Int J Clin Exp Med 2016;9(2):4059-4064
www.ijcem.com /ISSN:1940-5901/IJCEM0015916

Original Article

Association between T-cadherin gene (CDH13) variants and severity of coronary heart disease manifestation

Fatima R Chotchaeva[1*], Alexander V Balatskiy[2*], Larisa M Samokhodskaya[2], Vsevolod A Tkachuk[1], Viktor A Sadovnichiy[3]

[1]Faculty of Fundamental Medicine, Lomonosov Moscow State University, Moscow, Russia; [2]Medical Scientific and Educational Center, Lomonosov Moscow State University, Moscow, Russia; [3]Lomonosov Moscow State University, Moscow, Russia. [*]Equal contributors.

Received September 9, 2015; Accepted December 6, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Recent data shows that T-cadherin (encoded by CDH13 gene) plays an important role in atherosclerosis and coronary heart disease (CHD) onset and development. Several single nucleotide polymorphisms in CDH13 gene are associated with T-cadherin, serum adiponectin and lipid levels, but their role in CHD development is not investigated. Materials and methods: The study sample included 187 men with CHD. Association between four SNPs (rs12051272, rs4783244, rs12444338 and rs11646213) variants and type of CHD onset (myocardial infarction or stable angina pectoris) was studied. Results: G/T genotype of rs12051272 is associated with type of CHD onset (for onset with myocardial infarction OR=0.13 (0.04-0.50)). This association was confirmed for patients with arterial hypertension without dyslipidemia and obesity and for smokers. No associations between genotype and type of CHD onset were found for rs4783244, rs12444338 and rs11646213. Conclusion: This study provides evidence that genetically predetermined changes in T-cadherin expression can influence atherogenesis and CHD development.

Keywords: T-cadherin, CDH13, coronary heart disease, myocardial infarction

Introduction

Coronary heart disease (CHD) is an important medical and social problem. Currently, it has become one of the leading causes of death and disability worldwide [1]. Moreover, myocardial infarction (MI) makes a significant contribution to the structure of mortality.

Sudden heart attack is often a primary manifestation of CHD. Intravascular thrombosis leading to MI usually occurs on damaged surface of existing atherosclerotic plaque [2]. Frequently, the vulnerable plaque is not occlusive and constricts the lumen of the artery by an average of 48% [3], so subjects with such plaques are considered healthy, but they have high odds of sudden MI without previous symptoms of angina. In the other case, atherosclerotic plaque and CHD and develop slower, and the first symptom of the disease is the stable angina pectoris (SAP).

The mechanism of vulnerable plaque formation is not fully understood. Recent data shows that T-cadherin (encoded by CDH13 gene) plays an important role in atherosclerosis and CHD development [4-7]. T-cadherin, a glycosylphosphatidylinositol (GPI)-anchored member of cadherin superfamily, is a receptor for low-density lipoprotein (LDL) [8] and high-molecular-weight forms of adiponectin, adipose tissue hormone [9]. The current opinion is that anti-atherosclerotic effects of adiponectin are realized by increased formation of high-density lipoprotein (HDL) cholesterol in the liver, reduction of cholesterol in atheromatous plaque [10-12] and suppression of transformation of macrophages into foam cells [13]. Joosten et al. have shown that low levels of adiponectin are associated with development of atherosclerosis: reduced concentration of adiponectin was associated with presence of multiple atherosclerotic vascular lesions [14, 15]. MI develops as a result of arterial thrombosis due to rupture of the thin fibrous cap of atherosclerotic plaque. Cai et al. have shown that adiponectin inhibits proliferation, migration and transformation of adventitial fibroblasts [16] and inhibition of these pro-

Table 1. Clinical characteristics of the study population (data are presented as median (upper quartile; lower quartile)

Risk factors	MI (n=108)	SAP (n=79)	P
Age of CHD onset, years	46.7 (26.0; 55.0)	46.7 (28.0; 55.0)	0.23
Dyslipidemia, % (n)	26.8 (29)	30.3 (24)	0.35
Obesity, % (n)	26.8 (29)	36.7 (29)	0.10
BMI, kg/m^2	27.6 (12.6; 41.2)	28.6 (20.9; 37.1)	0.77
Smokers, % (n)	53.7 (58)	44.3 (35)	0.13
AH, % (n)	59.2 (64)	67.0 (53)	0.34

cesses may lead to a thinner cap of atherosclerotic plaque. T-cadherin also acts as an LDL receptor [8, 17], so it can play a role in vulnerable plaque formation independently from adiponectin.

