Int J Clin Exp Med 2017;10(3):5414-5421
www.ijcem.com /ISSN:1940-5901/IJCEM0042145

Original Article

Significant association of CXCL12 rs501120 with coronary artery disease and atorvastatin therapy

Guodong Xu, Lebo Sun, Dawei Zheng, Ni Li, Qiaoling Pan, Huoshun Shi, Bingchuan Hu, Guofeng Shao

Department of Thoracic & Cardiovascular Surgery, Lihuili Hospital, Ningbo Medical Center, Affiliated Hospital of Medical School of Ningbo University, NO. 57 Xingning Road, Ningbo 315041, China

Received August 25, 2016; Accepted December 10, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: Recent genome-wide association studies have shown that the chemokine C-X-C motif ligand 12 (CXCL12) is a susceptible biomarker for coronary artery disease (CAD) in Europeans. In this study, we investigated the possible association between *CXCL12* rs501120 and CAD risk in Han Chinese subjects. Five hundred patients with newly diagnosed, coronary angiography-confirmed CAD and five hundred age- and gender-matched control subjects were included in this study. The Mass-ARRAY iPLEX® assay platform was used for genotyping. The results showed that rs501120 was significantly related to CAD risk in Han Chinese (allele: P = 0.008; OR = 1.29, 95% CI = 1.07-1.55, Power = 75.6%; recessive model: P = 0.003, OR = 1.78, 95% CI = 1.21-2.62, Power = 84.2%). A significant association of *CXCL12* rs501120 with CAD was only found in males (genotype: P = 0.012; allele: P = 0.025; OR = 1.36, 95% CI = 1.04-1.77, Power = 61.7%; recessive model: P = 0.002. OR = 2.32, 95% CI = 1.32-4.08, Power = 84.9%). Moreover, rs501120 was likely to exert its effect in males aged older than 65 years ((genotype: P = 0.017; allele: P = 0.046; OR = 1.45, 95% CI = 1.01-2.11, Power = 50.3%). CAD patients with rs501120-GG showed a negative response for the levels of triglyceride (P > 0.05) and high-density lipoprotein-C (P > 0.05) before and after atorvastatin therapy. Thus, the results suggest that *CXCL12* rs501120 is significantly associated with CAD risk in Han Chinese males aged 65 years and older. Additionally, *CXCL12* rs501120-GG may affect the response to atorvastatin therapy by affecting the concentrations of triglycerides and high-density lipoprotein-C in CAD patients.

Keywords: CXCL12, rs501120, coronary artery disease, atorvastatin

Introduction

Coronary artery disease (CAD) is the leading cause of death in developing and developed countries [1]. The prevalence and incidence of CAD is increasing in Asian countries, including China [2]. CAD is a complex disease resulting from the interaction of several genetic and environmental factors such as unhealthy lifestyles and psychosocial factors [3]. Although extensive efforts [4] have been made to identify genetic factors related to the susceptibility for CAD development, the underlying mechanisms remain unclear [5].

The C-X-C motif ligand 12 (CXCL12) is a chemokine protein in humans that can direct the formation of large blood vessels during embryogenesis [6]. CXCL12 plays an important role in angiogenesis by recruiting endothelial progenitor cells from the bone marrow [7]. Previous studies suggested that CXCL12 plays a role in recruiting leucocytes in response to vascular injuries [8] and is involved in atherosclerosis in rodent models [9]. Several genome-wide association studies (GWAS) have revealed that *CXCL12* variants are genetic susceptibility loci for CAD risk [10]. GWAS confirmed that two highly replicated single-nucleotide polymorphisms (SNPs) of CXCL12 (rs1746048 and rs501120) increased the CAD risk in Europeans [11]. These two SNPs showed high linkage disequilibrium (LD) with each other [12]. However, the results for these SNPs were not consistent. Particularly, the results in different ethnicities are controversial. A recent study reported that *CXCL12* rs1746048 was significantly associated with CAD risk in Chinese subjects aged 65 years or older [13]. Gender analysis showed that rs1746048 was likely a CAD risk factor in males. However, another replication study indicated that *CXCL12* rs501120 was associated

