载脂蛋白A5基因多态性与冠心病患者血脂及冠脉狭窄程度的相关性

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摘 要：【目的】探讨中国汉族人群载脂蛋白A5(APOA5)基因rs2075291和rs3135507多态性位点与冠心病(CHD)患者血脂水平及冠脉狭窄程度的关系。【方法】应用聚合酶链式反应-限制性片段长度多态性法(PCR-RFLP)对324例CHD患者和152例非CHD对照者进行rs2075291和rs3135507多态性分型并比较不同基因型之间血脂水平的差异。采用Gensini评分系统评价CHD患者的冠脉狭窄程度，并使用多因素线性回归法分析rs2075291和rs3135507多态性以及其他因素与Gensini得分之间的相关性。【结果】CHD组高血压患病率、甘油三酯(TG)、总胆固醇(TC)、载脂蛋白B100(APOB100)、脂蛋白a[Lp(a)]、TG/高密度脂蛋白胆固醇(HDL-C)、TC/HDL-C、低密度脂蛋白胆固醇(LDL-C)/HDL-C和APOB100/载脂蛋白AI(APOAI)水平高于对照组，HDL-C和APOAI水平低于对照组，差异均有统计学意义($P<0.05$)。rs2075291和rs3135507多态性等位基因及基因型分布频率在CHD组与对照组之间差异无统计学意义。在对照组中，rs2075291多态性GT基因型TG和TG/HDL-C水平高于GG基因型，HDL-C水平低于GG基因型，差异均有统计学意义($P<0.05$)；在CHD组中，rs2075291多态性GT基因型TG/HDL-C和TC/HDL-C高于GG基因型，差异有统计学意义($P<0.05$)。在CHD组中，rs3135507位点A等位基因携带者APOB100水平低于GG基因型，差异有统计学意义($P<0.05$)。多因素回归分析结果显示，rs2075291和rs3135507多态性与Gensini得分的相关性无统计学意义($P>0.05$)。【结论】APOA5 rs2075291影响血脂水平，但与CHD发生发展无明显相关性，此研究结果需大样本多中心的病例-对照研究加以证实。

关键词：载脂蛋白A5；多态性；冠心病；rs2075291；rs3135507
中图分类号：R541.4 **文献标志码**：A **文章编号**：1672-3554(2017)05-0710-07

Association of APOA5 Polymorphisms with Plasma Lipid Levels and Severity of Coronary Stenosis in Patients with Coronary Heart Disease

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Abstract: 【Objective】To explore the possible effects of the apolipoprotein A5 (APOA5) gene rs2075291 and rs3135507 polymorphisms on plasma lipid levels and the severity of coronary stenosis in patients with coronary heart disease (CHD) in Chinese Han people. 【Methods】Polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP) was used to identify the genotypes of the rs2075291 or rs3135507 polymorphism for the 324 patients with CHD and the 152 CHD-free controls, and the lipid levels between the genotypes were compared. The severity of coronary stenosis was assessed by the Gensini scoring system, and

收稿日期：2017-05-06
基金项目：四川省教育厅重点项目(17ZA0172)；川北医学院科研创新团队项目(CBY13-TD02)
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the associations of the rs2075291 and rs3135507 polymorphisms as well as other factors with the Gensini scores were analyzed by multivariate linear regression.【Results】The CHD patients had higher prevalence of hypertension, and higher levels of triglycerides (TG), total cholesterol (TC), apolipoprotein B100 (APOB100), lipoprotein (a) [Lp(a)], TG/high-density lipoprotein cholesterol (HDL-C), TC/HDL-C, low-density lipoprotein cholesterol (LDL-C)/HDL-C and APOB100/apolipoprotein AI (APOAI), and lower levels of HDL-C and APOAI than the controls ($P < 0.05$ for all). The rs2075291 or rs3135507 allele and genotype frequencies were similar between the CHD group and the control group. The subjects with the rs2075291 GT genotype had higher levels of TG and TG/HDL-C, and lower levels of HDL-C than the subjects with the GG genotype in controls ($P < 0.05$ for all). In CHD patients, those with the rs2075291 GT genotype had higher levels of TG/HDL-C and TC/HDL-C than the patients with the GG genotype ($P < 0.05$ for both). Regarding the rs3135507 polymorphism, the A allele carriers had lower level of APOB100 than the patients with the GG genotype ($P < 0.05$). No significant association between the rs2075291 or rs3135507 polymorphism and the Gensini scores were detected by multivariate linear regression ($P > 0.05$).【Conclusion】The APOA5 rs2075291 polymorphism had significant effects on plasma lipid levels, but no effects on the occurrence and development of CHD. Further multicenter case-control studies with large samples are needed to validate these findings.

