroke or not is controversial [15]. It was found that the changes in the ratio of lipid level, such as TC (total cholesterol) to HDL-C (high-density lipoprotein- cholesterol), LDL-C (low-density lipoprotein- cholesterol) to HDL-C and TG (triglyceride) to HDL-C predicted atherosclerosis progression better than LDL-C or HDL-C alone [16].

Therefore, we analyzed the relationship between SNPs and the changes in the ratio of lipid level before and after atorvastatin treatment. The changes of lipid ratio include ΔTG (TG level before treatment minus TG level after treatment), ΔTC (TC level before treatment minus TC level after treatment), ΔHDL (HDL level before treatment minus HDL level after treatment), ΔLDL (LDL level before treatment minus LDL level after treatment), ΔTG/TG (TG level before treatment minus TG level after treatment, and then divided by TG level before treatment), ΔTC/TC (TC level before treatment minus TC level after treatment, and then divided by TC level before treatment), ΔHDL/HDL (HDL level before treatment minus HDL level after treatment, and then divided by HDL level before treatment), ΔLDL/LDL (LDL level before treatment minus LDL level after treatment, and then divided by LDL level before treatment), Δ(TC/HDL) (The ratio of TC/HDL before treatment minus the ratio of TC/HDL after treatment), Δ(LDL/HDL) (The ratio of LDL/HDL before treatment minus the ratio of LDL/HDL after treatment), Δ(TC/HDL)/(TC/HDL) (The ratio of TC/HDL before treatment minus the ratio of TC/HDL after treatment and then divided by the ratio of TC/HDL before treatment) and Δ(LDL/HDL)/(LDL/HDL) (The ratio of LDL/HDL before treatment minus the ratio of LDL/HDL after treatment and then divided by the ratio of LDL/HDL before treatment).

Table 3. Therapeutic effect of atorvastatin in rs662799 genotype

rs662799	AA		GA		GG		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	110	63.11±12.29	76	63.17±12.15	14	62.29±10.89	0.968
ΔTG (mmol/L)	110	-0.49±0.99	76	-0.40±0.97	14	-0.86±1.31	0.287
ΔTC (mmol/L)	110	-0.70±1.18	76	-0.52±1.12	14	-0.44±1.27	0.485
ΔHDL (mmol/L)	110	-0.03±0.30	76	0.03±0.29	14	0.06±0.56	0.390
ΔLDL (mmol/L)	110	-0.59±1.00	76	-0.22±0.91	14	-0.28±1.61	0.043
ΔTG/TG	110	-0.12±0.76	76	-0.13±0.39	14	-0.24±0.42	0.798
ΔTC/TC	110	-0.12±0.28	76	-0.08±0.25	14	-0.07±0.26	0.500
ΔHDL/HDL	110	0.00±0.27	76	0.05±0.27	14	0.16±0.37	0.108
ΔLDL/LDL	110	-0.14±0.36	76	0.00±0.39	14	0.03±0.52	0.022
Δ(TC/HDL)	110	-0.50±1.50	76	-0.61±1.32	14	-0.82±1.60	0.707
Δ(LDL/HDL)	110	-0.46±1.20	76	-0.27±1.15	14	-0.62±1.70	0.456
Δ(TC/HDL)/(TC/HDL)	110	-0.07±0.38	76	-0.09±0.28	14	-0.09±0.46	0.952
Δ(LDL/HDL)/(LDL/HDL)	110	-0.09±0.48	76	0.04±0.60	14	0.11±1.01	0.242