Table 1. Comparison of characteristics between cases and controls#

Character	Control (500)	CAD (500)	P
Age	52.98±10.67	53.88±15.75	0.841
Man (n)	250	250	1.000
TG (mmol/L)	1.47±0.83	3.21±1.01	< 0.001
TC (mmol/L)	4.33±1.02	6.28±1.11	< 0.001
HDL-C (mmol/L)	1.34±0.31	1.04±0.68	< 0.001
LDL-C (mmol/L)	2.45±0.76	3.16±0.98	< 0.001

#: There were 102 patients with smoking and drinking, 69 patients with hypertension and 39 patients with diabetes. The *P* values were adjusted by smoking, drinking, hypertensions and diabetes.

with coronary atherosclerosis only in Han Chinese females [14]. Liyun et al. found rs501120-CC was associated with CAD in people younger than 60 years, but the results showed no significant difference between the frequency of rs501120 genotypes and CAD risk [15]. A study by López-Mejías [16] revealed no association between the *CXCL12* rs501120 polymorphism and cardiovascular disease in 1321 Spanish patients.

In this study, we recruited 500 angiography-confirmed CAD patients and 500 age- and gender-matched controls and performed a case-control analysis to validate the contribution of *CXCL12* rs501120 to CAD risk in Han Chinese. A total of 432 CAD patients were compared to determine blood lipid levels before and after one month of atorvastatin therapy according to the *CXCL12* rs501120 genotypes.

Material and methods

Subjects

The present retrospective case-control study consisted of 500 patients with newly diagnosed and coronary angiography-confirmed CAD and 500 age- and gender-matched control subjects. All subjects were recruited randomly between October 2014 and December 2015 from the Lihuili Hospital in Ningbo city. All individuals with congenital heart disease, cardiomyopathy, and liver and renal disease were excluded. Blood samples from 432 CAD patients were collected to compare blood lipid levels before and after one month of atorvastatin therapy according to the genotypes. The study protocol was approved by the Institutional Research Ethics Committee.

The present retrospective case-control study consisted of 500 patients with newly diagnosed and coronary angiography-confirmed CAD and 500 age- and gender-matched control subjects. All subjects were recruited randomly between October 2014 and December 2015 from the Lihuili Hospital in Ningbo city. All individuals with congenital heart disease, cardiomyopathy, and liver and renal disease were excluded. Blood samples from 432 CAD patients were collected to compare blood lipid levels before and after one month of atorvastatin therapy according to the genotypes. The study protocol was approved by the Institutional Research Ethics Committee.

Biochemical variables

Five milliliters of venous blood samples were collected from each subject, added to 3.2% citrate sodium-treated tubes, processed in the central clinical laboratory of the hospital, and stored at -20°C. Lipid profiles in patients with different genotypes were compared before and after one month of atorvastatin therapy. Plasma levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an enzymatic end-point assay [17].

Single-nucleotide polymorphism genotyping

Total genomic DNA was isolated from peripheral blood leukocytes using the salting out procedure [21]. Polymerase chain reaction (PCR) amplification was performed on the GeneAmp® PCR System 9700 (Applied Biosystems, Foster City, CA, USA) and genotyping was performed on the Mass-ARRAY iPLEX® assay platform (Sequenom, San Diego, CA, USA). The genotype system used in the present study had been described previously [13, 18].

