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Original Article

Polymorphisms in ApoB gene are associated with risk of myocardial infarction and serum ApoB levels in a Chinese population

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Abstract: Myocardial infarction (MI) is a serious result of coronary artery disease. Recent data from clinical trials have showed that the risk of MI was associated with high plasma apolipoprotein B (apoB) levels. Mutations in ApoB gene were also found to be associated with plasma lipid levels. The aim of this study is to evaluate the effect of ApoB polymorphisms on the risk of MI and plasma apoB levels in a Chinese population. Eight polymorphisms (rs676210, rs679899, rs3791980, rs2854725, rs11676704, rs512535, rs12720841 and rs2678379) in ApoB gene were genotyped in a case-control study in China, including 550 MI cases and 550 healthy controls. Carriers of GG genotype of rs676210 had significant increased risk of MI [odd ratio (OR) = 1.93, 95% confidence interval (CI): 1.23-3.03] compared to carriers of AA genotype. Haplotype analysis also showed that GTTGG (rs676210-rs2854725-rs11676704-rs3791980-rs2678379) haplotype had significant increased risk of MI (OR = 2.82, 95% CI: 1.49-5.33) compared with ATTGA haplotype. Furthermore, apoB rs676210 and rs2678379 polymorphisms were significantly associated with plasma levels of apoB in healthy controls (P = 0.01 and 0.02). Our findings indicated that ApoB mutations may be associated with the risk of MI and plasma ApoB levels in healthy controls in Chinese population.

Keywords: Myocardial infarction, ApoB, genetic mutation, haplotype, susceptibility

Introduction

Myocardial infarction (MI), a common presentation of ischemic heart disease, remains a leading cause of morbidity and mortality worldwide and affects approximately 7 million people a year according to statistics [1, 2].

Although the exact etiology of MI has not been clearly explained, researches have proved that like other complex diseases, multiple environmental factors, genetic factors, and their interactions may responsible for the pathogenesis of MI [3]. Environmental risk factors contribute to MI including old age, tobacco smoking, diabetes, hypertension, obesity, high blood levels of high density lipoprotein cholesterol (HDL-C) and total cholesterol (TC), and low blood levels of low density lipoprotein cholesterol (LDL-C) [4-6]. Molecular epidemiological studies also identified a set of genetic mutations that can modify the risk of MI [7-11]. It is estimated that the overall genetic heritability of CAD/MI is around 40-60%, and this proportion includes mainly genes that regulate known risk factors (e.g., lipid metabolism), and also genes involved in as yet unknown metabolic pathways [12].

Apolipoprotein B (apoB), a key component of VLDL particles and microsomal triacylglycerol transfer protein (MTP), plays an important role in lipid metabolism [13]. Reduced secretion of apoB protein can result in reduced production of chylomicron and VLDL and then leading to malabsorption of fats and fat-soluble vitamins [14]. So, plasma apoB level is an important predictor of MI [15, 16]. Twin studies also suggested that 50-60% of the variation in plasma levels of apoB in human is genetically determined [17, 18]. Rare missense mutations in the ApoB gene may not only result in severe hypercholesterolemia and ischemic cardiovascular disease, but also in hypocholesterolemia [19, 20]. But till now, studies on ApoB single nucleotide poly-

Table 1. Characteristics of cases and controls

Characteristics	Controls (n = 550)	Cases (n = 550)	*P* value
Age (year)	57.68±8.65	57.88±8.53	0.72
Sex (Male/Female)	398/152	396/154	0.89
Smoking (Yes/No)	183/367	272/278	< 0.001
Diabetes (Yes/No)	75/472	189/361	< 0.001
Hypertension (Yes/No)	231/319	264/286	0.05
BMI (kg/m^2)	23.83±2.51	24.34±2.61	0.001
Total cholesterol (mmol/L)	5.10±1.78	4.72±1.17	< 0.001
HDL-C (mmol/L)	1.47±0.66	1.22±0.38	< 0.001
LDL-C (mmol/L)	2.77±1.09	2.91±0.66	0.01
ApoB (g/L)	0.82±0.23	0.88±0.25	< 0.001

morphisms (SNP) and risk of MI were rare and have not been fully studied in Chinese population.

To help clarify whether mutations in ApoB gene are associated with risk of MI and plasma apoB levels in healthy controls, we examined eight SNPs in the ApoB gene (rs676210, rs679899, rs3791980, rs2854725, rs11676704, rs512-535, rs12720841 and rs2678379) in a case-control study in Chinese population.

