Int J Clin Exp Pathol 2017;10(1):804-810
www.ijcep.com /ISSN:1936-2625/IJCEP0039729

Original Article

CDKN2BAS polymorphisms are associated with coronary artery disease in Chinese Han population

Xiaoli Li[1*], Huijun Ma[2*], Fei Li[1], Yizhou Li[3], Zhilan Xie[4,5], Huaisheng Bai[1], Bo Gao[1], Qian Liang[1], Feng Gao[1], Tianbo Jin[4,5]

[1]Department of The Cardiology, Yan'an University Affiliated Hospital, Yan'an, China; [2]Department of Cardiology, The First Hospital of Xi'an, Xi'an, China; [3]Inner Mongolia Medical University, Hohhot, Inner Mongolia, China; [4]Key Laboratory of Resource Biotechnology in Western China (Northwest University), Ministry of Education, School of Life Sciences, Northwest University, Xi'an, Shaanxi, China; [5]Xi'an Tiangen Precision Medical Institute, Xi'an, Shaanxi, China. [*]Equal contributors and co-first authors.

Received September 9, 2016; Accepted November 1, 2016; Epub January 1, 2017; Published January 15, 2017

Abstract: Background: Previous studies have identified various SNPs in *CDKN2BAS* gene that influence the risk of developing coronary artery disease (CAD). In our study, we evaluated the association between *CDKN2BAS* polymorphisms and CAD risk in the Chinese Han population. Methods: In our study, among 1,141 participants (456 CAD patients, and 685 normal individuals), eight single nucleotide polymorphisms within the *CDKN2BAS* loci were genotyped and examined for their correlation with the risk of CAD and treatment response using Pearson's χ^2 test and unconditional logistic regression analysis. Results: Overall, the strongest associations were found between rs10757274 in *CDKN2BAS* gene with the risk of CAD in the allele model (P=0.013). Moreover, we discovered a notable association between SNP rs10757274 and CAD in co-dominant, dominant and log-additive models (P=0.027, P=0.008, P=0.013 respectively). The results, adjusted by confounding factors, were also significant in co-dominant, dominant models (P=0.015, P=0.045 respectively). Moreover, the haplotypes "AA" and "AG" exhibited a protective factors for the risk of CAD after adjusted for age and gender (P=0.013, P=0.034 respectively). Conclusion: We found a remarkable association between rs10757274 and CAD in the Chinese Han population.

Keywords: Coronary artery disease (CAD), *CDKN2BAS*, polymorphism

Introduction

Coronary artery disease (CAD) is the most cause of human death in the European countries and Asian countries especially containing China [1]. CAD comes to be a complex disease caused by a combination of genetic and environmental factors [2]. Over the past years, much progress has been made in the pharmacotherapy of major risk factors like dyslipidemias, diabetes mellitus and hypertension [3]. Clinical observation has found that all of the risk factors result in the induction of atherosclerosis, which is one of the major pathophysiological mechanisms of CAD [4]. Recently, genome-wide association studies of the relations between single nucleotide polymorphisms (SNPs) and CAD risk have been focused to identify the cause of the CAD [5], and also found a relationship between *CDKN2BAS* gene and CAD risk [6].

CDKN2BAS gene is a large antisense non-coding RNA, which is differentially expressed in a variety of tissues such as vascular endothelial cells and smooth coronary muscle cells [7, 8]. Non-coding RNAs are involved in the regulation of gene expression through transcriptional and translational control. *CDKN2BAS* expression is shown to be associated with multiple phenotypes comprising the risk of coronary disease [9]. Interestingly, *CDKN2BAS* expression has been shown to be regulated by a CAD-associated genetic variant. Regulation of cardiac *CDKN2BAS* expression has been found to play a pivotal role in the development of CAD by altering the dynamics of vascular cell proliferation [10]. Moreover, evidence has shown that *CDKN2BAS* gene variants are associated with CAD [11]. *CDKN2BAS* may serve as a biomarker for the risk of myocardial infarction and hemorrhagic stroke, and their recurrence [12-14].