Statistical analysis

Genotype distribution was analyzed by Pearson's chi-square test and Hardy-Weinberg equilibrium. Discrete data were compared using Pearson's chi-square test or Fisher's exact test. Quantitative data were compared using one-way analysis of variance or the Kruskal Wallis test. The odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to test the association between risk fac-

Table 2. Distribution comparison of *CXCL12* gene rs501120 polymorphism between CAD and control groups

Gender	Group	Genotype (n)			χ^2	P (df = 2)	HWE	Allele (n)		χ^2	P (df = 1)	OR (95% CI)	Power
		AA	AG	GG				A	T				
All	Control (N = 500)	254	199	47			0.383	707	293				
	Case (N = 500)	230	192	78	9.000	0.011		652	348	6.950	0.008	1.29 (1.07-1.55)	75.6%
Female	Control (N = 250)	126	97	27			0.228	349	151				
	Case (N = 250)	113	101	36	2.070	0.355		327	173	2.21	0.137	1.22 (0.94-1.59)	31.2%
Male	Control (N = 250)	128	102	20			1.000	358	142				
	Case (N = 250)	117	91	42	8.927	0.012		325	175	5.03	0.025	1.36 (1.04-1.77)	61.7%

Table 3. Comparison of the dominant model and recessive model between cases and controls in different genders

Gender	Group	Dominant		χ^2	P (df = 2)	OR (95% CI)	Power	Recessive		χ^2	P (df = 2)	OR (95% CI)	Power
		AA	AG+GG					AA+AG	GG				
All	Control	254	246					453	47				
	Case	230	270	2.310	0.128	1.21 (0.94-1.55)	32.5%	422	78	8.790	0.003	1.78 (1.21-2.62)	84.2%
Female	Control	126	124					223	27				
	Case	113	137	1.35	0.245	1.23 (0.87-1.75)	21.1%	214	36	1.47	0.225	1.39 (0.82-2.37)	22.8%
Male	Control	128	122					230	20				
	Case	117	133	0.97	0.325	1.19 (0.84-1.69)	16.3%	208	42	8.91	0.002	2.32 (1.32-4.08)	84.9%

tors and CAD. All data were analyzed using SPSS statistical software version 16.0 (SPSS, Inc., Chicago, IL, USA). Power analysis was performed using Power and Sample Size Calculation Software version 3.0.43. A two-sided *P* value of < 0.05 was considered to indicate a statistically significant result.

Results

As shown in the **Table 1**, the concentrations of TG, TC, HDL-C and LDL-C were significantly different between CAD and control groups (P < 0.001). The comparisons of both genotype and allele frequencies for *CXCL12* rs501120 were shown in **Table 2**. This SNP was found to be in Hardy-Weinberg equilibrium (P > 0.05). Significant associations were found between *CXCL12* rs501120 and CAD at both the genotype (χ^2 = 9.00, df = 2, P = 0.011) and allele (χ^2 = 6.95, df = 1, P = 0.008) levels. The rs501120-G allele frequency was significantly higher in CADs than in controls (34.8% versus 29.3%; P = 0.008; OR = 1.29, 95% CI = 1.07-1.55, Power = 75.6%). Analysis by gender indicated a significant difference in rs501120 between male CADs and controls (genotype: χ^2 = 8.93, df = 2, P = 0.012; allele: χ^2 = 5.03, df = 1, P = 0.025; OR = 1.36, 95% CI = 1.04-1.77, Power = 61.7%). However, no significant difference was found in the female groups (P > 0.05).

As shown in **Table 3**, significant correlation was found between cases and controls under the recessive model (AA+AG versus GG: χ^2 = 8.79, P = 0.003, OR = 1.78, 95% CI = 1.21-2.62, Power = 84.2%). In gender analysis, a positive association was also observed between rs501120 and CAD under the recessive model in males (χ^2 = 8.91, df = 1, P = 0.002. OR = 2.32, 95% CI = 1.32-4.08, Power = 84.9%).

