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Single nucleotide polymorphisms rs102313, rs118231 and rs201832 of CTEP TaqIB gene correlated with lipid metabolism abnormalities and cerebral infarction in patients with atherosclerosis

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Abstract. – OBJECTIVE: The purpose of this study was to investigate the correlations of cholesterol ester transfer protein (CTEP) TaqIB gene polymorphism with lipid metabolism abnormalities and cerebral infarction (CI) in patients with atherosclerosis (AS).

PATIENTS AND METHODS: A case-control study was conducted on 100 AS patients complicated with (CI) as AS+CI group, and 200 AS patients with matched age, gender and race as controls (AS group). Single nucleotide polymorphisms (SNPs) rs102313, rs118231 and rs201832 in the promoter region of CTEP TaqIB gene were classified by conformational differential gel electrophoresis. Then, Chi-square test was carried out to determine whether the distribution frequency of CTEP TaqIB genotypes conforms to the law of genetic equilibrium. In the meantime, the correlations of gene polymorphisms and allelotypes in the promoter region of CTEP TaqIB with CI and lipid metabolism abnormalities in AS patients were analyzed.

RESULTS: Hardy-Weinberg genetic equilibrium analysis showed that the three polymorphisms of CTEP TaqIB gene were in accordance with the genetic equilibrium distribution ($p>0.05$). Moreover, the results of gene association analysis revealed that the polymorphisms rs102313 and rs118231 and allelotypes in the promoter region of CTEP TaqIB gene were correlated with CI in AS patients ($p<0.05$). Specifically, AS patients with GG genotype and allele G at rs102313 and those with TT genotype and allele T at rs118231 had a higher risk of CI ($p<0.05$). Besides, the polymorphism rs102313 in the promoter region of CTEP TaqIB gene was markedly related to lipid metabolism abnormalities in AS patients ($p<0.05$).

CONCLUSIONS: The polymorphisms rs102313 and rs118231 in the promoter region of CTEP TaqIB gene are associated with CI in AS patients, and the polymorphism rs102313 is remarkably correlated with lipid metabolism abnormalities in AS patients.

Key Words:
Atherosclerosis, Lipid metabolism, Cerebral infarction, Polymorphism, Cholesterol ester transfer protein TaqIB.

Introduction

Cerebral infarction (CI), also known as ischemic stroke, refers to ischemic necrosis or softening of localized brain tissues caused by cerebral blood circulation disorder, ischemia and hypoxia[1]. As people's diet structure changes and the aging of the population becomes increasingly serious in recent years, the risk factors for CI and population at risk of CI have increased, and the incidence rate and disability rate of CI have shown an upward trend, which seriously hazards human health and life and brings heavy economic burdens to the patient's family and society[2]. Atherosclerosis (AS)-induced carotid artery stenosis is closely correlated with acute CI and will directly affect the clinical outcome of patients with acute CI. Carotid AS leads to cerebral artery stenosis, hemodynamic changes, plaque formation and shedding, which is the main mechanism of cerebral ischemia. It can damage multiple blood supply

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regions with disability and lethality, endangering the life and health of patients[3,4].

Genetic factors have been proved to play an important role in the pathogenesis of AS-induced CI through various methods such as animal model analysis, analysis of human twins, familial aggregation and segregation analysis and genetic pattern analysis[5]. CI triggered by AS is a polygenic genetic disease, and different genes modulate different pathophysiological mechanisms. Currently, it has been found that AS-triggered CI is intimately associated with gene polymorphisms in a variety of metabolic pathways[6]. Although a single gene exerts a limited effect on the risk of AS-induced CI, the interaction among different genes or between genes and the environment has multiplied the risk of CI.

Cholesteryl ester transfer protein (CETP) is a crucial component involved in the reverse transport of cholesterol mediated by high-density lipoprotein (HDL)[7], which regulates HDL level, particle size and composition in plasma. The enhanced CETP activity increases the levels of triglyceride (TG), low-density lipoprotein cholesterol (LDL-c) and very-low-density lipoprotein (VLDL) and decreases the level of high-density lipoprotein cholesterol (HDL-c)[8,9]. CETP gene expression plays a decisive role in lipid transport activity and lipoprotein composition *in vivo*. At present, more than a dozen gene polymorphisms and new genotypes caused by gene mutations have been discovered successively[10], among which TaqIB gene polymorphism is especially common. Therefore, it is speculated that CTEP TaqIB gene polymorphisms may have a correlation with lipid metabolism abnormalities and CI in AS patients.