Key words: APOA5; polymorphism; coronary heart disease; rs2075291; rs3135507

[J SUN Yat-sen Univ(Med Sci), 2017, 38(5): 710-716]

血脂紊乱(dyslipidemia)是冠状动脉粥样硬化性心脏病(coronary heart disease, CHD)的主要危险因素，约占人群归因危险度的50%[1]。血脂紊乱一般是指血浆甘油三酯(triglycerides, TG)，总胆固醇(total cholesterol, TC)，低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)升高和/或高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)降低[2]。近年来，流行病学调查和临床研究结果显示，脂蛋白比值[包括TG/HDL-C、TC/HDL-C和LDL-C/HDL-C和载脂蛋白B100(apolipoprotein B100, APOB100)/载脂蛋白AI(apolipoprotein AI, APOAI)]在预测CHD的发生发展及预后等方面可能优于单项血脂指标[3-4]。载脂蛋白A5(apolipoprotein A5, APOA5)存在于乳糜微粒、极低密度脂蛋白(very low-density lipoprotein, VLDL)和高密度脂蛋白(high-density lipoprotein, HDL)中，是富含甘油三酯脂蛋白代谢的重要调节因子[5]。APOA5基因敲除小鼠血浆TG水平显著升高，而过表达该基因血浆TG水平显著降低[6]。在人类肝组织中，Shou等[7]发现APOA5基因3'端非翻译区变异位点rs2266788次要等位基因C可使APOA5基因表达降低，同时血浆TG水平和CHD风险增加。在APOA5基因第4外显子存在两个错义变异位点，rs2075291和rs3135507。rs3135507由G变异成A形成，导致APOA5蛋白第153位缬氨酸残基变成甲硫氨酸残基；rs2075291由G变异成T形成，导致APOA5蛋白第185位甘氨酸残基变成半胱氨酸残基。rs2075291位点被广泛报道与血浆TG水平升高[8-10]，HDL-C水平降低[8,11]相关联。rs3135507也被报道与TG水平升高相关联[12]，但较少有研究去探讨这两个多态性位点与CHD发病风险及CHD患者冠脉狭窄程度的相关性。本研究以冠状动脉造影术确诊为CHD的患者324例，非CHD的对照者152例为研究对象，系统地探讨APOA5基因rs2075291和rs3135507多态性位点与血脂紊乱、CHD发病风险及CHD患者冠脉狭窄程度的关系。

1　材料与方法

1.1　研究对象

研究对象为2014年4月至2015年7月期间在川北医学院附属医院心内科就诊和治疗的无血缘关系的汉族人群。经冠状动脉造影术确诊为CHD的患者324例，其中男性204例，平均年龄(64.7 ± 9.4)岁；女性120例，平均年龄(64.6 ± 8.3)岁。非CHD对照者152例，其中男性81例，平均年龄(60.1 ± 12.4)岁；女性71例，平均年龄(59.3 ± 9.7)岁。本研究所使用的操作程序符合伦理学要求，并经本院伦理委员会批准。所有参试者均签署知情同意书。

1.2　临床资料收集

通过生理生化检查，获得高血压、糖尿病、体质量指数(body mass index, BMI)、TG、TC、LDL-C、HDL-C、APOB100和APOAI等临床资料，并计算TG/HDL-C、TC/HDL-C、LDL-C/HDL-C和