It is well known that aging is a risk factor for CAD. Therefore, we performed stratified analysis according to age. Strong associations were found between rs501120 and CAD in all genders (genotype: χ^2 = 6.05, df = 2, P = 0.048; allele: χ^2 = 4.04, df = 1, P = 0.044, OR = 1.31, 95% CI = 1.01-1.71, Power = 51.9%, **Table 4**) and in male groups aged older than 65 years (genotype: χ^2 = 8.09, df = 2, P = 0.017; allele: χ^2 = 3.97, df = 1, P = 0.046; OR = 1.45, 95% CI = 1.01-2.11, Power = 50.3%, **Table 4**). No significant difference was observed for the remaining subjects of younger ages (P > 0.05).

A total of 432 patients were treated with atorvastatin for one month. The lipid profiles in patients undergoing atorvastatin therapy were compared according to the genotypes (**Table 5**). The results showed that the concentrations of TC and LDL-C were significantly reduced in patients with the three different genotypes

Table 4. Post hoc analysis of *CXCL12* gene rs501120 with the risk of CAD in different age subgroups

Age	Group	Genotype (n)			χ^2	P (df = 2)	HWE	Allele (n)		χ^2	P (df = 1)	OR (95% CI)	Power
		AA	AG	GG				A	T				
All < 65	Control	122	103	20			0.878	347	143				
	Case	110	106	32	3.42	0.181		326	170	2.95	0.086	1.26 (0.97-1.66)	39.0%
All ≥ 65	Control	132	96	27			0.134	360	150				
	Case	120	86	46	6.05	0.048		326	178	4.04	0.044	1.31 (1.01-1.71)	51.9%
Female < 65	Control	70	50	10			0.824	190	70				
	Case	65	55	16	1.67	0.431		185	87	1.64	0.200	1.27 (0.88-1.86)	24.0%
Female ≥ 65	Control	56	47	17			0.218	159	81				
	Case	48	46	20	0.72	0.699		142	86	0.80	0.371	1.19 (0.82-1.74)	14.7%
Male < 65	Control	52	53	10			0.665	157	73				
	Case	45	51	16	1.88	0.396		141	83	1.42	0.233	1.27 (0.86-1.87)	22.6%
Male ≥ 65	Control	76	49	10			0.649	201	69				
	Case	72	40	26	8.09	0.017		184	92	3.97	0.046	1.45 (1.01-2.11)	50.3%

Table 5. The comparison of blood lipid levels before and after atorvastatin treatment in different genotypes of *CXCL12* gene rs501120[a]

Characters	T (treatment)	AA (197)	P_1	AG (185)	P_1	GG (50)	P_1	P_2
TG (mmol/L)	0	2.99±1.29		3.10±2.03		3.38±2.64		> 0.05
	1	1.64±0.29	< 0.01	1.61±0.96	< 0.01	3.23±1.89	> 0.05	< 0.01
TC (mmol/L)	0	6.07±0.59		6.24±1.27		6.40±1.20		> 0.05
	1	4.23±0.76	< 0.01	4.18±1.31	< 0.01	4.30±0.97	< 0.01	> 0.05
HDL-C (mmol/L)	0	1.23±0.58		1.03±0.67		0.89±0.45		< 0.01
	1	1.56±0.82	< 0.01	1.34±0.50	< 0.01	1.02±0.20	> 0.05	< 0.01
LDL-C (mmol/L)	0	3.09±0.53		3.13±1.02		3.34±1.14		> 0.05
	1	2.02±0.38	< 0.01	2.13±1.03	< 0.01	1.96±0.88	< 0.01	> 0.05

a: The *P* values were adjusted for the history of smoking, drinking, diabetes and hypertension. P_1: The lipid levels before and after atorvastatin treatment were calculated using the t test. P_2: The bioparameters among different genotypes were calculated using the one way ANOVA test.

after atorvastatin therapy (P < 0.01). TG and HDL-C concentrations showed significant differences after atorvastatin therapy in those carrying rs501120-AA/AG (P < 0.01). However, there were no significant differences in the levels of TG (P > 0.05) and HDL-C (P > 0.05) before and after atorvastatin therapy in rs501120-GG carriers. The TG concentrations were significant different in the three genotypes after atorvastatin therapy (P < 0.01).