Materials and methods

Study subjects

Between March 2009 and February 2013, a total of 550 MI patients and 550 healthy controls were consecutively enrolled in the Gongren Hospital in Hebei, China. All patients were diagnosed according to the criteria of the WHO, including chest pain plus either electrocardiographic changes or elevated levels of cardiac enzymes [21]. Healthy control subjects, without MI, were selected in the same period and from the same hospital, and were frequency matched to the cases by age (5-year age groups) and gender. At enrollment, demographic characteristics, anthropometric measures, medical histories were collected from each subject by a trained interviewer using a structured questionnaire. Written informed consent was obtained from all enrolled participants. This study was approved by the Ethics Committee of the Gongren Hospital.

Laboratory tests

Blood samples were collected from all participants after a 12-hour overnight fast and then separated into plasma, red blood cells, and buffy coat. Plasma levels of TC (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L) and apoB (g/L) were determined by commercial kits from the Nanjing Jiancheng Bio-company (Nanjing, China).

Genotyping

Genomic DNA was extracted from buffy coat using Promega DNA Extraction Kit (Promega, Madison, WI, USA). Genotyping was performed using the TaqMan assay on the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA), in a 384-well format, with VIC and FAM fluorescent reporter probes. The genotyping call rate was > 95%, and the completion rate was > 99%. The quality and potential misclassification of the genotyping were assessed by re-genotyping 10% of samples that were randomly selected from the whole population. The concordance rate for the quality control samples was 100%.

Statistical analysis

We used SAS 9.3 (SAS Institute, Inc.) for the statistical analyses. Chi-square test and the t test were used to evaluate the differences in the distribution of risk factors between cases and controls. The ORs and 95% CIs for the associations between the SNPs and MI risk were estimated by unconditional logistic regression model. Hardy-Weinberg equilibrium for genotypic distribution and linkage disequilibrium between loci were assessed by HaploView version 4.0 (Daly Lab at the Broad Institute, Cambridge, MA, USA) [22]. Associations between haplotypes (> 1% frequency) and risk of MI were evaluated by computing ORs and 95% CIs using HAPSTAT, assuming an additive model, using the most common haplotype as the referent category [23]. Both univariate ANOVA and multivariate ANCOVA analyses adjusting for age, smoking, diabetes, hypertension and BMI were performed to determine the effects of the ApoB polymorphisms on plasma ApoB levels. A two tailed *P*-value of 0.05 was considered statistically significant.

Results

Selected characteristics of the study population are shown in **Table 1**. Cases and controls were evenly matched by age and gender. Cases