Table 1. The characteristic of controls and cases in this study

Characteristic	Case (n=456)	Control (n=685)	*P*
Sex, N (%)			0.01[a]
Female	165 (36.2%)	300 (43.8%)	
Male	291 (63.8%)	385 (56.2%)	
Age (Mean Age ± SD)	61.17±11.86	48.59±9.556	<0.001[b]

P[a] value was calculated by Pearson's Chi-square test. *P*[b] value was calculated by Welch's t test. P<0.05 indicates statistical significance.

And common variants of *CDKN2BAS* are shown to be associated with myocardial infarction (MI) in European whites and Hispanic population [15, 16].

In Chinese population, *CDKN2BAS* gene variants are related to Type 2 diabetes risk [17]. However, there is a lack of investigation for the association between polymorphism of *CDKN2BAS* gene and CAD risk in Han Chinese. The purpose of the present case-control study was to identify the association between eight high frequency SNPs *CDKN2BAS* of and CAD risk in Han Chinese.

Materials and methods

Study population

All of the cases and control individuals were the members of the Chinese Han population. The control participants and CAD cases were recruited between 2013 and 2015 from Yan'an University Affiliated Hospital and the First Hospital of Xi'an. This case-control study strictly obeyed the principles of the Declaration on Helsinki of the World Medical Association and got the permission from the Ethics Committee of Yan'an University Affiliated Hospital, the First Hospital of Xi'an, Inner Mongolia Medical University and Northwest University. All of the participants were informed the case-control study and their consent were obtained.

Demographic information

We used a standard epidemiological questionnaire and in-person interview to collect personal data, including the residential regions; age; gender; histories of medication use. The case information was collected through a consultation with the treating physicians or from a medical chart review. All of the participants signed an informed consent agreement.

Selection of SNPs and methods of genotyping

According to the previous reports, we selected eight SNPs for this study and they were rs7865618, rs11790231, rs1412832, rs6475606, rs1333040, rs1537370, rs10757274 and rs1333042. The minor allele frequencies of these SNPs were >5% in the Hap Map of the Chinese Han Beijing (CHB) population. The procedure included DNA extraction and genotyping. Extraction of DNA from whole blood samples was performed using the Gold Mag-Mini Whole Blood Genomic DNA Purification Kits (Gold Mag Co., Ltd.; Hainan City, China), and the DNA concentration was measured using a Nano Drop 2000 spectrophotometer.

Genotyping steps include PCR and single base extension. Firstly, we designed primers for amplification and extension reactions using Sequenom Mass ARRAY Assay Design 3.0 Software (Sequenom Inc., San Diego, CA, USA) (**Table 1**). Then, Genotyping was performed using the Sequenom Mass ARRAY RS1000 system and the standard protocol recommended by the manufacturer. After the experimentation progress mentioned above, data management and analysis was conducted using Sequenom Typer4.0 software [18, 19].

Statistical analysis

We used Microsoft Excel and SPSS 18.0 statistical package (SPSS, Chicago, IL, USA) to perform statistical analyses. In our study, all *P*-values were based on two-sided tests and we achieved P≤0.05 among all the *p* values as the threshold of statistical significance. The validation of each SNP frequency in control subjects was tested for departure from Hardy-Weinberg Equilibrium (HWE) using an exact test. In order to clearly evaluated the association between the polymorphism of eight SNPs and CAD risk, the method of the chi-square test was used to calculate the difference in genotype frequencies between case and control [20]. Furthermore, five genetic models (allele, co-dominant, dominant, recessive and log-additive model) were used to test the association of certain SNPs with the risk of CAD.

Finally, the SHEsis software platform (http://www.nhgg.org/analysis) and Haploview soft-

Table 2. The basic information of SNPs in *CDKN2BAS* gene

Gene	SNP No.	Chromosome	Location	Allele	MAF in case group	MAF in control group	HWE p^a	P^b-value	O (HET)
CDKN2BAS	rs7865618	9p21.3	Intron	G/A	0.124	0.120	1	0.789	0.212
	rs11790231	9p21.3	Intron	A/G	0.148	0.150	0.369	0.882	0.265
	rs1412832	9p21.3	Intron	C/T	0.264	0.285	0.707	0.264	0.415
	rs6475606	9p21.3	Intron	C/T	0.285	0.300	0.318	0.431	0.437
	rs1333040	9p21.3	Intron	C/T	0.281	0.294	0.41	0.507	0.429
	rs1537370	9p21.3	Intron	C/T	0.284	0.298	0.236	0.477	0.438
	rs10757274	9p21.3	Intron	G/A	0.474	0.421	0.696	0.013*	0.480
	rs1333042	9p21.3	Intron	A/G	0.315	0.347	0.735	0.117	0.447