APOB100/APOAI等比值指标。

1.3 冠心病诊断及冠脉狭窄程度评分

CHD组和对照组所有成员均接受冠状动脉造影术,至少一支主要冠脉分支的管腔狭窄程度在50%以上者诊断为CHD,正常冠状动脉者或轻微狭窄者(小于50%狭窄)归为对照组。由两名经验丰富的心内科医生在对受试者病史和生理生化指标不知情的情况下行冠脉造影术。按Judkins法进行,在左冠脉系统设定至少4个观测点,右冠状动脉至少2个观测点。冠脉造影仪采用飞利浦Allura Xper FD20(Philips Medical Systems Nederland B.V. Netherlands)。冠脉狭窄程度评价采用Gensini评分系统[13]。在这个系统中,管腔狭窄程度为1%~25%时赋值1分,26%~50%时赋值2分,51%~75%时赋值4分,76%~90%时赋值8分,91%~99%时赋值16分,完全闭塞时赋值32分。每个分值再乘以该段血管按重要程度赋予的分值,比如,左主干(left main coronary artery, LM)为5分;前降支(left anterior descending branches, LAD)和左回旋支(left circumflex branch, LCX)近端为2.5分,中段为1.5分,远段为1分;右冠状动脉(right coronary artery, RCA)各段均为1分。所有分值加权获得患者的Gensini得分。

1.4 APOA5 rs2075291和rs3135507多态性分析

1.4.1 DNA提取 基因组DNA从外周血白细胞中提取,采用TIANGEN公司的血液基因组DNA提取试剂盒,操作过程按试剂盒说明书进行。

1.4.2 PCR扩增反应 PCR扩增含有APOA5 rs2075291和rs3135507多态性位点的DNA片段。引物序列由上海生工合成,正向引物为5′-GGCAGCAACTGAAGCCCTACAC-3′,反向引物为5′-TCGGCGTATGGGTGGAAGAG-3′。PCR反应体系为25 μL,其中DNA模板1 μL,上游和下游引物各1 μL,2×PCR TaqMix 12.5 μL,ddH_2O补充至25 μL。PCR扩增程序包括三个阶段:95 ℃ 5 min;95 ℃ 30 s,61 ℃ 30 s,72 ℃ 45 s,循环30次;72 ℃ 5 min。

1.4.3 限制性核酸内切酶分析 酶切反应体系(10 μL):PCR产物3 μL,*Msp*I(rs2075291)或*Nsb*I(rs3135507)内切酶5 U,10×NEB缓冲液1 μL,ddH_2O补至10 μL。37 ℃酶切过夜,3%琼脂糖凝胶电泳和溴乙锭-紫外显色鉴定基因型。

1.5 统计学方法

采用SPSS 13.0软件进行统计分析。所有数据采用均数±标准差($\bar{x} \pm s$)表示。不符合正态分布的计量资料(如TG、Gensini得分)进行对数转换后纳入统计分析。采用χ^2检验比较对照组和CHD组之间、不同基因型之间计数资料的差异;采用单因素方差分析比较对照组和CHD组之间、不同基因型之间计量资料的差异。采用χ^2检验比较对照组与CHD组之间基因型和等位基因频率的差异。APOA5 rs2075291和rs3135507多态性以及其它因素与Gensini得分之间的相关性采用多因素线性回归分析。卡方检验和方差分析均采用双尾检验。$P \leqslant 0.05$为差异有统计学意义。

2 结 果

2.1 冠心病组与对照组临床资料比较

CHD组年龄($F = 27.45$, $P < 0.001$)、高血压患病率($\chi^2 = 18.04$, $P < 0.001$)、TG($F = 7.39$, $P = 0.007$)、TC($F = 4.33$, $P = 0.04$)、APOB100($F = 9.67$, $P = 0.002$)、脂蛋白a[lipoprotein (a), Lp(a)]($F = 4.35$, $P = 0.04$)、TG/HDL-C($F = 9.75$, $P = 0.002$)、TC/HDL-C($F = 21.79$, $P < 0.001$)、LDL-C/HDL-C($F = 13.68$, $P < 0.001$)和APOB100/APOAI($F = 17.95$, $P < 0.001$)水平高于对照组,HDL-C($F = 10.65$, $P = 0.001$)和APOAI($F = 11.17$, $P = 0.001$)水平低于对照组,差异均有统计学意义。体质量、BMI、糖尿病患病率和LDL-C水平在两组之间差异无统计学意义(表1)。