Table 2. Association of genetic variants in ApoB gene with risk of MI

SNP	Controls, n (%)	Cases, n (%)	OR (95% CI)†	OR (95% CI)‡	*P* value
rs676210					
AA	280 (50.9)	245 (44.5)	1.00	1.00	
AG	235 (42.7)	246 (44.7)	1.20 (0.93-1.53)	1.19 (0.92-1.54)	0.16
GG	35 (6.4)	59 (10.7)	1.93 (1.23-3.03)	1.89 (1.18-3.03)	0.005
AG+GG	270 (49.1)	305 (55.5)	1.29 (1.02-1.64)	1.28 (1.00-1.64)	0.04
rs679899					
AA	385 (70.0)	380 (69.1)	1.00	1.00	
AG	153 (27.8)	154 (28.0)	1.02 (0.78-1.33)	0.99 (0.75-1.31)	0.89
GG	12 (2.2)	16 (2.9)	1.34 (0.63-2.88)	1.65 (0.75-3.65)	0.45
AG+GG	165 (30.0)	170 (30.9)	1.04 (0.81-1.35)	1.04 (0.79-1.36)	0.75
rs2854725					
TT	404 (73.5)	388 (70.5)	1.00	1.00	
TG	139 (25.3)	147 (26.7)	1.10 (0.84-1.44)	1.09 (0.82-1.45)	0.49
GG	7 (1.3)	15 (2.7)	2.23 (0.90-5.53)	2.11 (0.82-5.40)	0.08
TG+GG	146 (26.6)	162 (29.4)	1.16 (0.89-1.50)	1.15 (0.87-1.51)	0.28
rs11676704					
TT	284 (51.6)	281 (51.1)	1.00	1.00	
TG	215 (39.1)	216 (39.3)	1.01 (0.79-1.30)	1.02 (0.79-1.33)	0.91
GG	51 (9.3)	53 (9.6)	1.05 (0.69-1.59)	1.13 (0.73-1.74)	0.83
TG+GG	266 (48.4)	269 (48.9)	1.02 (0.81-1.29)	1.04 (0.81-1.34)	0.86
rs3791980					
GG	304 (55.3)	302 (54.9)	1.00	1.00	
GT	205 (37.3)	206 (37.5)	1.01 (0.79-1.30)	1.00 (0.77-1.30)	0.92
TT	41 (7.5)	42 (7.6)	1.03 (0.65-1.63)	0.97 (0.60-1.57)	0.90
GT+TT	246 (44.7)	248 (45.1)	1.02 (0.80-1.29)	1.00 (0.78-1.28)	0.90
rs512535					
CC	396 (72.0)	392 (71.3)	1.00	1.00	
CT	144 (26.2)	147 (26.7)	1.03 (0.79-1.35)	1.04 (0.78-1.38)	0.81
TT	10 (1.8)	11 (2.0)	1.11 (0.47-2.64)	1.03 (0.41-2.61)	0.81
CT+TT	154 (28.0)	158 (28.7)	1.04 (0.80-1.35)	1.04 (0.79-1.37)	0.78
rs12720841					
TT	486 (88.4)	470 (85.5)	1.00	1.00	
TC	64 (11.6)	80 (14.6)	1.29 (0.91-1.84)	1.36 (0.94-1.97)	0.15
CC	- (-)	- (-)	-	-	-
rs2678379					
AA	293 (53.3)	270 (49.1)	1.00	1.00	
AG	216 (39.3)	226 (41.1)	1.13 (0.88-1.46)	1.14 (0.88-1.48)	0.32
GG	41 (7.5)	54 (9.8)	1.43 (0.92-2.21)	1.40 (0.88-2.22)	0.11
AG+GG	257 (46.7)	280 (50.9)	1.18 (0.93-1.50)	1.18 (0.92-1.52)	0.17

†Adjusted for age. ‡Adjusted for age, smoking, diabetes, hypertension and BMI.

Table 3. Association of haplotypes in the ApoB gene with risk of MI

Haplotype*	Controls, %	Cases, %	OR (95% CI)†	OR (95% CI)‡	*P* value
ATTGA	43.9	38.0	1.00	1.00	
ATGGA	27.0	28.4	1.11 (0.90-1.37)	1.13 (0.91-1.42)	0.32
GGTTG	11.9	13.1	1.27 (0.97-1.68)	1.25 (0.93-1.67)	0.09
GTTTG	12.8	11.7	1.05 (0.80-1.38)	1.04 (0.78-1.40)	0.73
GTTGG	1.0	3.3	2.82 (1.49-5.33)	3.06 (1.57-5.95)	0.002

*In the order of rs676210, rs2854725, rs11676704, rs3791980 and rs2678379. †Adjusted for age. ‡Adjusted for age, smoking, diabetes, hypertension and BMI.

Table 4. Association between ApoB polymorphisms and plasma apoB levels in healthy controls

SNP	M/m	ApoB (g/L)			*P* value
		MM	Mm	mm	
rs676210	A/G	0.79±0.18	0.85±0.27	0.86±0.21	0.01
rs679899	A/G	0.81±0.21	0.85±0.25	0.84±0.30	0.13
rs2854725	T/G	0.82±0.17	0.84±0.25	0.82±0.22	0.70
rs11676704	T/G	0.81±0.22	0.80±0.21	0.84±0.24	0.13
rs3791980	G/T	0.81±0.20	0.84±0.26	0.83±0.21	0.20
rs512535	C/T	0.81±0.22	0.85±0.23	0.73±0.21	0.09
rs12720841	T/C	0.82±0.23	0.84±0.24	-	0.48
rs2678379	A/G	0.80±0.18	0.85±0.27	0.83±0.21	0.02

M indicates major allele; m: indicates minor allele.

were more likely to smoke cigarettes (49.5% vs. 33.2%), have diabetes (34.4% vs. 13.6%), have hypertension (48.0% vs. 42.0%) and have higher BMI levels (24.34±2.61 vs. 23.83±2.51). Besides, cases have significant lower levels of plasma total cholesterol and HDL-C, but higher levels of LDL-C and ApoB than that in controls.