In this study, the correlations of single nucleotide polymorphisms (SNPs) rs102313, rs118231 and rs201832 in the promoter region of CTEP TaqIB gene with lipid metabolism abnormalities and CI in AS patients were assessed, so as to provide certain reference bases for further exploring the genetic pathogenesis of CI caused by AS.

Patients and Methods

Research Subjects

A total of 100 AS patients admitted to our hospital from March 2017 to November 2019 were selected as the research subjects (AS+CI group). The patients were at the age of (61.45± 2.83) years old, and they all had a history of CI. The diagnosis of CI was in accordance with the Guidelines for Diagnosis and Early Intravascular Intervention for Acute Ischemic Stroke in China (2015) and confirmed by head CT or MRI scans. Meanwhile, 200 AS patients not complicated with CI were selected as controls (AS group), with an age of (59.35±3.97) years old. The patients in AS group were admitted to the Department of Neurology of our hospital and had no CI history, CI family history, basic diseases or major risk factors for CI confirmed by medical history, physical examination and auxiliary examination. A total of 4 mL of venous blood was extracted from each participant after 8 h of fasting, anticoagulated with ethylene diamine tetraacetic acid (EDTA) and stored in a refrigerator at -20°C for later use. This study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University, and all the participants signed the informed consent.

Laboratory Examinations

Following fasting for 8 h, 4 mL of venous blood was extracted in the morning, and the total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) in serum were measured using an automatic biochemical analyzer.

Deoxyribonucleic Acid (DNA) Extraction

A total of 4 mL of EDTA-anticoagulated blood was taken from the two groups of patients, and genomic DNAs were extracted according to the instructions of a DNA extraction kit (Wuhan Sevier Biotechnology Co. LTD., Wuhan, China). Then, 2 μL of the DNAs were subjected to 1.5% agarose gel electrophoresis to measure the mass, and the concentration of DNAs was detected using an ultraviolet spectrophotometer.

Polymerase Chain Reaction (PCR) Amplification

The primers designed for rs102313, rs118231 and rs201832 in the promoter region of CTEP TaqIB gene were amplified. The primer sequences of each gene polymorphism were shown in Table I. The PCR system (20 μL) consisted of 2.0 μL of DNA templates, 10.0 μL of 2′ Mix, 0.4 μL of forward primers, 0.4 μL of reverse primers and 7.2 μL of ddH_2O. PCR amplification conditions are as follows: (95°C ′120 s, 94°C ′30 s, 57°C ′90 s and 72°C ′60 s) ′35 cycles, followed by extension for 10 min at 72°C. Subsequently, the amplification of gene fragments was detected by agarose gel electrophoresis.

Table I. Primer sequences and product size at different loci in the promoter region of CTEP TaqIB gene.

Polymorphism	Primer sequence (5′-3′)	Product (bp)
rs102313	Forward: TGTCGATGTCGTAAAGTGCT	
	Reverse: AACGTAGACGCCGTCGCTAA	211
rs118231	Forward: CCATCGACTAGCTAGCTACT	
	Reverse: ACGACTAGCTGATGAATGTG	185
rs201832	Forward: CACGATCCCCTAGTCGTGTG	
	Reverse: ACATGTCGTAGTGCTGTAGTC	313

Ligase Detection Reaction

The forward and reverse probes used in this reaction were designed and synthesized by BGI. All forward probes were modified by 5' phosphorylation to prepare a probe mixture with a concentration of 12.5 pmol/μL. The system of ligase detection reaction (3.05 μL) contained 0.05 μL of ligases, 1 μL of buffer, 1 μL of PCR products and 1 μL of probe mixture, and the amplification was conducted under the following conditions: (95°C ′120 s, 94°C ′15 s and 50°C ′25 s) ′30 cycles. At the end of the cycle, the concentration was measured with the ultraviolet spectrophotometer. Next, BGI was entrusted to sequence and analyze the target gene, and all data were analyzed by Genemapper. The sequences of ligase reaction probes at different polymorphisms of CTEP TaqIB and the size of the products were displayed in Table II.