2.2 冠心病组和对照组基因型及等位基因频率分布

APOA5 rs2075291和rs3135507位点基因型及等位基因频率在CHD组与对照组之间差异无统计学意义(表2)。

2.3 APOA5 rs2075291位点不同基因型之间临床资料比较

在对照组中,rs2075291位点GT基因型受试者TG($F = 5.09$, $P = 0.03$)和TG/HDL-C($F = 12.05$, $P = 0.001$)水平高于GG基因型受试者,HDL-C($F = 8.57$, $P = 0.004$)水平低于GG基因型受试者,差异均有统计学意义。在CHD组中,rs2075291位点GT基因型受试者TG/HDL-C($F = 5.56$, $P = 0.02$)和TC/HDL-C($F = 5.13$, $P = 0.02$)水平显著高于GG基因型受试者,差异均有统计学意义($P < 0.05$)。其他指标在基因型之间差异无统计学意义(表3)。

表1　研究人群的临床特征

Table 1　Clinical characteristics of the study population

Variables	Control subjects (n = 152)	CHD patients (n = 324)	F or χ^2	P
Demographic characteristics				
Age/years	59.7 ± 11.2	64.7 ± 9.0	27.45	< 0.001
Weight/kg	62.52 ± 10.14	63.24 ± 9.33	0.35	0.55
BMI/(kg/m^2)	23.89 ± 3.46	24.18 ± 3.30	0.57	0.45
Hypertension[n(%)]	56(36.84)	187(57.72)	18.04	< 0.001
Diabetes[n(%)]	14(9.21)	50(15.43)	3.44	0.06
Lipid levels				
TG/(mmol/L)	1.35 ± 0.68	1.62 ± 1.24	7.39	0.007
TC/(mmol/L)	3.99 ± 1.03	4.22 ± 1.19	4.33	0.04
LDL-C/(mmol/L)	2.50 ± 1.44	2.66 ± 0.94	2.26	0.13
HDL-C/(mmol/L)	1.07 ± 0. 28	0.99 ± 0.24	10.65	0.001
APOAI/(g/L)	1.11 ± 0.17	1.04 ± 0.19	11.17	0.001
APOB100/(g/L)	0.73 ± 0.23	0.81 ± 0.28	9.67	0.002
Lp(a)/(mg/L)	258.18 ± 289.51	312.88 ± 334.19	4.35	0.04
TG/HDL-C	1.39 ± 0.94	1.81 ± 1.56	9.75	0.002
TC/HDL-C	3.84 ± 1.05	4.42 ± 1.34	21.79	< 0.001
LDL-C/HDL-C	2.40 ± 1.19	2.82 ± 1.10	13.68	< 0.001
APOB100/APOAI	0.67 ± 0.22	0.82 ± 0.41	17.95	< 0.001

CHD: coronary heart disease; BMI: body mass index; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; APOAI: apolipoprotein AI; APOB100, apolipoprotein B100; Lp(a), lipoprotein (a). The differences between CHD patients and control subjects were calculated by Chi-square test for categorical variables, and one-way ANOVA analysis for continuous variables.

表2　CHD组和对照组rs2075291和rs3135507多态性的基因型和等位基因频率分布

Table 2　The genotype and allele frequencies of the rs2075291 and rs3135507 polymorphisms in the CHD group or in control group

Variables	Control subjects (n = 152)	CHD patients (n = 324)	χ^2	P
APOA5 rs2075291				
GG[n(%)]	141(92.76)	292(90.12)	0.88	0.35
GT[n(%)]	11(7.24)	32(9.88)		
G allele frequency	0.964	0.951	0.84	0.36
T allele frequency	0.036	0.049		
APOA5 rs3135507				
GG[n(%)]	131(86.18)	276(85.19)	0.11	0.74
GA[n(%)]	20(13.16)	45(13.89)		
AA[n(%)]	1(0.66)	3(0.92)		
G allele frequency	0.928	0.921	0.12	0.73
A allele frequency	0.072	0.079		

The frequency differences between CHD patients and control subjects were calculated by Chi-square test.