The associations of ApoB polymorphisms with risk of MI are presented in **Table 2**. The genotype distributions of these eight variants showed no deviation from the expected Hardy-Weinberg equilibrium among controls ($P > 0.05$). Of these SNPs, carriers of the GG genotype of rs676210 had significant higher risk of MI [odds ratio (OR) = 1.93, 95% confidence interval (CI): 1.23-3.03] compared with carriers of the major genotype. This association remained statistically significant after further adjustment for age, smoking, hypertension, diabetes and BMI. None of the other SNPs examined was associated with MI.

Five SNPs in the ApoB gene (rs676210-rs2854725-rs11676704-rs3791980-rs2678379) were in linkage disequilibrium with D' ranging from 0.79 to 1.00 and r^2 ranging from 0.06 to 0.87. We found that GTTGG haplotype was significantly associated with increased risk of MI (OR = 2.82, 95% CI: 1.49-5.33) compared with the referent haplotype ATTGA (**Table 3**).

Finally, we investigated the associations between the eight SNPs and plasma apoB levels in 550 healthy controls. In univariate analyses, ApoB rs676210 and rs2678379 were significantly associated with plasma level of apoB ($P = 0.01$ and 0.02). Specifically, carriers of the mutant allele of rs676210 (A/G: 0.85±0.27 g/L; G/G: 0.86±0.21 g/L) had significantly increased plasma apoB levels compared with subjects with AA genotype (0.79±0.18 g/L). A/G (0.85±0.27 g/L) and G/G (0.83±0.21 g/L) genotypes of rs2678379 also conferred elevated level of apoB compared with A/A genotype (0.80±0.18 g/L). When ANCOVA model was applied, the significance remained. None of the other studied SNP was associated with plasma apoB level (**Table 4**).

Discussion

Considering the crucial role of apoB in lipid metabolism, we investigated the association of eight SNPs in this gene and the risk of MI in a Chinese population. Our results showed that rs676210 mutation may increase the risk of MI and plasma apoB levels in healthy controls, and mutant allele of rs2678379 may confer elevated plasma apoB level in our control population.

The human ApoB gene is located on chromosome 2p24-p23. There are two main protein products of ApoB gene, a short version called apolipoprotein B-48 and a longer version known as apolipoprotein B-100, both of which play central roles in human lipoprotein metabolism. So far, certain mutations in the ApoB gene have been found to have relation with

obesity [24], familial hypobetalipoproteinemia (FHBL) [25], coronary heart disease [26], gallstone and gallbladder cancer [27], and etc. Rare mutations in *ApoB* also have profound influence on plasma apoB and LDL-C levels [28].

ApoB rs676210 is a missense mutation involving A to G substitution that results in the conversion of leucine to proline. Studies on rs676210 and risk of lipid metabolic disorders are relatively rare. In an earlier study, rs676210 was found to be strongly associated with plasma VLDL-related fractions, triglycerides, and mean VLDL/LDL size [29]. Chasman et al. [30] also found that the A allele of rs676210 was associated with lower triglyceride, total cholesterol, and LDL cholesterol levels and higher HDL cholesterol levels in comparison with G allele. Recently, a Genome-Wide Association Study (GWAS) showed that rs676210 is an important factor for regulating oxidized low-density lipoprotein (oxLDL) levels, which increases the atherogenic potential of LDL and is regarded as a key event in the development of fatty streaks and the early atherosclerotic lesions [31]. Besides, rs676210 mutation may modify the response of hypertriglyceridemia patients to fenofibrate (a commonly used drug to treat hypertriglyceridemia), as individuals with the TT genotype of rs676210 had greater TG lowering than those with the CC genotype (additive model, P = 0.0017) [32]. In our study, we found that carriers of G allele of rs676210 conferred increased risk of MI and elevated plasma level of apoB, which was in accordance with previous studies. We also found the same trend of association when analyzed the rs676210 mutation in relation with serum LDL-C levels in healthy controls, although it did not reach statistically significance (P = 0.14).

We found another genetic mutation, rs2678379, in ApoB gene was also associated with plasma apoB levels in our population. Rs2678379 was once reported to have an interaction with dietary plasma cholesterol levels by influencing the absorption and transport of dietary cholesterol in Carotid Lesion Epidemiology and Risk (CLEAR) cohort in USA [33]. In our study, rs2678379 is in high linkage disequilibrium with rs676210 (D' = 0.87), and rs2678379 GG genotype showed a non-significant increased risk of MI (OR = 1.43, 95% CI: 0.92-2.21).