Several studies have shown that single nucleotide polymorphisms (SNPs) in T-cadherin gene (CDH13) may influence the level of adiponectin in blood, thus some CDH13 gene SNPs possibly may lead to the development of cardiovascular disease.

In the present study we selected four SNPs in CDH13 gene and investigated the association of these SNPs with the type of CHD onset. SNPs rs12051272 (G→T) [18, 19] and rs4783244 (G→T) [18, 19] are associated with serum adiponectin levels, and rs12444338 (G→T) is also associated with CDH13 promoter activity [20]. There are no data about on rs11646213 (A→T) [19, 21], but A-allele of this SNP is associated with decreased risk of arterial hypertension (AH) and increased risk of metabolic syndrome development [21, 22]. Also all selected SNPs are associated with plasma lipids levels [21, 23-25].

Materials and methods

This study was approved by Ethics Committee at Faculty of Fundamental Medicine, Lomonosov Moscow State University.

The study population included 187 men aged 26-55 years with CHD. Blood samples and clinical data were obtained from Faculty of Fundamental Medicine (Lomonosov Moscow State University) biobank. SAP was present in 42.3% (n=79) and MI without previously diagnosed CHD was present in 57.7% (n=108). The criterion for inclusion in the first group was SAP (confirmed by stress testing or coronary angiography) without MI. The criterion for inclusion in the second group was clinically, laboratory and instrumentally confirmed MI (typical evaluation of cardiac biomarkers of necrosis combined with electrocardiographic signs or visualization of myocardial necrosis by echocardiography or radionuclide imaging) without previously diagnosed CHD. Exclusion criteria for both groups were impaired glucose tolerance and diabetes mellitus.

AH was defined as blood pressure ≥140/90 mmHg, or current treatment for hypertension, dyslipidaemia was defined as total cholesterol >5.3 mmol/L or low-density lipoprotein cholesterol >3.0 mmol/L or current treatment for dyslipidaemia, obesity was defined as body mass index (BMI) ≥30. Arterial hypertension was present in 62.5% (n=117), obesity was present in 31.0% (n=58), dyslipidemia was present in 28.3% (n=53), 93 (49.7%) participants were smokers.

Genomic DNA was extracted from EDTA-stabilized peripheral venous blood using QIAmp DNA Blood Mini Kit and QIAcube™ automatic station (QIAGEN). Genotyping was performed by SNP Genotyping TaqMan® Assays (Applied Biosystems®).

Group differences for categorical variables were assessed by χ^2-test. Distributions of continuous variables were tested for normality by Shapiro-Wilk test. Normally distributed variables were examined by Student's t-test, other continuous variables were examined by Mann-Whitney U-test. A *P*-value less than 0.05 was considered statistically significant for all tests. Odds ratios (OR) and their corresponding 95% confidence interval (CI) were used for evaluation of associations between genotype and type of CHD onset. SNP data was evaluated by SNPStats online tool. Akaike information criterion (AIC) was used for choosing the inheritance model that best fits the data (co-dominant, dominant, recessive, over-dominant and log-additive) [26].

Results

Study groups (MI and SAP) were compared against each other, taking into account the major risk factors for cardiovascular diseases. **Table 1** shows that the frequency of major risk factors for cardiovascular disease did not differ between groups.

Table 2. Association between genotype of rs12051272 and type of CHD onset (adjusted by AH + obesity + dyslipidaemia + smoking)

Model	Genotype	SAP, n (%)	MI, n (%)	OR (95% CI)	*P*-value	AIC
-	G/G	66 (83.5%)	105 (97.2%)	1.00	6e-04	250.9
	G/T	13 (16.5%)	3 (2.8%)	0.13 (0.04-0.50)		

Table 3. Association between genotype of rs12051272 and type of CHD onset in groups with presence and absence of major cardiovascular risk factors

Risk factor		rs12051272 genotype	SAP, n	MI, n	OR (95% CI)
AH	No	G/G	24	43	1.00
		G/T	2	1	0.30 (0.02-3.59)
	Yes	G/G	42	62	1.00
		G/T	11	2	0.10 (0.02-0.50)
Dyslipidaemia	No	G/G	44	76	1.00
		G/T	11	3	0.15 (0.04-0.57)
	Yes	G/G	22	29	1.00
		G/T	2	0	NA
Obesity	No	G/G	41	77	1.00
		G/T	9	2	0.11 (0.02-0.55)
	Yes	G/G	25	28	1.00
		G/T	4	1	0.21 (0.02-2.07)
Smoking	No	G/G	38	49	1.00
		G/T	6	1	0.12 (0.01-1.02)
	Yes	G/G	28	56	1.00
		G/T	7	2	0.15 (0.03-0.78)