Discussion

Chemokines are crucial mediators and regulators of leukocyte trafficking during immune surveillance and inflammation [19]. Current studies have shown that chemokines are involved in directing leukocytes to sites of vascular inflammation and may represent attractive targets for drug therapy. The inflammatory chemokine CXCL12 plays an important role in vascular repair during cardiovascular disease [8]. CXCL12 is highly expressed in endothelial cells, smooth muscle cells, and macrophages in atherosclerotic plaques, but not in normal vessels [20]. The expression of CXCL12 protein in CAD patients is upregulated [21] and is induced after vascular injury in the context of apoptosis [8]. Thus, CXCL12 is considered a novel target for CAD [22]. In the present study, we evaluated the association between *CXCL12* and CAD risk. The results showed that *CXCL12* rs501120 was significantly associated with CAD in Han Chinese.

Age and gender are known to be predictors of CAD risk [23]. The number of older patients is

increasing and these patients exhibit higher cardiovascular morbidity and mortality in China [24]. Epidemiologic studies indicated that CAD events account for approximately 64% of atherosclerotic cardiovascular events in men and 60% in women aged 65 years and older [25]. Sex-specific differences are often observed in the prevalence and severity of cardiovascular diseases. Multiple genetic risk factors for CAD have been identified in different genders and ages in Han Chinese. A previous study reported that the *APOC4* rs1132899 polymorphism was associated with an increased risk of premature CAD in Chinese subjects. The association was more significant among male subjects [26]. Huang et al. suggested that *CDKN2BAS* rs4977574 increased the risk of coronary heart disease in females younger than 65 years [27]. However, Han et al. [28] showed that rs382-8329 of *ACP1* gene was a risk factor for CAD in Han Chinese females aged 65 years and older. In the present study, we found that rs501120 was associated with CAD risk in males aged 65 years and older. These findings agreed with the results for CXCL12 rs1746048 found by Huang et al. in Ningbo city [13].

The blood circulation lipid concentrations were considered to be independent risk factors for CAD. Manochehri et al. [29] suggested that both the fasting and postprandial TG levels were significantly higher in CAD patients. And the postprandial TG was more sensitive for the CAD patients. TC and LDL-C were indicated to play important role in the CAD development and physiological processes [30]. At the same time, HDL-C seemed to have a protective role and neutralize the effects of risk factors in CAD patients [31]. Our results showed that the concentrations of TG, TC, LDL-C were significantly higher in CAD patients than that in controls. The HDL-C level was lower in patients than in the controls.

Atorvastatin is a statin that is widely used to treat dyslipidemia and cardiovascular diseases. It reduces the levels of TG, TC, and LDL-C and increases HDL-C. However, the curative effect differed in various patients. Genetic variants were suggested to be associated with a higher incidence of undesirable side effects of atorvastatin. Gundapaneni et al. [32] suggested that atorvastatin may help in the regression of the lipid profile as well as DNA damage of CAD patients. Fukunaga et al. [33] confirmed that *ABCB1* rs2032582 was associated with atorvastatin-induced liver injury in a Japanese population. Cuevas et al. [34] reported that *HMGCR* rs17671591 may be a genetic marker of lower plasma LDL-C and enhanced HDL-C concentration after atorvastatin therapy in a Chilean population. Hou et al. [35] suggested that *SLCO1B1* polymorphisms were related to an increased risk of statin-related myopathy, particularly in individuals receiving simvastatin. In this study, we found that rs501120-AA/AG carriers were more responsive than rs501120-GG carriers in terms of TG and HDL-C concentrations after atorvastatin therapy for one month. Thus, a genetic test before initiation of statins may be useful for personalizing treatment.

Power analysis showed that our study had great power to explore the significant association between rs501120 and CAD risk (75.6% power in additive model, and 84.2% power in the recessive model). The power analysis in gender showed that rs501120 could increase CAD risk in females with 61.7% power in additive model and 84.9% power in the recessive model. The negative relationships might be due to lack of power in the test (power < 50%).