Statistical Analysis

All data were analyzed by Statistical Product and Service Solutions (SPSS) 22.0 (IBM, Armonk, NY, USA). Count data were expressed as frequency and percentage, and measurement data were expressed as mean ± standard deviation. Besides, count data were detected using chi-square test and subjected to multiple comparisons, whereas measurement data were assessed by *t*-test and analysis of variance. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of Basic Clinical Data Between the Two Groups of Patients

As shown in Table III, there were no statistically significant differences in age and gender ratio between the two groups of patients ($p>0.05$). The proportions of cases of smoking, drinking, diabetes, carotid intima thickening, carotid plaque formation and carotid stenosis in AS+CI group were remarkably higher than those in AS group ($p<0.05$). In the meantime, the levels of serum TC and LDL-C in AS+CI group were evidently higher than those in AS group ($p<0.05$), while TG and HDLC levels in the former were markedly lower than those in the latter ($p<0.05$).

Analysis Results of rs102313, rs118231 and rs201832 of CTEP TaqIB Gene

After CTEP TaqIB gene rs102313, rs118231 and rs201832 were cleaved by BSTU I restriction enzyme in AS+CI group and AS group, it was found that rs102313 had two alleles (A and G) and three genotypes (AA, AG and GG), rs118231 had two alleles (A and T) and three genotypes (AA, AT

Table II. Ligase reaction probe sequences and product size at different polymorphisms of CTEP TaqIB.

Polymorphism	Probe	Probe sequence (5′-3′)	Product (bp)
rs102313	rs102313	P-CGTAGTCAAGTTTTTTTTTTTTTTTTTT-FAM	183
	rs102313-A	TTTTTTACGATGCTAGTCGAATTTTTTTTTAT	
	rs102313-G	TTTTTTTTTTTTACGATGTGCATTTTTTTTTAAA	
rs118231	rs118231	P-ATAGTCGTAGTCGTTTTTTTTTTTTTTTTT-FAM	147
	rs118231-A	TTTTTTTTTTTTTTTTTTTTATCGTAGTCGTAGTC	
	rs118231-T	TTTTTTTTTTTTTTTTTTTTACGTAGTCGATACG	
rs201832	rs201832	P-AAGCTGATGTCGTAGTTTTTTTTTTTTT-FAM	179
	rs201832-C	TTTTTTTTTTTTTTTTTCAGCTGATGCTGATGC	
	rs201832-T	TTTTTTTTTTTTTTTAGCTGATGTCGATGCTGAT	

Table III. Comparisons of general clinical data and biochemical indexes (mean ± standard deviation) between AS group and AS+CI group.

Index	AS+CI group (n=100)	AS group (n=200)	p
Age (years old)	61.45±2.83	59.35±3.97	0.647
Gender (male/female)	172/28	168/32	0.421
Smoking (%)	53%	51%	0.637
Drinking (%)	46%	48%	0.273
Diabetes (%)	41%	43%	0.561
Carotid intima thickening (%)	52%	15%	0.000
Carotid plaque formation (%)	45%	22%	0.000
Carotid stenosis (%)	48%	8%	0.000*
History of cerebral stroke (%)	100%	0%	0.000*
TG (mmol/L)	0.23±0.06	0.24±0.13	0.871
TC (mmol/L)	5.61±0.66	5.32±0.53	0.671
HDL-c (mmol/L)	1.01±0.41	1.03±0.22	0.632
LDL-c (mmol/L)	3.31±0.672	3.45±1.03	0.721

*$p<0.05$ *vs.* AS group.

and TT), and rs201832 had two alleles (C and T) and three genotypes (CC, CT and TT).

Hardy-Weinberg Equilibrium Test

The linkage disequilibrium test results of different polymorphisms of CTEP TaqIB gene detected using Hardy-Weinberg equilibrium formula were shown in Table IV. It was discovered that the gene polymorphisms in each group met the equilibrium test standards (r^2 <0.33).

Correlation Between CTEP TaqIB Gene Polymorphisms and CI in AS Patients

The genotype frequency of polymorphisms in the two groups of patients was displayed in Table V. It was discovered that polymorphisms rs102313 and rs118231 of CTEP TaqIB gene were notably associated with CI in AS patients ($p<0.05$). Specifically, the proportion of GG genotype at rs102313 and that of TT genotype at rs118231 in AS group were markedly higher. However, rs201832 had no evident correlation with CI in AS patients ($p>0.05$).

Table IV. Results of linkage equilibrium test results of the polymorphisms of CTEP TaqIB gene.

Locus	r^2 rs102313	rs118231	rs201832
rs102313	-	0.003	0.167
rs118231	0.003	-	0.211
rs201832	0.167	0.211	-

Relationship Between CTEP TaqIB Alleles and CI in AS Patients

The distribution of different alleles at various gene polymorphisms in AS+CI patients and AS patients was shown in Table VI. It could be observed that the allelic polymorphisms rs102313 and rs118231 of CTEP TaqIB gene exhibited an evident correlation with the pathogenesis of CI in AS patients ($p<0.05$), while no significant relationship was observed between the allelic polymorphism rs201832 and CI in AS patients ($p>0.05$).