Table 4. Therapeutic effect of atorvastatin in rs320 genotype

rs320	TT		TG		GG		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	145	62.62±12.50	53	64.15±11.12	2	67.50±2.12	0.642
ΔTG	145	-0.52±1.02	53	-0.35±0.98	2	-1.23±0.62	0.336
ΔTC	145	-0.67±1.18	53	-0.40±1.09	2	-1.61±0.38	0.163
ΔHDL	145	-0.02±0.33	53	0.06±0.28	2	-0.05±0.38	0.319
ΔLDL	145	-0.44±1.07	53	-0.43±0.90	2	0.64±1.36	0.340
ΔTG/TG	145	-0.13±0.67	53	-0.11±0.48	2	-0.47±0.21	0.731
ΔTC/TC	145	-0.12±0.27	53	-0.06±0.26	2	-0.31±0.03	0.239
ΔHDL/HDL	145	0.02±0.28	53	0.08±0.27	2	-0.06±0.43	0.360
ΔLDL/LDL	145	-0.08±0.37	53	-0.10±0.34	2	0.96±1.47	0.001
Δ(TC/HDL)	145	-0.56±1.51	53	-0.55±1.21	2	-1.17±2.54	0.863
Δ(LDL/HDL)	145	-0.37±1.26	53	-0.53±1.00	2	1.09±3.23	0.160
Δ(TC/HDL)/(TC/HDL)	145	-0.07±0.38	53	-0.10±0.27	2	-0.17±0.41	0.834
Δ(LDL/HDL)/(LDL/HDL)	145	-0.01±0.55	53	-0.13±0.37	2	1.73±2.81	$<10^{4}$

Table 5. Therapeutic effect of atorvastatin in rs708272 genotype

rs708272	GG		GA		AA		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	70	62.73±11.67	94	63.83±12.00	36	61.78±13.27	0.660
ΔTG	70	-0.35±0.86	94	-0.53±1.02	36	-0.61±1.25	0.383
ΔTC	70	-0.54±1.19	94	-0.57±1.05	36	-0.86±1.37	0.357
ΔHDL	70	0.00±0.28	94	0.00±0.34	36	0.02±0.33	0.952
ΔLDL	70	-0.40±0.90	94	-0.29±0.95	36	-0.84±1.34	0.021
ΔTG/TG	70	-0.10±0.48	94	-0.13±0.77	36	-0.18±0.39	0.847
ΔTC/TC	70	-0.09±0.27	94	-0.10±0.25	36	-0.14±0.29	0.661
ΔHDL/HDL	70	0.02±0.25	94	0.04±0.30	36	0.04±0.28	0.874
ΔLDL/LDL	70	-0.09±0.33	94	-0.04±0.37	36	-0.13±0.53	0.441
Δ(TC/HDL)	70	-0.47±1.34	94	-0.54±1.46	36	-0.84±1.58	0.437
Δ(LDL/HDL)	70	-0.34±1.07	94	-0.29±1.14	36	-0.78±1.60	0.114
Δ(TC/HDL)/(TC/HDL)	70	-0.07±0.34	94	-0.07±0.36	36	-0.13±0.36	0.657
Δ(LDL/HDL)/(LDL/HDL)	70	-0.06±0.40	94	0.00±0.53	36	-0.05±0.90	0.791

SNP rs662799, rs320 and rs708272 affected the effectiveness of atorvastatin

Among all patients treated with atorvastatin, rs662799 (ApoA5) affected the ΔLDL, ΔLDL/LDL level ($p < 0.05$, Table 3); rs320 (LPL) affected ΔLDL/LDL, Δ(LDL/HDL)/(LDL/HDL) level ($p < 0.01$, Table 4) and rs708272 (CETP) affected ΔLDL level ($p < 0.05$, Table 5) significantly. However, other SNPs (rs12916 (HMGCR), rs3846662 (HMGCR), rs328 (LPL), rs688 (LDLR), rs2266788 (ApoA5) and rs505151 (PCSK9) did not affect any changes of ratio of blood lipid level significantly (data not shown).

SNP rs662799 and rs320 affected the effectiveness of atorvastatin in Han population

Among patients from Han population, the SNP rs662799 (ApoA5) affected the ΔTG level ($p < 0.05$, Table 6) and rs320 (LPL) affected ΔLDL/LDL, Δ(LDL/HDL)/(LDL/HDL) level significantly ($p < 0.01$, Table 7). However, other SNPs (rs12916 (HMGCR), rs3846662 (HMGCR), rs328 (LPL), rs688 (LDLR), rs708272 (CETP), rs2266788 (ApoA5) and rs505151 (PCSK9)) did not affect any changes of ratio of blood lipid level significantly (data not shown).