2.4　APOA5 rs3135507位点不同基因型之间临床资料比较

在CHD组中，A等位基因携带者APOB100水平低于GG基因型(F = 4.84, P = 0.03)。其他指标在基因型之间的差异无统计学意义(表4)。

2.5　APOA5 rs2075291和rs3135507多态性影响冠心病冠脉狭窄程度的多因素分析

以rs2075291多态性、rs3135507多态性、年

表3 APOA5 rs2075291多态性不同基因型参试者的临床特征和血脂水平

Table 3 Clinical characteristics and lipid levels of the subjects according to the rs2075291 genotypes

Variables	Controls				CHD patients			
	GG genotype (n = 141)	GT genotype (n = 11)	F or χ^2	P	GG genotype (n = 292)	GT genotype (n = 32)	F orχ^2	P
Non-lipid variables								
Age/(years)	59.7 ± 11.2	61.0 ± 11.4	0.15	0.70	64.5 ± 9.0	65.8 ± 8.8	0.57	0.45
Mass/kg	62.31 ± 9.98	65.30 ± 12.30	0.81	0.37	63.18 ± 9.26	63.93 ± 10.27	0.17	0.68
BMI/(kg/m^2)	23.81 ± 3.41	24.91 ± 4.11	0.84	0.36	24.17 ± 3.32	24.30 ± 3.28	0.04	0.85
Hypertension[n(%)]	50(35.46)	6(54.55)	1.60	0.21	171(58.56)	16(50.00)	2.17	0.14
Diabetes[n(%)]	13(9.22)	1(9.09)	0	1.00	46(15.75)	4(12.50)	0.23	0.63
Lipid variables								
TG/(mmol/L)	1.31 ± 0.66	1.79 ± 0.84	5.09	0.03	1.58 ± 1.23	2.01 ± 1.25	3.56	0.06
TC/(mmol/L)	4.02 ± 1.02	3.67 ± 1.01	1.14	0.29	4.20 ± 1.21	4.34 ± 0.98	0.37	0.54
LDL-C/(mmol/L)	2.52 ± 1.48	2.22 ± 0.92	0.45	0.51	2.65 ± 0.95	2.72 ± 0.85	0.17	0.68
HDL-C/(mmol/L)	1.09 ± 0.28	0.84 ± 0.18	8.57	0.004	1.00 ± 0.24	0.92 ± 0.22	3.23	0.07
APOAI/(g/L)	1.12 ± 0.17	1.02 ± 0.19	3.30	0.07	1.04 ± 0.20	1.02 ± 0.14	0.32	0.57
Lp(a)/(mg/L)	266 ± 296	138 ± 94	1.65	0.20	315 ± 343	299 ± 253	0.07	0.79
TG/HDL-C	1.32 ± 0.85	2.31 ± 1.52	12.05	0.001	1.73 ± 1.53	2.42 ± 1.77	5.56	0.02
TC/HDL-C	3.79 ± 1.03	4.41 ± 1.07	3.56	0.06	4.36 ± 1.33	4.92 ± 1.34	5.13	0.02
LDL-C/HDL-C	2.38 ± 1.20	2.62 ± 1.02	0.43	0.51	2.77 ± 1.08	3.11 ± 1.12	2.77	0.10
APOB100/APOAI	0.66 ± 0.22	0.74 ± 0.19	1.21	0.27	0.81 ± 0.41	0.86 ± 0.34	0.38	0.54

CHD: coronary heart disease; BMI: body mass index; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; APOAI: apolipoprotein AI; APOB100: apolipoprotein B100; Lp(a): lipoprotein (a). The differences between the subjects with different genotypes were calculated by Chi-square test for categorical variables, and one-way ANOVA analysis for continuous variables.

表4 APOA5 rs3135507多态性不同基因型参试者的临床特征和血脂水平

Table 4 clinical characteristics and lipid levels of the subjects according to the rs3135507 genotypes