SNPs: Single nucleotide polymorphisms; A: Miner alleles, B: Major alleles; MAF: Minor allele frequency; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio. CI: Confidence interval; p^a: *p* value was calculated using exact test; p^b: *p* value was calculated using Chi-square test; *P<0.05 indicates statistical significance.

ware package (version 4.2) were used to analyze the association between haplotypes and risk of CAD [21, 22]. Control samples were used to the haplotype construction. The linkage disequilibrium degree of the Two SNPs is measured by D' value, and D' confidence interval is used to divide haplotype block. The D' value is close to 1, the level of linkage disequilibrium between the loci is stronger. For the LD plot, the color of the box reflects the strength of the linkage disequilibrium, and that darker shades of red indicate higher D' display statistically significant associations between a pair of SNPs. To make the information more valuable, unconditional logistic regression analysis with adjustment for age and gender was performed to test odds ratios (ORs) and 95% confidence intervals (CIs) [23].

Results

We conducted a case-control study, 456 patients and 685 normal individuals enrolled, to identify association between *CDKN2BAS* polymorphisms and CAD. All candidates SNPs in *CDKN2BAS* gene were in accordance with 5% HWE *P* level. The associations between risk alleles and the susceptibility of CAD were all performed by chi-squared analysis. All of the results are shown in **Table 2**. The result showed that risk alleles "G" of rs10757274 had a significant relevance to CAD risk (P=0.013).

We assumed that the minor allele of each SNP was a risk factor compared with the wild-type allele. Five genetic analysis models, co-dominant, dominant, recessive, over-dominant and log-additive were applied in order to analyze the associations between SNPs and CAD risks using the logistic test. We discovered an association regarding increased risks between SNP rs11790231 and CAD in Recessive model (OR=2.16, 95% CI=1.02-4.57, P=0.042 for A/A), however, the results mentioned about rs11790231 were not remarkable while calculated using the unconditional logistic regression analyses adjusted for age and gender. That another SNP rs1075274 was found had a notably increased the risk of CAD under Dominant model (OR=1.42, 95% CI=1.09-1.84, P=0.008 for A/G-G/G), and the "G" risk allele could increase 1.5 fold and 1.24 fold CBD risk under Co-dominant model and Log-additive model (Co-dominant model OR=1.5, 95% CI=1.06-2.12, P=0.027; Log-additive model OR=1.24, 95% CI=1.05-1.47, P=0.013); furthermore, we also found the significant difference under Co-dominant model and Dominant model after adjusted for gender and age (Co-dominant model OR=1.69, 95% CI=1.12-2.55, P=0.015; Dominant model OR=1.56, 95% CI=1.14-2.12, P=0.045) (**Table 3**).

Pairwise LD analysis was performed for the *CDKN2BAS* gene using the polymorphisms detected in this study. The pattern of LD was analyzed using two parameters, r^2 and D'. Two main linkage blocks were observed across the locus (**Figure 1**). Block1 was constituted by four closely linked SNPs: rs1412832, rs6475606, rs1333040, rs1537370. Then, the association between inferred haplotypes and CAD risk among the individuals was analyzed. We found no risk haplotype in block1. Block2 was constituted by two closely linked SNPs: rs10757274, rs1333042. Protective factors was confirmed by logistic analysis adjusted for age and gender

Table 3. Logistic regression analysis of the association between SNPs and risks of CHD