Table 6. Therapeutic effect of atorvastatin in rs662799 genotype in Han population

rs662799	AA		GA		GG		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	51	64.92±11.70	52	63.29±12.05	9	62.78±11.51	0.745
ΔTG	51	-0.40±1.12	52	-0.42±1.04	9	-1.37±1.33	0.047
ΔTC	51	-0.80±1.23	52	-0.53±1.13	9	-0.17±1.36	0.263
ΔHDL	51	-0.02±0.35	52	0.03±0.30	9	0.23±0.41	0.118
ΔLDL	51	-0.63±1.21	52	-0.22±0.89	9	0.04±1.81	0.103
ΔTG/TG	51	0.00±1.06	52	-0.14±0.39	9	-0.38±0.36	0.356
ΔTC/TC	51	-0.14±0.30	52	-0.09±0.26	9	-0.01±0.26	0.388
ΔHDL/HDL	51	0.02±0.33	52	0.05±0.28	9	0.27±0.33	0.081
ΔLDL/LDL	51	-0.12±0.47	52	0.01±0.42	9	0.18±0.59	0.126
Δ(TC/HDL)	51	-0.63±1.53	52	-0.62±1.26	9	-1.06±1.76	0.680
Δ(LDL/HDL)	51	-0.52±1.31	52	-0.25±1.17	9	-0.57±1.89	0.530
Δ(TC/HDL)/(TC/HDL)	51	-0.09±0.39	52	-0.10±0.28	9	-0.13±0.48	0.933
Δ(LDL/HDL)/(LDL/HDL)	51	-0.07±0.54	52	0.05±0.68	9	0.10±1.03	0.573

Table 7. Therapeutic effect of atorvastatin in rs320 genotype in Han population

rs320	TT		TG		GG		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	81	63.48±12.50	29	65.17±10.01	2	67.50±2.12	0.736
ΔTG	81	-0.56±1.17	29	-0.25±0.99	2	-1.23±0.62	0.290
ΔTC	81	-0.70±1.21	29	-0.34±1.14	2	-1.61±0.38	0.191
ΔHDL	81	0.00±0.34	29	0.10±0.33	2	-0.05±0.38	0.369
ΔLDL	81	-0.42±1.17	29	-0.36±1.06	2	0.64±1.36	0.438
ΔTG/TG	81	-0.11±0.84	29	-0.04±0.60	2	-0.47±0.21	0.726
ΔTC/TC	81	-0.12±0.28	29	-0.05±0.26	2	-0.31±0.03	0.284
ΔHDL/HDL	81	0.03±0.31	29	0.12±0.32	2	-0.06±0.43	0.356
ΔLDL/LDL	81	-0.06±0.43	29	-0.06±0.41	2	0.96±1.47	0.008
Δ(TC/HDL)	81	-0.64±1.48	29	-0.67±1.23	2	-1.17±2.54	0.871
Δ(LDL/HDL)	81	-0.37±1.31	29	-0.57±1.10	2	1.09±3.23	0.203
Δ(TC/HDL)/(TC/HDL)	81	-0.09±0.38	29	-0.12±0.26	2	-0.17±0.41	0.873
Δ(LDL/HDL)/(LDL/HDL)	81	0.00±0.59	29	-0.12±0.41	2	1.73±2.81	<0.001

Table 8. Therapeutic effect of atorvastatin in rs2266788 genotype in Uygur population

rs2266788	AA		GA		GG		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	61	62.31±11.88	23	60.57±14.40	4	63.50±11.39	0.823
ΔTG	61	-0.55±0.85	23	-0.31±0.94	4	-0.20±0.35	0.420
ΔTC	61	-0.62±1.13	23	-0.39±1.14	4	-1.29±0.71	0.312
ΔHDL	61	-0.03±0.25	23	0.04±0.24	4	-0.35±0.76	0.044
ΔLDL	61	-0.54±0.78	23	-0.29±0.98	4	-0.88±1.29	0.330
ΔTG/TG	61	-0.22±0.30	23	-0.07±0.44	4	-0.15±0.31	0.233
ΔTC/TC	61	-0.11±0.25	23	-0.05±0.25	4	-0.26±0.14	0.223
ΔHDL/HDL	61	-0.01±0.21	23	0.06±0.24	4	-0.12±0.39	0.250
ΔLDL/LDL	61	-0.16±0.24	23	-0.02±0.34	4	-0.21±0.25	0.111
Δ(TC/HDL)	61	-0.40±1.49	23	-0.58±1.44	4	-0.36±1.54	0.877
Δ(LDL/HDL)	61	-0.38±1.11	23	-0.44±1.13	4	-0.52±1.65	0.953
Δ(TC/HDL)/(TC/HDL)	61	-0.06±0.37	23	-0.06±0.28	4	0.00±0.52	0.945
Δ(LDL/HDL)/(LDL/HDL)	61	-0.09±0.42	23	-0.03±0.39	4	0.26±1.20	0.322