In conclusion, our results suggest that *CXCL12* rs501120 is significantly associated with CAD risk in Han Chinese males aged 65 years and older. Additionally, *CXCL12* rs501120-GG may affect the response to atorvastatin therapy by affecting the concentrations of TG and HDL-C in CAD patients.

Acknowledgements

The research was supported by the grants from: Natural Science Fund of Ningbo (No. 2016A610196) and Natural Science Fund of Zhejiang Province (No. LQ16H160002).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Guofeng Shao, Department of Thoracic & Cardiovascular Surgery, Lihuili Hospital, Ningbo Medical Center, Affiliated

Hospital of Medical School of Ningbo University, No. 57 Xingning Road, Ningbo 315041, China. Tel: 86-574-87018565; Fax: 86-574-87018565; E-mail: sgf1958@sina.com

References

[1] Lopez AD, Mathers CD, Ezzati M, Jamison DT and Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367: 1747-1757.

[2] Zhang XH, Lu ZL and Liu L. Coronary heart disease in China. Heart 2008; 94: 1126-1131.

[3] Prabhakaran D and Jeemon P. Should your family history of coronary heart disease scare you? Mt Sinai J Med 2012; 79: 721-732.

[4] Dehghan A, Bis JC, White CC, Smith AV, Morrison AC, Cupples LA, Trompet S, Chasman DI, Lumley T, Volker U, Buckley BM, Ding J, Jensen MK, Folsom AR, Kritchevsky SB, Girman CJ, Ford I, Dorr M, Salomaa V, Uitterlinden AG, Eiriksdottir G, Vasan RS, Franceschini N, Carty CL, Virtamo J, Demissie S, Amouyel P, Arveiler D, Heckbert SR, Ferrieres J, Ducimetiere P, Smith NL, Wang YA, Siscovick DS, Rice KM, Wiklund PG, Taylor KD, Evans A, Kee F, Rotter JI, Karvanen J, Kuulasmaa K, Heiss G, Kraft P, Launer LJ, Hofman A, Markus MR, Rose LM, Silander K, Wagner P, Benjamin EJ, Lohman K, Stott DJ, Rivadeneira F, Harris TB, Levy D, Liu Y, Rimm EB, Jukema JW, Volzke H, Ridker PM, Blankenberg S, Franco OH, Gudnason V, Psaty BM, Boerwinkle E and O'Donnell CJ. Genome-wide association study for incident myocardial infarction and coronary heart disease in prospective cohort studies: the charge consortium. PLoS One 2016; 11: e0144997.

[5] Roberts R and Stewart AF. Genes and coronary artery disease: where are we? J Am Coll Cardiol 2012; 60: 1715-1721.

[6] Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, Rovner A, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ and Penn MS. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet 2003; 362: 697-703.

[7] Zheng H, Fu G, Dai T and Huang H. Migration of endothelial progenitor cells mediated by stromal cell-derived factor-1alpha/CXCR4 via PI3K/Akt/eNOS signal transduction pathway. J Cardiovasc Pharmacol 2007; 50: 274-280.

[8] Zernecke A, Schober A, Bot I, von Hundelshausen P, Liehn EA, Mopps B, Mericskay M, Gierschik P, Biessen EA and Weber C. SDF-1alpha/CXCR4 axis is instrumental in neointimal hyperplasia and recruitment of smooth muscle progenitor cells. Circ Res 2005; 96: 784-791.

[9] Shen J, Chandrasekharan UM, Ashraf MZ, Long E, Morton RE, Liu Y, Smith JD and DiCorleto PE. Lack of mitogen-activated protein kinase phosphatase-1 protects ApoE-null mice against atherosclerosis. Circ Res 2010; 106: 902-910.

[10] Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig 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.