Association Between CTEP TaqIB Gene Polymorphisms and Lipid Metabolism Abnormalities in AS Patients

According to the level of TG, 200 patients with AS and 100 patients with AS+CI were assigned into High TG group and Low TG group, with the median TG as the cutoff point. Firstly, the incidence rate of CI in AS patients with AS was compared between High TG group and Low TG group. The results manifested that the incidence rate of CI in AS patients in High TG group was 3 times higher than that in Low TG group.

Furthermore, the correlation between CTEP TaqIB gene polymorphisms and lipid metabolism abnormalities in AS patients was examined. According to the results (Table VII), CTEP TaqIB gene polymorphism rs102313 had a remarkable correlation with lipid metabolism abnormalities in patients with AS. More precisely, the probability of lipid metabolism abnormalities in GG genotype was prominently higher than that in AA genotype and AG genotype at rs102313 ($p<0.05$).

Table V. Distribution of different genotypes at the polymorphisms of CTEP TaqIB gene in AS patients..

	rs102313			rs118231			rs201832		
Group	**AA**	**AG**	**GG**	**AA**	**AT**	**TT**	**CC**	**CT**	**TT**
AS+CI	8%	28%	64%	16%	32%	52%	34%	34%	32%
AS	26%	49%	25%	24%	51%	25%	28%	36%	36%
x^2		1.482			1.293			0.871	
p		0.000			0.000			0.081	

Table VI. Distribution of allelotypes of CTEP TaqIB gene polymorphisms in AS patients.

	rs1920453		rs1022436		rs1035627	
Group	**C**	**G**	**A**	**G**	**A**	**T**
AS+CI	22%	78%	32%	68%	51%	49%
AS	50.5%	49.5%	49.5%	50.5%	46%	54%
x^2	1.134		0.892		0.523	
p	0.000		0.000		0.081	

Table VII. Correlations of different genotypes at the polymorphisms of CTEP TaqIB gene with lipid metabolism abnormalities in AS patients.

	rs102313			rs118231			rs201832		
Group	**AA**	**AG**	**GG**	**AA**	**AT**	**TT**	**CC**	**CT**	**TT**
High TG	13%	33%	54%	25%	49%	26%	28%	44%	28%
Low TG	28%	40%	22%	27%	47%	26%	33%	34%	33%
x^2	2.928			0.763			0.849		
p	0.002			0.243			0.424		

Discussion

Cerebrovascular diseases characterized by high morbidity rate, high disability rate and high mortality rate are currently one of the major diseases endangering human health. Investigations have shown that cerebrovascular diseases have become one of the most major causes of death in China[11]. The annual morbidity and mortality rates of stroke in China are higher than the worldwide average level. Therefore, it is one of the current urgent medical tasks to carry out in-depth research on the etiology, pathogenesis, prevention and treatment of cerebrovascular diseases. AS-triggered CI is a common type of CI, and its pathogenesis has attracted increasing attention. Moreover, it is a polygenic disease with extensive genetic heterogeneity as well as regional and ethnic differences[12]. The location, function, expression and regulation mechanism of related genes involved in the pathogenesis of AS-induced CI have also become the focus of research. Although the pathogenesis of AS has not been fully elucidated, it is intimately associated with the abnormal metabolism of lipids, apolipoproteins and lipoproteins *in vivo*, among which LDL peroxidation is a primary link in the process of AS.

SNPs refer to the polymorphism of DNA sequences caused by a single deoxynucleotide variation, which is related to many complex diseases and phenotypic differences in human beings, and they are one of the most common genetic variations in human beings[13]. Moreover, SNPs are usually genetic variations of binary or bi-allelic gene composed of four kinds of bases. A SNP should have a mutation frequency greater than 1%. As a kind of genetic markers, SNPs have high stability, and they are the most reliable basis for finding the cause of disease and diagnosis, which also lay the foundation for screening therapeutic drugs[14].