SNP rs2266788, rs662799 and rs708272 affected the effectiveness of atorvastatin in Uighur population

Among patients from Uighur population, the SNP rs2266788 (ApoA5) affected the ΔHDL level ($p < 0.05$, Table 8), rs662799 (ApoA5) affected ΔLDL/LDL level ($p < 0.05$, Table 9) and rs708272 (CETP) affected ΔLDL level significantly ($p < 0.05$, Table 10). However, other SNPs (rs12916 (HMGCR), rs3846662 (HMGCR), rs328 (LPL), rs688 (LDLR), rs708272 (CETP), rs2266788 (ApoA5) and rs505151 (PCSK9)) did not affect any changes of ratio of blood lipid level significantly (data not shown).

Discussion

Atherosclerosis is a common risk factor for ischemic stroke and it is tightly related to lipid metabolism. Therefore lipid-lowering therapy is the most common strategy to treat ischemic stroke [17]. Data have shown that high level of blood TC, especially LDL-C,

Table 9. Therapeutic effect of atorvastatin in rs662799 genotype in Uygur population

rs662799	AA		GA		GG		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	59	61.54±12.67	24	62.92±12.62	5	61.40±10.92	0.899
ΔTG	59	-0.57±0.87	24	-0.35±0.82	5	0.06±0.64	0.204
ΔTC	59	-0.61±1.14	24	-0.48±1.12	5	-0.90±1.05	0.725
ΔHDL	59	-0.03±0.25	24	0.02±0.26	5	-0.23±0.71	0.197
ΔLDL	59	-0.57±0.79	24	-0.21±0.96	5	-0.86±1.11	0.148
ΔTG/TG	59	-0.22±0.31	24	-0.10±0.39	5	0.01±0.44	0.153
ΔTC/TC	59	-0.11±0.26	24	-0.06±0.25	5	-0.18±0.22	0.567
ΔHDL/HDL	59	-0.01±0.21	24	0.05±0.25	5	-0.04±0.38	0.549
ΔLDL/LDL	59	-0.16±0.24	24	0.01±0.32	5	-0.23±0.22	0.033
Δ(TC/HDL)	59	-0.40±1.48	24	-0.60±1.48	5	-0.38±1.34	0.852
Δ(LDL/HDL)	59	-0.41±1.11	24	-0.31±1.13	5	-0.71±1.49	0.771
Δ(TC/HDL)/(TC/HDL)	59	-0.06±0.38	24	-0.07±0.29	5	-0.02±0.45	0.966
Δ(LDL/HDL)/(LDL/HDL)	59	-0.10±0.42	24	0.04±0.38	5	0.12±1.09	0.445

Table 10. Therapeutic effect of atorvastatin in rs708272 genotype in Uygur population

rs708272	GG		GA		AA		*p*
	n	Mean ± S.D.	n	Mean ± S.D.	n	Mean ± S.D.	
Age	33	61.00±11.89	37	62.62±12.52	18	62.11±13.86	0.863
ΔTG	33	-0.53±0.85	37	-0.42±0.56	18	-0.50±1.31	0.864
ΔTC	33	-0.31±1.18	37	-0.70±0.85	18	-0.87±1.43	0.180
ΔHDL	33	0.01±0.24	37	-0.07±0.36	18	-0.01±0.20	0.435
ΔLDL	33	-0.35±0.86	37	-0.37±0.74	18	-0.99±0.96	0.018
ΔTG/TG	33	-0.18±0.40	37	-0.18±0.27	18	-0.16±0.39	0.963
ΔTC/TC	33	-0.04±0.28	37	-0.14±0.17	18	-0.14±0.31	0.171
ΔHDL/HDL	33	0.03±0.22	37	-0.02±0.26	18	0.00±0.19	0.695
ΔLDL/LDL	33	-0.07±0.30	37	-0.11±0.25	18	-0.25±0.25	0.068
Δ(TC/HDL)	33	-0.30±1.33	37	-0.44±1.55	18	-0.75±1.53	0.586
Δ(LDL/HDL)	33	-0.34±1.08	37	-0.24±1.19	18	-0.84±0.99	0.163
Δ(TC/HDL)/(TC/HDL)	33	-0.03±0.36	37	-0.05±0.38	18	-0.13±0.31	0.611
Δ(LDL/HDL)/(LDL/HDL)	33	-0.04±0.36	37	0.01±0.58	18	-0.23±0.29	0.188