The limitations of our study including the hospital-based study design that may not avoid selection bias and recall bias completely; the relatively small sample size may reduce the statistical power of our study; and the results should be confirmed in other prospective cohort studies. Although the exact pathological mechanisms of MI are still unclear, the linkage between ApoB polymorphisms and MI risk and plasma apoB level may provide a possible mechanism that merits further investigation.

In summary, the present study demonstrating that the G allele of the rs676210 may confer increased risk of MI, and rs676210 and rs2678379 may exert effect on plasma apoB levels in Chinese population. Future studies in prospective cohorts as well as functional studies are needed to confirm our findings.

Disclosure of conflict of interest

None.

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References

[1] McDermott MM. The international pandemic of chronic cardiovascular disease. JAMA 2007; 297: 1253-1255.

[2] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015; 131: e29-322.

[3] Kathiresan S and Srivastava D. Genetics of human cardiovascular disease. Cell 2012; 148: 1242-1257.

[4] Brown R, Shantsila E, Varma C, Lip G. 34 Ethnic and Gender Differences in Symptom-to-Door Times in Patients Presenting with St Elevation Myocardial Infarction. Heart 2004; 100: A18.

[5] Kessler T, Erdmann J, Schunkert H. Genetics of coronary artery disease and myocardial infarction--2013. Curr Cardiol Rep 2013; 15: 368.

[6] Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the interheart study): case-control study. Lancet 2004; 364: 937-952.

[7] Scheffold T, Kullmann S, Huge A, Binner P, Ochs HR, Schöls W, Thale J, Motz W, Hegge FJ, Stellbrink C, Dorsel T, Gülker H, Heuer H, Dinh W, Stoll M, Haltern G. Six sequence variants on chromosome 9p21.3 are associated with a positive family history of myocardial infarction: a multicenter registry. BMC Cardiovasc Disord 2011; 11: 9.

[8] Erdmann J, Linsel-Nitschke P, Schunkert H. Genetic causes of myocardial infarction: new insights from genome-wide association studies. Dtsch Arztebl Int 2010; 107: 694-9.

[9] Topol EJ, Smith J, Plow EF, Wang QK. Genetic susceptibility to myocardial infarction and coronary artery disease. Hum Mol Genet 2006; 15: R117-R123.

[10] Gu JY, Li LW. ALDH2 Glu504Lys Polymorphism and Susceptibility to Coronary Artery Disease and Myocardial Infarction in East Asians: A Meta-analysis. Arch Med Res 2014; 45: 76-83.

[11] Wang J, Xu D, Wu X, Zhou C, Wang H, Guo Y, Cao K. Polymorphisms of matrix metalloproteinases in myocardial infarction: a meta-analysis. Heart 2011; 97: 1542-1546.

[12] Girelli D, Martinelli N, Peyvandi F, Olivieri O. Genetic architecture of coronary artery disease in the genome-wide era: implications for the emerging "goldendozen" loci. Semin Thromb Hemost 2009; 35: 671-82.

[13] Malaguarnera M, Vacante M, Russo C, Malaguarnera G, Antic T, Malaguarnera L, Bella R, Pennisi G, Galvano F, Frigiola A. Lipoprotein(a) in cardiovascular diseases. Biomed Res Int 2013; 2013: 650989.

[14] Kane JP, Havel RJ. Disorders of the biogenesis and secretion of lipoproteins containing the B apolipoproteins. In: Kane JP and Havel RJ, editors. New York: McGraw-Hill; 2001. pp. 2717-52.

[15] Schmidt C, Bergström G. Apolipoprotein B/Apolipoprotein A-I Ratio and Apolipoprotein B: Long-Term Predictors of Myocardial Infarction in Initially Healthy Middle-Aged Men-a 13-Year Follow-Up. Angiology 2014; 65: 901-5.

[16] Misciagna G, Logroscino G, De Michele G, Guerra V, Cisternino AM, Caruso MG and Trevisan M. Glycated apolipoprotein B and myocardial infarction. Nutr Metab Cardiovasc Dis 2007; 17: 6-12.

[17] Lamon-Fava S, Jimenez D, Christian JC, Fabsitz RR, Reed T, Carmelli D, Castelli WP, Ordovas JM, Wilson PW, Schaefer EJ. The NHLBI Twin Study: heritability of apolipoprotein A-I, B, and low density lipoprotein subclasses and concordance for lipoprotein (a). Atherosclerosis 1991; 91: 97-106.