Significant differences between groups with MI and SAP were found only for rs12051272 (G→T) (**Table 2**). Because no TT homozygous patients were found, OR calculations for rs12051272 GT genotype were performed without regard to the mode of inheritance. No relationship was found between type of CHD onset and rs4783244 (P=0.83), rs11646213 (P=0.39) and rs12444338 (P=0.49) (Tables S1-S3).

Further, associations between genotype of studied variants and type of CHD onset were analyzed taking into account presence of major cardiovascular risk factors. The sample of 187 patients was divided into subgroups according to presence of the major risk factors for myocardial infarction: AH, dyslipidemia, obesity and smoking. Associations were tested using the inheritance model with the lowest AIC value.

No differences were found for rs4783244, rs11646213, rs12444338, but significant differences were discovered for rs12051272 in groups with AH, without dyslipidaemia and obesity and in smokers (**Table 3**).

Discussion

T-cadherin levels in human plasma is negatively associated with coronary lesion severity and acute coronary syndrome [7], so SNPs altering this levels can be assosiated with MI development and the type of CHD onset. rs12444338 (G→T) is associated not only with adiponectin levels, but also with CDH13 promoter activity [20], so we suppose presence of the effect on CHD onset firstly for this SNP.

No relationship was found between type of CHD onset and presence of rs4783244, rs11646213 and rs12444338 variants. Similar data were obtained by Morisaki et al. for rs12444338: different variants had no effect on the development of myocardial infarction, adiponectin and LDL levels [19].

Significant differences between groups with MI and SAP were found for SNP rs12051272 (G→T): GT genotype frequency in patients with MI was lower than in group with SAP, so it is possible to suggest a protective role for T-allele. This results may seem paradoxical because T-allele carriers have lower adiponectin levels [19].

There are various reasons for this discrepancy. Firstly, we should pay attention to difficulties in evaluation of circulating adiponectin levels in patients with MI. Adiponectin accumulates in the area of heart muscle damage, binding T-cadherin [27], so decreased levels of circulating adiponectin may be secondary to myocardial infarction [28]. Also, adiponectin may have ambiguous effects on atherosclerotic plaque formation and MI development. On the one

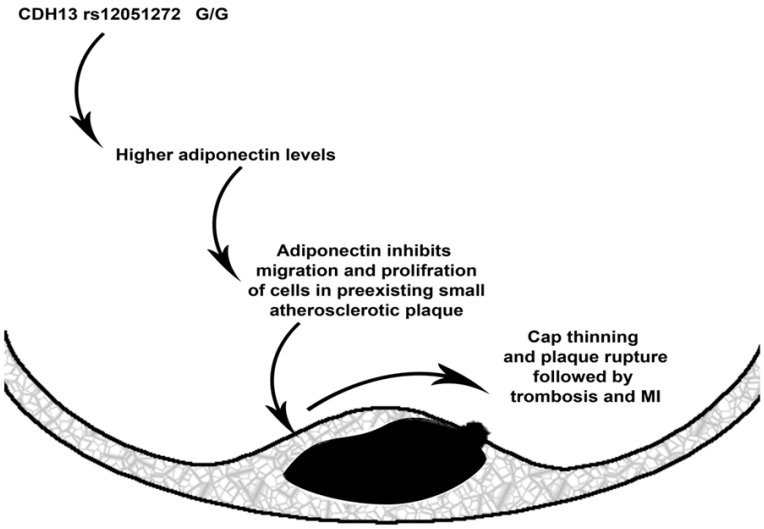

Figure 1. A possible mechanism of MI development in patients with rs12051272 G/G genotype.

hand, high adiponectin levels prevent the development of myocardial infarction due to normalization of lipid profile [10] and suppression of transformation of macrophages into foam cells [13]. On the other hand, some studies have shown that adiponectin suppresses the migration of fibroblasts and their transformation into myofibroblasts [16], so high levels of adiponectin may cause atherosclerotic plaque cap thinning and promote cap rupture with consequent arterial thrombosis. Possible mechanism of this effect is shown on **Figure 1**.