Variables	Controls				CHD patients			
	GG genotype (n = 131)	A carriers (n = 21)	F or χ^2	P	GG genotype (n = 276)	A carriers (n = 48)	F or χ^2	P
Non-lipid variables								
Age/(years)	60.4 ± 10.7	55.5 ± 13.3	3.52	0.06	64.9 ± 9.0	63.3 ± 9.2	1.28	0.26
Weight/kg	62.60 ± 10.04	62.00 ± 11.04	0.06	0.81	63.43 ± 9.42	62.22 ± 8.97	0.64	0.43
BMI/(kg/m^2)	23.95 ± 3.47	23.56 ± 3.45	0.19	0.66	24.29 ± 3.37	23.56 ± 2.88	1.85	0.18
Hypertension[n(%)]	48(36.64)	8(38.10)	0.02	0.90	162(58.70)	25(52.08)	0.73	0.39
Diabetes[n(%)]	12(9.16)	2(9.52)	0.00	1.00	42(15.22)	8(16.67)	0.07	0.80
Lipid variables								
TG/(mmol/L)	1.32 ± 0.63	1.52 ± 0.91	1.54	0.22	1.65 ± 1.26	1.47 ± 1.12	0.86	0.36
TC/(mmol/L)	4.00 ± 1.05	3.97 ± 0.91	0.02	0.89	4.26 ± 1.22	3.95 ± 0.97	2.72	0.10
LDL-C/(mmol/L)	2.54 ± 1.53	2.25 ± 0.64	0.71	0.40	2.69 ± 0.96	2.46 ± 0.80	2.52	0.11
HDL-C/(mmol/L)	1.07 ± 0.28	1.10 ± 0.29	0.17	0.68	0.99 ± 0.24	0.99 ± 0.22	0.03	0.86
APOAI/(g/L)	1.11 ± 0.17	1.13 ± 0.21	0.45	0.50	1.04 ± 0.20	1.05 ± 0.17	0.03	0.86
APOB100/(g/L)	0.74 ± 0.24	0.68 ± 0.16	1.36	0.25	0.83 ± 0.29	0.73 ± 0.24	4.84	0.03
Lp(a)/(mg/L)	259 ± 282	255 ± 340	0.003	0.96	312 ± 336	323 ± 334	0.05	0.83
TG/HDL-C	1.37 ± 0.90	1.56 ± 1.16	0.74	0.39	1.83 ± 1.57	1.63 ±1.55	0.69	0.41
TC/HDL-C	3.86 ± 1.09	3.69 ± 0.67	0.49	0.49	4.46 ± 1.32	4.16 ±1.40	2.00	0.16
LDL-C/HDL-C	2.45 ± 1.26	2.08 ± 0.48	1.70	0.20	2.84 ± 1.09	2.61 ±1.11	1.68	0.20
APOB100/APOAI	0.68 ± 0.23	0.60 ± 0.11	2.32	0.13	0.84 ± 0.42	0.72 ± 0.30	3.08	0.08

CHD: coronary heart disease; BMI: body mass index; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; APOAI: apolipoprotein AI; APOB100: apolipoprotein B100; Lp(a): lipoprotein (a). The differences between the subjects with different genotypes were calculated by Chi-square test for categorical variables, and one-way ANOVA analysis for continuous variables.

龄、体质量、BMI、高血压、糖尿病、血糖水平、TG、TC、LDL-C、HDL-C、APOAI、APOB100、Lp(a)、TG/HDL-C、TC/HDL-C、LDL-C/HDL-C和APOB100/APOAI等19个变量为自变量，以Gensini得分为因变量进行多元线性回归分析。结果如表5所示，高血压(β = 0.04, 95% CI = 0.003, 0.09)、APOB100/APOAI(β = 0.27, 95% CI = 0.12, 0.42)和Lp(a)(β = 0.19, 95% CI=0.07, 0.32)与Gensini得分显著正相关；APOAI(β = −0.44, 95% CI = −0.75, −0.13)与Gensini得分显著负相关。rs2075291和rs3135507多态性以及其他指标与Gensini得分的相关性无统计学意义。

表5　遗传、生理生化因素(自变量)与Gensini得分(因变量)的多因素线性回归分析

Table 5　Multivariate linear regression analysis of the Gensini scores (dependent variable) and the genetic, physiological and biochemical factors (independent variables) in CHD patients

Variables	β(95% CI)	*P*
APOA5 rs2075291	−0.17(−0.20, 0.17)	0.86
APOA5 rs3135507	−0.17(−0.17, 0.13)	0.82
Age	0.004(−0.002, 0.01)	0.15
Weight	−0.001(−0.11, 0.01)	0.84
BMI	−0.003(−0.03, 0.02)	0.83
Hypertension	0.04(0.003, 0.09)	0.04
Diabetes	0.04(−0.12, 0.195)	0.64
Glucose	−0.003(−0.03, 0.03)	0.82
TG	0.08(−0.16, 0.31)	0.51
TC	0.20(−0.67, 1.07)	0.65
LDL-C	−0.35(−1.29, 0.58)	0.46
HDL-C	0.02(−1.21, 1.25)	0.98
APOAI	−0.44(−0.75, −0.13)	0.01
APOB100	0.28(−0.43, 0.98)	0.44
Lp(a)	0.19(0.07, 0.32)	0.002
TG/HDL-C	−0.001(−0.30, 0.10)	0.32
TC/HDL-C	0.11(−0.92, 0.70)	0.79
LDL-C/HDL-C	0.26(−0.61, 1.14)	0.55
APOB100/APOAI	0.27(0.12, 0.42)	0.001