[11] Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, Stoll M, Girelli D, McKeown PP, Patterson CC, Siscovick DS, O'Donnell CJ, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Melander O, Altshuler D, Merlini PA, Berzuini C, Bernardinelli L, Peyvandi F, Tubaro M, Celli P, Ferrario M, Fetiveau R, Marziliano N, Casari G, Galli M, Ribichini F, Rossi M, Bernardi F, Zonzin P, Piazza A, Yee J, Friedlander Y, Marrugat J, Lucas G, Subirana I, Sala J, Ramos R, Meigs JB, Williams G, Nathan DM, MacRae CA, Havulinna AS, Berglund G, Hirschhorn JN, Asselta R, Duga S, Spreafico M, Daly MJ, Nemesh J, Korn JM, McCarroll SA, Surti A, Guiducci C, Gianniny L, Mirel D, Parkin M, Burtt N, Gabriel SB, Thompson JR, Braund PS, Wright BJ, Balmforth AJ, Ball SG, Hall A, Linsel-Nitschke P, Lieb W, Ziegler A, Konig I, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Ouwehand W, Deloukas P, Scholz M, Cambien F, Li M, Chen Z, Wilensky R, Matthai W, Qasim A, Hakonarson HH, Devaney J, Burnett MS, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Knouff CW, Waterworth DM, Walker MC, Mooser V, Epstein SE, Scheffold T, Berger K, Huge A, Martinelli N, Olivieri O, Corrocher R, McKeown P, Erdmann E, Konig IR, Holm H, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Do R, Xie C and Siscovick D. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 2009; 41: 334-341.

[12] Qi L, Ma J, Qi Q, Hartiala J, Allayee H and Campos H. Genetic risk score and risk of myocar-