SNP No.	Model	Genotype	OR[a] (95% CI)	*P*[a]	OR[b] (95% CI)	*P*[b]
rs11790231	Co-dominant	G/G	1		1	
		A/G	0.81 (0.61-1.07)	0.04	0.90 (0.65-1.25)	0.36
		A/A	2.05 (0.97-4.35)		1.72 (0.72-4.11)	
	Dominant	G/G	1		1	
		A/G-A/A	0.88 (0.68-1.16)	0.37	0.96 (0.70-1.32)	0.81
	Recessive	G/G-A/G	1		1	
		A/A	2.16 (1.02-4.57)	0.042*	1.76 (0.74-4.20)	0.2
	Over-dominant	G/G-A/A	1		1	
		A/G	0.79 (0.60-1.04)	0.091	0.88 (0.64-1.23)	0.46
	Log-additive	---	0.98 (0.78-1.24)	0.88	1.03 (0.78-1.35)	0.84
rs10757274	Co-dominant	A/A	1		1	
		A/G	1.39 (1.05-1.83)	0.027*	1.51 (1.09-2.09)	0.015*
		G/G	1.50 (1.06-2.12)		1.69 (1.12-2.55)	
	Dominant	A/A	1		1	
		A/G-G/G	1.42 (1.09-1.84)	0.008*	1.56 (1.14-2.12)	0.045*
	Recessive	A/A	1		1	
		A/G-G/G	1.22 (0.91-1.64)	0.19	1.31 (0.92-1.86)	0.14
	Over-dominant	A/A-G/G	1		1	
		A/G	1.18 (0.93-1.50)	0.17	1.23 (0.93-1.62)	0.15
	Log-additive	---	1.24 (1.05-1.47)	0.013*	1.32 (1.08-1.61)	0.066

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. OR[a] and *P*[a] without adjustment; OR[b] and *P*[b] adjusted for gender and age. *: *P*<0.05 indicates statistical significance.

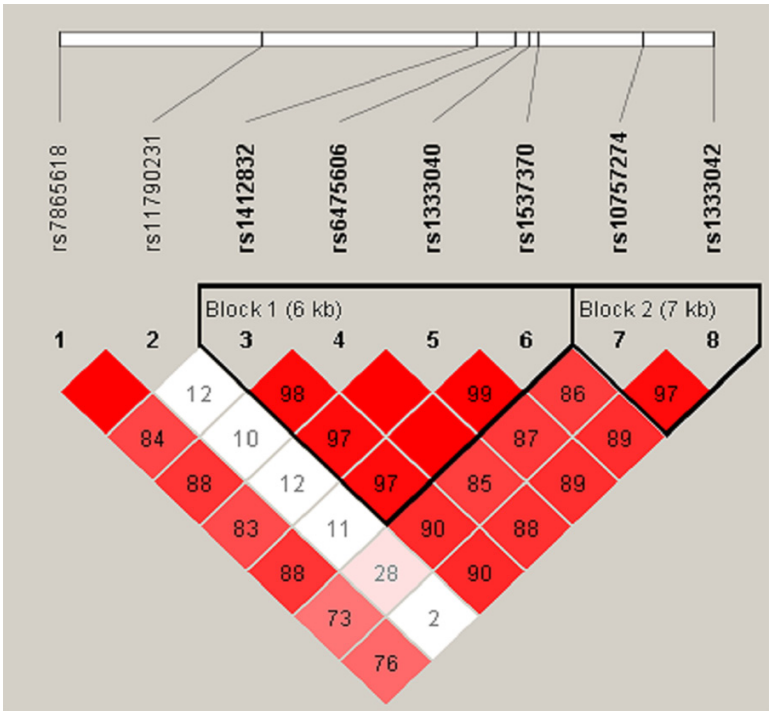

Figure 1. Haplotype block map for part of the SNPs in the *CDKN2BAS* gene. Linkage disequilibrium plots containing five SNPs from 9p21.3. Standard color frame is used to show LD pattern. Two blocks in the figure showed higher LD. Block1 includes rs1412832, rs6475606, rs1333040 and rs1537370. Block2 includes rs10757274, rs1333042. That darker shades of red indicate higher D' and display statistically significant associations between a pair of SNP.

between the haplotypes "AA" "AG" of this two SNPs in block2 and CAD risk (haplotype: AA OR=0.75, 95% CI=0.6-0.94, P=0.013; haplotype: AG OR=0.75, 95% CI=0.58-0.98, P=0.034) (**Table 4**).