CHD: coronary heart disease; 95% CI: 95% confidence interval; BMI: body mass index; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; APOAI: apolipoprotein AI; APOB100: apolipoprotein B100; Lp(a): lipoprotein (a). The associations of the APOA5 rs2075291 and rs3135507 polymorphisms and other CHD risk factors with the Gensini scores were analyzed by multivariate linear regression analysis.

3　讨　论

APOA5存在于乳糜微粒、VLDL和HDL中，是调节富含TG脂蛋白代谢的重要因子[6]。血浆APOA5与TG呈负相关，APOA5水平降低，TG水平升高[6-7]。高甘油三酯血症是心脑血管疾病的重要危险因素[14]。在对照组中，rs2075291位点GT基因型受试者TG水平显著高于GG基因型受试者，与其他类似研究结果一致[8-10]。血浆TG水平升高常伴随HDL-C水平降低[2]，因此在对照组中，rs2075291位点GT基因型受试者HDL-C降低，这也导致TG/HDL-C比值在GT基因型受试者中显著升高。rs2075291多态性影响血脂水平的分子机制还未阐明，其中一个可能的原因是rs2075291多态性导致甘氨酸被半胱氨酸取代，半胱氨酸含有一功能基团巯基(SH-)，可以与其他半胱氨酸残基相互作用形成二硫键，二硫键在蛋白质的空间结构形成中有重要影响。因此，当被半胱氨酸取代后，APOA5分子结构可能发生变化而影响其分子功能，从而影响富含TG的脂蛋白代谢，导致血浆TG水平改变。

在对照组和CHD组中，TC和LDL-C水平在rs2075291位点基因型之间差异无统计学意义，提示rs2075291位点主要通过APOA5影响甘油三酯代谢，对胆固醇代谢影响较小或没有影响。以往研究结果也显示rs2075291位点与血浆TG水平升高相关联，但不影响血浆TC和LDL-C水平[11,15-17]。来自中国台湾的一项研究中，Chien等[17]发现在成人中，rs2075291位点T等位基因携带者血浆TG水平较GG基因型受试者显著升高，在青少年中T等位基因携带者血浆HDL-C水平较GG基因型受试者显著降低，但在成人和青少年中TC和LDL-C水平在基因型之间无显著性差异。在另一项来自南京医科大学的病例-对照研究[16]中，研究者们发现在CHD组和对照组中，rs2075291位点T等位基因携带者血浆TG水平较非携带者显著升高，而TC和LDL-C在基因型之间差异无统计学意义。

在本研究中，虽然发现rs2075291位点与TG和HDL-C相关联，但没有发现该位点与CHD发病风险及严重程度相关联。我国其他实验室也对该多态性位点与CHD关联性进行了研究报道，但结

果不尽一致。Zhou等[18]报道在我国汉族人群中，rs2075291位点基因型和等位基因频率在病例组和对照组之间差异无统计学意义，这与本研究结果一致，但在男性CHD患者中，研究者发现rs2075291多态性与冠脉狭窄程度相关。另外，Tang等[19]报道rs2075291多态性与血浆TG水平和CHD发病均显著相关。rs2075291位点与CHD发病风险及严重程度的关联性有待进一步研究。

本研究发现rs3135507位点在CHD人群中与APOB100水平相关联，但与其他血脂指标的相关性没有统计学意义。在rs3135507多态性位点中，153位缬氨酸被甲硫氨酸所取代，两种氨基酸均不含有羟基、巯基等功能基团，理化性质差别也不大，因此对APOA5的分子结构功能不构成大的影响，也就对富含TG的脂蛋白代谢和血脂水平没有大的影响。

综上，在我国汉族人群中，APOA5 rs2075291位点与血浆TG升高、HDL-C降低相关联，但与CHD发病风险及CHD患者冠脉狭窄程度没有明显相关性；APOA5 rs3135507位点与血浆脂质水平及CHD发生发展均无显著相关性。

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(编辑 孙慧兰)