CETP is a signal peptide composed of 476 amino acid residues and 17 amino acids, and since as high as 45% of them are non-polar amino acid residues, they are easy to be oxidized and inactivated. Known organs and tissues capable of synthesizing CETP include liver, adrenal gland, adipose tissue, spleen, small intestine and macrophages. The molecular weight of CETP is 74,000, and its structural coding gene is located at the long arm of chromosome 16[15]. The main function of CETP is to coordinate and balance the exchange and transport between plasma lipoproteins, thereby exerting a pivotal effect in the reverse transport of cholesterol. The reverse transport of cholesterol is mediated by HDL that plays an important role in preventing AS and reducing the concentration of cholesterol in blood. CETP is currently the only protein involved in the metabolic process of cell cholesterol, and it significantly influences HDL-c[16]. Westerterp et al[17] have illustrated that HDL-c has a negative association with the CETP level in plasma, so raising the HDL-c level by effectively suppressing CETP activity can reduce the prevalence rate of coronary heart disease. Research on the population genetics in Asian and European countries has manifested that there are many types of mutations in CETP gene, a majority of which can reduce CETP activity, cause changes in various lipoprotein levels, and increase the incidence rate of coronary heart disease in mutation carriers[18]. Jensen et al[19] have denoted that the CETP concentration and activity of patients with CETP gene mutations are reduced, resulting in notable changes in lipoprotein metabolism. It has also been found that the exchange between TG in CETP-mediated lipoprotein (including apolipoprotein B) and cholesteryl ester in HDL-c is decreased, cholesteryl ester accumulates in HDLC, and the quality and quantity of HDL-c change, in which increased HDL-c is a significant feature[19]. Genetic and environmental factors affect the activity and transport of CETP, and the expression of CETP gene determines lipid transport activity and lipoprotein composition *in vivo*. CETP gene has 16 exons, about 25000 bases, and many polymorphisms. Of them, the polymorphism at the 277 base of the first intron can be recognized by TaqI endonuclease to form B1 and B2 alleles, which are combined into B181, B182 and B282 genotypes. Its polymorphisms influence the HDL level, and some or all structural gene mutations with CETP defects increase HDL[20]. In the current study, the distribution of SNPs rs102313, rs118231 and rs201832 in the promoter region of CTEP TaqIB gene in AS-induced CI patients was detected, and it was found that polymorphisms rs102313 and rs118231 of CTEP TaqIB gene were markedly correlated with CI in AS patients. In particular, the risk of CI was higher in AS patients with GG genotype and allele G at rs102313 and in those with genotype TT and allele T at rs118231. Additionally, the probability of lipid metabolism abnormalities in AS patients with GG genotype at rs102313 was evidently higher than that in AS patients with AA genotype and AG genotype.

Conclusions

Briefly, this study revealed for the first time that the gene polymorphisms and alleles at rs102313 and rs118231 in the promoter region of CTEP TaqIB gene are susceptible factors for CI in AS patients, the gene polymorphism rs102313 is a susceptible factor for lipid metabolism abnormalities in AS patients, and this gene locus can be used a genetic marker for CI and lipid metabolism abnormalities caused by AS in the future.

Conflicts of interest

The authors declare no conflicts of interest.

References

1) Perera AH, Rudarakanchana N, Monzon L, Bicknell CD, Modarai B, Kirmi O, Athanasiou T, Hamady M, Gibbs RG. Cerebral embolization, silent cerebral infarction and neurocognitive decline after thoracic endovascular aortic repair. Br J Surg 2018; 105: 366-378.
2) Rabinstein AA, Weigand S, Atkinson JL, Wijdicks EF. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke 2005; 36: 992-997.
3) Yoo JH, Chung CS, Kang SS. Relation of plasma homocyst(e)ine to cerebral infarction and cerebral atherosclerosis. Stroke 1998; 29: 2478-2483.
4) Dahl A, Lund C, Russell D. [Atherosclerosis and cerebral infarction]. Tidsskr Nor Laegeforen 2007; 127: 892-896.
5) Tang ZY, Zhu QY, Xu LJ, Deng LY, Zeng Y, Ding WJ, Huang W. Artificial cold wave-induced cerebral infarction in rats with carotid atherosclerosis. J Mol Neurosci 2012; 47: 278-285.
6) Liang Q, Cai Y, Chen R, Chen W, Chen L, Xiao Y. The Effect of Naoxintong Capsule in the Treatment of Patients with Cerebral Infarction and Carotid Atherosclerosis: A Systematic Review and Meta-Analysis of Randomized Trials. Evid Based Complement Alternat Med 2018; 2018: 5892306.