Discussion

The goal of our case-control study was to explore the significant association of *CDKN2BAS* polymorphism with the risk of CAD in Han Chinese. Our results showed that rs10757274 was significantly associated with CAD. Interestingly, this SNP was more likely to increase the risk of CAD under the co-dominant mode and Dominant model (P<0.05). Furthermore, the major allele "A" of rs10757274 might significantly decreased the CAD risk in haplotypes model by logistic analysis adjusted for age and gender (P<0.05).

Table 4. Multiple genes haplotype frequencies and the association with the risk of CHD

SNPs	Haplotype	Freq. (case)	Freq. (control)	OR[a] (95% CI)	*P*[a]-value	OR[b] (95% CI)	*P*[b]-value
rs1412832|rs6475606|rs1333040|rs1537370	TTTT	0.711	0.697	1	---	1	---
	CCCC	0.256	0.279	0.90 (0.74-1.09)	0.29	0.84 (0.67-1.05)	0.13
	TCCC	0.024	0.015	1.64 (0.88-3.06)	0.12	1.68 (0.79-3.56)	0.18
rs10757274|rs1333042	GG	0.469	0.417	1	---	1	---
	AA	0.312	0.343	0.81 (0.66-0.98)	0.03*	0.75 (0.60-0.94)	0.013*
	AG	0.215	0.236	0.81 (0.65-1.01)	0.057	0.75 (0.58-0.98)	0.034*

OR, odds ratio; CI, confidence interval; OR[a] and *P*[a] were calculated without adjustment; OR[b] and *P*[b] were calculated with adjusted for gender and age. *: *P*<0.05 indicates statistical significance.

SNP rs10757274 on chromosome 9p21.3 is located in *CDKN2BAS* (also known as *ANRIL*). *CDKN2BAS* has been known to be involved in regulating the expression of *CDKN2A* and *CDKN2B* genes, and these two genes can encode cyclin dependent kinase inhibitors which could block cell division. Though the exact function of *CDKN2BAS* is still unknown, the transcript level of this gene shows close connection with the severity of atherosclerosis [8]. Many statistics showed the modulation of *CDKN2BAS* gene expression mediates susceptibility to some fearful human diseases such as CAD and pediatric brain tumor cancer so on [24]. All the evidences above have demonstrated that *CDKN2BAS* is a new susceptibility gene for the risk of CAD. Thus, we explored the association between *CDKN2BAS* gene polymorphism with CAD risk, and the results exhibited that SNP rs10757274 of *CDKN2BAS* has increased the risk of CAD in Chinese Han population.

SNP rs10757274 of *CDKN2BAS* has been considered as a risk locus for CAD and MI in ethnic Arabs, and this finding provide further insights into pathways contributing to the susceptibility for CAD [25]. Moreover, evidence has showed that SNP rs10757274, which has been found to predict CAD risk in Whites, was added to traditional risk factors modestly predict the CAD risk from Atherosclerosis Risk in Communities (AROC) study in Whites [26]. At the same time, this SNP were also strongly associated with early-onset CAD in the Irish population ($P= 2.7\times10^{-6}$) [27]. SNP rs10757274 polymorphism locus is near to the cyclin dependent kinase N2A and N2B which showed an additional association with CAD in a GWAS study, and the patients homozygous for "G" allele of rs10757-274 was confirmed increased the CAD risk compared to the patients at least one allele of this polymorphism (P<0.001) [28]. All the reports verified that rs10757274, an important polymorphism SNP locus, had a related association with CAD risk, and we also found this connection in Chinese Han population.

Despite the current study possessing enough energy, some limitations were inherent in the case-control study. Firstly, because our 1,141 participants (456 CAD patients, and 685 normal individuals) were not relatively large among CAD association studies published to date. The negative results of major SNPs in this study may convert into positive ones when we increase the sample size of CAD, which may drive the conclusion more powerful. In this case-control study, many blood biochemical indicators of case patients were detected, containing serum total cholesterol, serum triglyceride, high density lipoprotein cholesterol and low density lipoprotein cholesterol so on. According to different genotypes of different SNP locus, all the indicators were classified and analyzed, whereas no significant difference existed and we did not exhibited these results in this paper. So, if the sample size is big enough, the difference may appear. But this did not affect our results.