dial infarction in Hispanics. Circulation 2011; 123: 374-380.
[13] Huang Y, Zhou J, Ye H, Xu L, Le Y, Yang X, Xu W, Huang X, Lian J and Duan S. Relationship between chemokine (C-X-C motif) ligand 12 gene variant (rs1746048) and coronary heart disease: case-control study and meta-analysis. Gene 2013; 521: 38-44.
[14] Xie F, Chu X, Wu H, Sun W, Shen M, Yang L, Wang Y, Shi J and Huang W. Replication of putative susceptibility loci from genome-wide association studies associated with coronary atherosclerosis in Chinese Han population. PLoS One 2011; 6: e20833.
[15] Zhang LY, Zhou Y, He ZH, Chen MH, Zhang XM, Zhou L, Cheng LX and TC W. Association of rs501120 and rs17465637 gene polymorphisms with coronary heart disease in the Chinese Han population. Journal of Chinese Physician 2011; 3: 289-292.
[16] Lopez-Mejias R, Garcia-Bermudez M, Gonzalez-Juanatey C, Castaneda S, Miranda-Filloy JA, Gomez-Vaquero C, Fernandez-Gutierrez B, Balsa A, Pascual-Salcedo D, Blanco R, Gonzalez-Alvaro I, Llorca J, Martin J and Gonzalez-Gay MA. Lack of association between the CXCL12 rs501120 polymorphism and cardiovascular disease in Spanish patients with rheumatoid arthritis. Hum Immunol 2012; 73: 543-546.
[17] Jiang D, Zheng D, Wang L, Huang Y, Liu H, Xu L, Liao Q, Liu P, Shi X, Wang Z, Sun L, Zhou Q, Li N, Le Y, Ye M, Shao G and Duan S. Elevated PLA2G7 gene promoter methylation as a gender-specific marker of aging increases the risk of coronary heart disease in females. PLoS One 2013; 8: e59752.
[18] Huang Y, Lian J, Huang RS, Wang F, Xu L, Le Y, Yang X, Xu W, Huang X, Ye M, Zhou J and Duan S. Positive association between rs10918859 of the NOS1AP gene and coronary heart disease in male Han Chinese. Genet Test Mol Biomarkers 2013; 17: 25-29.
[19] Koenen RR and Weber C. Chemokines: established and novel targets in atherosclerosis. EMBO Mol Med 2011; 3: 713-725.
[20] Abi-Younes S, Sauty A, Mach F, Sukhova GK, Libby P and Luster AD. The stromal cell-derived factor-1 chemokine is a potent platelet agonist highly expressed in atherosclerotic plaques. Circ Res 2000; 86: 131-138.
[21] Stellos K, Bigalke B, Langer H, Geisler T, Schad A, Kogel A, Pfaff F, Stakos D, Seizer P, Muller I, Htun P, Lindemann S and Gawaz M. Expression of stromal-cell-derived factor-1 on circulating platelets is increased in patients with acute coronary syndrome and correlates with the number of CD34+ progenitor cells. Eur Heart J 2009; 30: 584-593.
[22] Mehta NN, Li M, William D, Khera AV, DerOhannessian S, Qu L, Ferguson JF, McLaughlin C, Shaikh LH, Shah R, Patel PN, Bradfield JP, He J, Stylianou IM, Hakonarson H, Rader DJ and Reilly MP. The novel atherosclerosis locus at 10q11 regulates plasma CXCL12 levels. Eur Heart J 2011; 32: 963-971.
[23] Shah T, Palaskas N and Ahmed A. An update on gender disparities in coronary heart disease care. Curr Atheroscler Rep 2016; 18: 28.
[24] Moran A, Zhao D, Gu D, Coxson P, Chen CS, Cheng J, Liu J, He J and Goldman L. The future impact of population growth and aging on coronary heart disease in China: projections from the coronary heart disease policy model-China. BMC Public Health 2008; 8: 394.
[25] Levine BS and Kannel W. Coronary heart disease risk in people 65 years of age and older. Prog Cardiovasc Nurs 2003; 18: 135-140.
[26] Xu S, Cheng J, Li NH, Chen YN, Cai MY, Tang SS, Huang H, Zhang B, Cen JM, Yang XL, Chen C, Liu X and Xiong XD. The association of APOC4 polymorphisms with premature coronary artery disease in a Chinese Han population. Lipids Health Dis 2015; 14: 63.
[27] 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.
[28] Han X, Zhang L, Zhang Z, Wang J, Yang J and Niu J. Association between phosphatase related gene variants and coronary artery disease: case-control study and meta-analysis. Int J Mol Sci 2014; 15: 14058-14076.
[29] Manochehri M and Moghadam AJ. Studying the relation of postprandial triglyceride with coronary artery disease (CAD). Med Arch 2016; 70: 261-264.
[30] Imes CC and Austin MA. Low-density lipoprotein cholesterol, apolipoprotein B, and risk of coronary heart disease: from familial hyperlipidemia to genomics. Biol Res Nurs 2013; 15: 292-308.
[31] Upadhyay RK. Emerging risk biomarkers in cardiovascular diseases and disorders. J Lipids 2015; 2015: 971453.
[32] Gundapaneni KK, Shyamala N, Galimudi RK, Sahu SK and Hanumanth SR. A therapeutic effects of atorvastatin on genetic damage in coronary artery disease. J Clin Diagn Res 2016; 10: OC28-30.
[33] Fukunaga K, Nakagawa H, Ishikawa T, Kubo M and Mushiroda T. ABCB1 polymorphism is associated with atorvastatin-induced liver injury in Japanese population. BMC Genet 2016; 17: 79.

[34] Cuevas A, Fernandez C, Ferrada L, Zambrano T, Rosales A, Saavedra N and Salazar LA. HMGCR rs17671591 SNP determines lower plasma LDL-C after atorvastatin therapy in Chilean individuals. Basic Clin Pharmacol Toxicol 2016; 118: 292-297.

[35] Hou Q, Li S, Li L, Li Y, Sun X and Tian H. Association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk: a meta-analysis of case-control studies. Medicine (Baltimore) 2015; 94: e1268.