[18] Beekman M, Heijmans BT, Martin NG, Pedersen NL, Whitfield JB, DeFaire U, van Baal GC, Snieder H, Vogler GP, Slagboom PE, Boomsma DI. Heritabilities of apolipoprotein and lipid levels in three countries. Twin Res 2002; 5: 87-97.

[19] Tybjarg-Hansen A, Steffensen R, Meinertz H, Schnohr P, Nordestgaard BG. Association of mutations in the apolipoprotein B gene with hypercholesterolemia and the risk of ischemic heart disease. N Engl J Med 1998; 338: 1577-84.

[20] Benn M, Nordestgaard BG, Jensen JS, Nilausen K, Meinertz H, Tybjaerg-Hansen A. Mutation in apolipoprotein B associated with hypobetalipoproteinemia despite decreased binding to the low density lipoprotein receptor. J Biol Chem 2005; 280: 21052-60.

[21] Rose GA and Blackburn H. Cardiovascular survey methods. Monogr Ser World Health Organ 1968; 56: 1-188.

[22] Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005; 21: 263-265.

[23] Lin DY, Zeng D, Millikan R. Maximum likelihood estimation of haplotype effects and haplotype-environment interactions in association studies. Genet Epidemiol 2005; 29: 299-312.

[24] Doo M, Won S, Kim Y. Association between the APOB rs1469513 polymorphism and obesity is modified by dietary fat intake in Koreans. Nutrition 2015; 31: 653-8.

[25] Tarugi P and Averna M. Hypobetalipoproteinemia: genetics, biochemistry, and clinical spectrum. Adv Clin Chem 2011; 54: 81-107.

[26] Huang G, Zhong H, Re HM, Mao HW, Niu Q, Chi YH. Coalition of DNA polymorphisms of ApoB and ApoAI genes is related with coronary artery disease in Kazaks. J Geriatr Cardiol 2012; 9: 33-7.

[27] Gong Y, Zhang L, Bie P, Wang H. Roles of ApoB-100 gene polymorphisms and the risks of gallstones and gallbladder cancer: a meta-analysis. PLoS One 2013; 8: e61456.

[28] Benn M. Apolipoprotein B levels, APOB alleles, and risk of ischemic cardiovascular disease in the general population, a review. Atherosclerosis 2009; 206: 17-30.

[29] Chasman DI, Paré G, Mora S, Hopewell JC, Peloso G, Clarke R, Cupples LA, Hamsten A, Kathiresan S, Mälarstig A, Ordovas JM, Ripatti S, Parker AN, Miletich JP, Ridker PM. Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis. PLoS Genet 2009; 5: e1000730.

[30] Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H,Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 2010; 466: 707-713.

[31] Mäkelä KM, Seppälä I, Hernesniemi JA, Lyytikäinen LP, Oksala N, Kleber ME, Scharnagl H, Grammer TB, Baumert J, Thorand B, Jula A, Hutri-Kähönen N, Juonala M, Laitinen T, Laaksonen R, Karhunen PJ, Nikus KC, Nieminen T, Laurikka J, Kuukasjärvi P, Tarkka M, Viik J, Klopp N, Illig T, Kettunen J, Ahotupa M, Viikari JS, Kähönen M, Raitakari OT, Karakas M, Koenig W, Boehm BO, Winkelmann BR, März W, Lehtimäki T. Genome-wide association study pinpoints a new functional apolipoprotein B variant influencing oxidized low-density lipoprotein levels but not cardiovascular events: AtheroRemo Consortium. Circ Cardiovasc Genet 2013; 6: 73-81.

[32] Wojczynski MK, Gao G, Borecki I, Hopkins PN, Parnell L, Lai CQ, Ordovas JM, Chung BH, Arnett DK. Apolipoprotein B genetic variants modify the response to fenofibrate: a GOLDN study. J Lipid Res 2010; 51: 3316-3323.

[33] Kim DS, Burt AA, Ranchalis JE, Jarvik ER, Rosenthal EA, Hatsukami TS, Furlong CE, Jarvik GP. Novel gene-by-environment interactions: APOB and NPC1L1 variants affect the relationship between dietary and total plasma cholesterol. J Lipid Res 2013; 54: 1512-1520.