Conclusions

In conclusion, we provided new evidence for the association between one SNP rs17057274 of the *CDKN2BAS* gene and CAD. These findings indicate that genetic variants of the *CDKN2BAS* gene play an intricate role in the development of CAD, and that interactions of loci in the *CDKN2BAS* gene may be more important than a single locus. This study offers important insights into the etiology of CAD in Chinese Han population.

Acknowledgements

We thank all the patients and individuals for their participation and all the physicians and nurses of Yan'an University Affiliated Hospital and The First Hospital of Xi'an, for their offers the blood samples.

Disclosure of conflict of interest

None.

Address correspondence to: Tianbo Jin, School of Life Sciences, Northwest University, Mailbox 386, 229 North Taibai Road, Xi'an 710069, Shaanxi, China. Tel: +86-29-88302831; E-mail: jintb@nwu.edu.cn; Feng Gao, Department of The Cardiology, Yan'an University Affiliated Hospital, #43 North Road, Yan'an 716000, Shaanxi, China. Tel: +86-0911-8895139; E-mail: gaofengyd@hotmail.com

References

[1] Chien KL, Hsu HC, Su TC, Chang WT, Chen PC, Sung FC, Lin HJ, Chen MF and Lee YT. Constructing a point-based prediction model for the risk of coronary artery disease in a Chinese community: a report from a cohort study in Taiwan. Int J Cardiol 2012; 157: 263-268.

[2] Kangas-Kontio T, Huotari A, Ruotsalainen H, Herzig KH, Tamminen M, Ala-Korpela M, Savolainen MJ and Kakko S. Genetic and environmental determinants of total and high-molecular weight adiponectin in families with low HDL-cholesterol and early onset coronary heart disease. Atherosclerosis 2010; 210: 479-485.

[3] Kibos A and Guerchicoff A. Susceptibility genes for coronary heart disease and myocardial infarction. Acute Card Care 2011; 13: 136-142.

[4] Zhou JP, Bai YP, Hu XL, Kuang DB, Shi RZ, Xiong Y, Zhang W, Xia J, Chen BL, Yang TL and Chen XP. Association of the AGXT2 V140I polymorphism with risk for coronary heart disease in a Chinese population. J Atheroscler Thromb 2014; 21: 1022-1030.

[5] Bressler J, Folsom AR, Couper DJ, Volcik KA and Boerwinkle E. Genetic variants identified in a European genome-wide association study that were found to predict incident coronary heart disease in the atherosclerosis risk in communities study. Am J Epidemiol 2010; 171: 14-23.

[6] Huang Y, Ye H, Hong Q, Xu X, Jiang D, Xu L, Dai D, Sun J, Gao X and Duan S. Association of CDKN2BAS polymorphism rs4977574 with coronary heart disease: a case-control study and a meta-analysis. Int J Mol Sci 2014; 15: 17478-17492.

[7] Jarinova O, Stewart AF, Roberts R, Wells G, Lau P, Naing T, Buerki C, McLean BW, Cook RC, Parker JS and McPherson R. Functional analysis of the chromosome 9p21.3 coronary artery disease risk locus. Arterioscler Thromb Vasc Biol 2009; 29: 1671-1677.

[8] Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Mohlke KL, Ibrahim JG, Thomas NE and Sharpless NE. INK4/ARF transcript expression is associated with chromosome 9p21 variants linked to atherosclerosis. PLoS One 2009; 4: e5027.

[9] Pasmant E, Sabbagh A, Vidaud M and Bièche I. ANRIL, a long, noncoding RNA, is an unexpected major hotspot in GWAS. FASEB J 2011; 25: 444-448.

[10] Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, Uitterlinden AG, Harris TB, Witteman JC and Boerwinkle E. Cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet 2009; 2: 73-80.

[11] Mcpherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio L, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH and Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. Science 2007; 316: 1488-1491.

[12] Tang Y and Zhang W. Variants on chromosome 9p21.3 correlated with ANRIL expression contribute to stroke risk and recurrence in a large prospective stroke population. Stroke 2012; 43: 14-21.

[13] Lotta LA. Genome-wide association studies in atherothrombosis. Eur J Intern Med 2010; 21: 74-78.