7) Armitage J, Holmes MV, Preiss D. Cholesteryl Ester Transfer Protein Inhibition for Preventing Cardiovascular Events: JACC Review Topic of the Week. J Am Coll Cardiol 2019; 73: 477-487.
8) Drayna D, Jarnagin AS, McLean J, Henzel W, Kohr W, Fielding C, Lawn R. Cloning and sequencing of human cholesteryl ester transfer protein cDNA. Nature 1987; 327: 632-634.
9) Mezdour H, Kora I, Parra HJ, Tartar A, Marcel YL, Fruchart JC. Two-site enzyme immunoassay of cholesteryl ester transfer protein with monoclonal and oligoclonal antibodies. Clin Chem 1994; 40: 593-597.
10) Kettunen J, Holmes MV, Allara E, Anufrieva O, Ohukainen P, Oliver-Williams C, Wang Q, Tillin T, Hughes AD, Kahonen M, Lehtimaki T, Viikari J, Raitakari OT, Salomaa V, Jarvelin MR, Perola M, Davey SG, Chaturvedi N, Danesh J, Di Angelantonio E, Butterworth AS, Ala-Korpela M. Lipoprotein signatures of cholesteryl ester transfer protein and HMG-CoA reductase inhibition. PLoS Biol 2019; 17: e3000572.
11) Crawford KM, Gallego-Fabrega C, Kourkoulis C, Miyares L, Marini S, Flannick J, Burtt NP, von Grotthuss M, Alexander B, Costanzo MC, Vaishnav NH, Malik R, Hall JL, Chong M, Rosand J, Falcone GJ. Cerebrovascular Disease Knowledge Portal: An Open-Access Data Resource to Accelerate Genomic Discoveries in Stroke. Stroke 2018; 49: 470-475.
12) Huang C, Zhao X, Lu Y, Wang L, Hu Y, Zhang J, Huang Q, Chen G. Changes in Life Expectancy From 2006 to 2015 in Suzhou, East China: Contributions of Age- and Cause-Specific Mortality. Asia Pac J Public Health 2018; 30: 75-84.
13) Reed GH, Wittwer CT. Sensitivity and specificity of single-nucleotide polymorphism scanning by high-resolution melting analysis. Clin Chem 2004; 50: 1748-1754.
14) Morino H, Kawarai T, Izumi Y, Kazuta T, Oda M, Komure O, Udaka F, Kameyama M, Nakamura S, Kawakami H. A single nucleotide polymorphism of dopamine transporter gene is associated with Parkinson's disease. Ann Neurol 2000; 47: 528-531.
15) Arsenault BJ, Boyer M, Kastelein JJ. What does the future hold for cholesteryl ester transfer protein inhibition? Curr Opin Lipidol 2015; 26: 526-535.
16) Ding YY, Zhang W, Zhang MQ, Fu K, Chen WP, Ding C, He XL, Zhang XD, Huang L, Yin ZJ. Functional and association studies of the cholesteryl ester transfer protein (CETP) gene in a Wannan Black pig model. Anim Genet 2015; 46: 702-706.
17) Westerterp M, van der Hoogt CC, de Haan W, Offerman EH, Dallinga-Thie GM, Jukema JW, Havekes LM, Rensen PC. Cholesteryl ester transfer protein decreases high-density lipoprotein and severely aggravates atherosclerosis in APOE*3-Leiden mice. Arterioscler Thromb Vasc Biol 2006; 26: 2552-2559.
18) Gudnason V, Kakko S, Nicaud V, Savolainen MJ, Kesaniemi YA, Tahvanainen E, Humphries S. Cholesteryl ester transfer protein gene effect on CETP activity and plasma high-density lipoprotein in European populations. The EARS Group. Eur J Clin Invest 1999; 29: 116-128.
19) Jensen MK, Mukamal KJ, Overvad K, Rimm EB. Alcohol consumption, TaqIB polymorphism of cholesteryl ester transfer protein, high-density lipoprotein cholesterol, and risk of coronary heart disease in men and women. Eur Heart J 2008; 29: 104-112.
20) Boekholdt SM, Sacks FM, Jukema JW, Shepherd J, Freeman DJ, McMahon AD, Cambien F, Nicaud V, de Grooth GJ, Talmud PJ, Humphries SE, Miller GJ, Eiriksdottir G, Gudnason V, Kauma H, Kakko S, Savolainen MJ, Arca M, Montali A, Liu S, Lanz HJ, Zwinderman AH, Kuivenhoven JA, Kastelein JJ. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: individual patient meta-analysis of 13,677 subjects. Circulation 2005; 111: 278-287.