promotes the atherosclerosis development and lowering the LDL-C level would attenuate the atherosclerosis process [18]. Atorvastatin is one of the most effective lipid lowering drugs, which could reduce the level of TC, TG and LDL-C and raise the level of HDL-C. It significantly reduced the mortality and morbidity of coronary diseases and ischemic stroke [19, 20]. However, the effectiveness of atorvastatin varies among different patients even with similar symptoms, indicating that the gene polymorphism might affect the drug effectiveness.

Pharmacogenomics uncovered the tight relationship between gene polymorphism and drug effectiveness [21]. Atorvastatin is one of those whose drug effectiveness is affected by both genetic factors and environment factors [22, 23]. Thus studying the association between lipid-lowering effectiveness and susceptible genes polymorphism is very important for clinical application of atorvastatin. Our study here showed that the SNPs rs662799 (ApoA5), rs320 (LPL), rs708272 (CETP) affected the effectiveness of atorvastatin significantly in all treated patients. In the Han population, the SNPs rs662799 (ApoA5) and rs320 (LPL) affected the effectiveness significantly while the SNPs rs2266788 (ApoA5), rs662799 (ApoA5) and rs708272 (CETP) affected the effectiveness significantly in the Uighur population. These data indicated that different genotypes could affect the effectiveness of atorvastatin and the susceptible genes might be different in Han and Uighur populations.

SNPs rs662799 and rs2266788 are located in the gene ApoA5, which plays an important role in lipid metabolism and its dysfunction would promote atherosclerosis development [24]. The polymorphism of ApoA5 has been demonstrated to be tightly associated with ischemic stroke and hyperlipidemia [25]. Our data showed here that the SNP rs662799 affects the effectiveness of atorvastatin in all patients and in both Han and Uighur populations, which is in accordance with previous report in Caucasians population [26]. Thus the polymorphisms of APOA5 affect the effectiveness of atorvastatin.

SNP rs320 is located in the gene LPL, which is one of key enzymes involved into blood TG metabolism. It has been demonstrated that the LPL polymorphisms are associated with

hypertension, coronary diseases and ischemic stroke [27]. And our data here indicated that the polymorphisms of LPL also affect the effectiveness of atorvastatin.

CETP mainly functions as lipid transferring among different lipoproteins and the SNP rs708272 is related to blood lipid level and coronary disease development [28]. Our data here showed that the SNP rs708272 (CETP) significantly affected the effectiveness of atorvastatin in Uighur population, which is in accordance with previously report in Caucasians population [29].

Conclusion

Our study showed that the SNP s662799 (ApoA5), rs320 (LPL) and rs708272 (CETP) affected the effectiveness of atorvastatin significantly in all the treated patients. The SNP rs662799 (ApoA5) and rs320 (LPL) affected the effectiveness of atorvastatin significantly in Han population while the SNP rs2266788 (ApoA5), rs662799 (ApoA5) and rs708272 (CETP) affected the effectiveness of atorvastatin significantly in Uighur population. Future studies with larger sample sizes are required to further validate our findings.

Abbreviations

Single nucleotide polymorphism (SNP); 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR); Apolipoprotein (APOA); Lipoprotein lipase (LPL); Cholesteryl ester transfer protein (CETP); Low-density lipoprotein receptor (LDLR); The first protein-converting enzyme (PCSK9); Low density lipoprotein (HDL); High density lipoprotein (HDL); Genome-wide association study (GWAS); MRI (magnetic resonance imaging); CT(computed tomography); Total cholesterol (TC).

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Disclosure Statement

The authors declare that they have no conflict of interests.

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