[14] Goncharova IA, Makeeva OA, Golubenko MV, Markov AV, Tarasenko NV, Sleptsov AA and Puzyrev VP. Genes for fibrogenesis in the determination of susceptibility to myocardial infarction. Mol Biol (Mosk) 2016; 50: 94-105.

[15] Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, König IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR and Schunkert H. Genomewide association analysis of coronary artery disease. N Engl J Med 2007; 357: 443-453.

[16] Qi L, Ma J, Qi Q, Hartiala J, Allayee H and Campos H. Genetic risk score and risk of myocardial infarction in Hispanics. Circulation 2011; 123: 374-380.

[17] Kong X, Xing X, Hong J, Zhang X and Yang W. Genetic variants associated with lean and obese type 2 diabetes in a Han Chinese population: a case-control study. Medicine 2016; 95: e3841.
[18] Gabriel S, Ziaugra L and Tabbaa D. SNP genotyping using the sequenom MassARRAY iPLEX platform. Curr Protoc Hum Genet 2009; Chapter 2: Unit 2.12.
[19] Thomas RK, Baker AC, Debiasi RM, Winckler W, Laframboise T, Lin WM, Wang M, Feng W, Zander T, Macconaill Lee JC, Nicoletti R, Hatton C, Goyette M, Girard L, Majmudar K, Ziaugra L, Wong KK, Gabriel S, Beroukhim R, Peyton M, Barretina J, Dutt A, Emery C, Greulich H, Shah K, Sasaki H, Gazdar A, Minna J, Armstrong SA, Mellinghoff IK, Hodi FS, Dranoff G, Mischel PS, Cloughesy TF, Nelson SF, Liau LM, Mertz K, Rubin MA, Moch H, Loda M, Catalona W, Fletcher J, Signoretti S, Kaye F, Anderson KC, Demetri GD, Dummer R, Wagner S, Herlyn M, Sellers WR, Meyerson M and Garraway LA. High-throughput oncogene mutation profiling in human cancer. Nat Genet 2007; 39: 347-351.
[20] Adamec C. Example of the use of the nonparametric test. Test X^2 for comparison of 2 independent examples. Cesk Zdrav 1964; 12: 613-619.
[21] Barrett JC, Fry B, Maller J and Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005; 21: 263-265.
[22] Shi YY and He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005; 15: 97-98.
[23] Bland JM and Altman DG. The odds ratio. BMJ 2000; 320: 381-382.
[24] Fahmideh MA, Lavebratt C, Schüz J, Röösli M, Tynes T, Grotzer MA, Johansen C, Kuehni CE, Lannering B, Prochazka M, Schmidt LS and Feychting M. CCDC26, CDKN2BAS, RTEL1 and TERT polymorphisms in pediatric brain tumor susceptibility. Carcinogenesis 2015; 36: 876-882.
[25] Wakil SM, Ram R, Muiya NP, Mehta M, Andres E, Mazhar N, Baz B, Hagos S, Alshahid M, Meyer BF, Morahan G and Dzimiri N. A genome-wide association study reveals susceptibility loci for myocardial infarction/coronary artery disease in Saudi Arabs. Atherosclerosis 2016; 245: 62-70.
[26] Brautbar A, Ballantyne CM, Lawson K, Nambi V, Chambless L, Folsom AR, Willerson JT and Boerwinkle E. Impact of adding a single allele in the 9p21 locus to traditional risk factors on reclassification of coronary heart disease risk and implications for lipid-modifying therapy in the atherosclerosis risk in communities study. Circ Cardiovasc Genet 2009; 2: 279-285.
[27] Meng W, Hughes AE, Patterson CC, Belton C, Kee F and Mckeown PP. Chromosome 9p21.3 is associated with early-onset coronary heart disease in the Irish population. Dis Markers 2008; 25: 81-85.
[28] Van der Net JB, Oosterveer DM, Versmissen J, Defesche JC, Yazdanpanah M, Aouizerat BE, Steyerberg EW, Malloy MJ, Pullinger CR, Kastelein JJ, Kane JP and Sijbrands EJ. Replication study of 10 genetic polymorphisms associated with coronary heart disease in a specific high-risk population with familial hypercholesterolemia. Eur Heart J 2008; 29: 2195-2201.