Statistically significant difference in frequencies of rs12051272 variants between groups with MI and SAP were found for patients with AH, without dyslipidemia and obesity and for smokers.

Statistically significant differences in patients without dyslipidemia and no difference in the group with dyslipidemia could be explained by larger number of patients in the first group. Nevertheless, high level of adiponectin associated with this SNP can lead to the normalization of the lipid profile. T-allele of rs12051272 is associated with higher HDL levels and lower triglycerides levels [25], and other CDH13 SNPs are associated not only with increased production of adiponectin but also with decreased levels of LDL [18, 21, 24].

Significant associations between rs12051272 variants and type of CHD onset in group of smokers have no obvious explanation. Smoking is a risk factor for MI and may have synergic effect with G/T genotype on CHD development and atherosclerotic plaque stability.

Significant association also was discovered in the group with arterial hypertension. There are two possible explanations for such results: the prevalence of hypertensive patients in study group and effects of rs12051272 on development of AH or a synergic effect with BP level. In the present study no associations between CDH13 SNPs and AH were discovered, but Teng and al. showed an association between rs1205-1272 and diastolic blood pressure [25]. Associations between other CDH13 SNPs and risk of hypertension or BP levels were also confirmed [18, 22, 29], so T-cadherin may be involved in BP regulation.

Significant differences were found in the group of patients without obesity. This result can be explained by a large number of non-obese patients. However, such association may be related to an excessive increment of plasma adiponectin levels in patients with G/G genotype and normal body weight, possibly leading to destabilization of atherosclerotic plaques.

Acknowledgements

This research was financially supported by Russian Scientific Foundation. Blood samples collection for biobank of Faculty of Fundamental Medicine was carried out as part of project No. 14-50-00029, genotyping of patients was performed as a part of project No 14-24-00086.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Alexander V Balatskiy, Medical Scientific and Educational Center, Lomonosov Moscow State University, Moscow, Russia. Tel: +74959328814; E-mail: balatsky@fbm.msu.ru

References

[1] Finegold JA, Asaria P and Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. Int J Cardiol 2013; 168: 934-945.

[2] Zaman AG, Helft G, Worthley SG and Badimon JJ. The role of plaque rupture and thrombosis in coronary artery disease. Atherosclerosis 2000; 149: 251-266.

[3] Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R and Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12: 56-62.

[4] Kostopoulos CG, Spiroglou SG, Varakis JN, Apostolakis E and Papadaki HH. Adiponectin/T-cadherin and apelin/APJ expression in human arteries and periadventitial fat: implication of local adipokine signaling in atherosclerosis? Cardiovasc Pathol 2014; 23: 131-138.

[5] Ivanov D, Philippova M, Antropova J, Gubaeva F, Iljinskaya O, Tararak E, Bochkov V, Erne P, Resink T and Tkachuk V. Expression of cell adhesion molecule T-cadherin in the human vasculature. Histochem Cell Biol 2001; 115: 231-242.

[6] Philippova M, Suter Y, Toggweiler S, Schoenenberger AW, Joshi MB, Kyriakakis E, Erne P and Resink TJ. T-cadherin is present on endothelial microparticles and is elevated in plasma in early atherosclerosis. Eur Heart J 2011; 32: 760-771.

[7] Pfaff D, Schoenenberger AW, Dasen B, Erne P, Resink TJ and Philippova M. Plasma T-cadherin negatively associates with coronary lesion severity and acute coronary syndrome. Eur Heart J Acute Cardiovasc Care 2015; 4: 410-8.

[8] Tkachuk VA, Bochkov VN, Philippova MP, Stambolsky DV, Kuzmenko ES, Sidorova MV, Molokoedov AS, Spirov VG and Resink TJ. Identifiation of an atypical lipoprotein-binding protein from human aortic smooth muscle as T-cadherin. FEBS Lett 1998; 421: 208-212.

[9] Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS and Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proc Natl Acad Sci U S A 2004; 101: 10308-10313.

[10] Matsuura F, Oku H, Koseki M, Sandoval JC, Yuasa-Kawase M, Tsubakio-Yamamoto K, Masuda D, Maeda N, Tsujii K, Ishigami M, Nishida M, Hirano K, Kihara S, Hori M, Shimomura I and Yamashita S. Adiponectin accelerates reverse cholesterol transport by increasing high density lipoprotein assembly in the liver. Biochem Biophys Res Commun 2007; 358: 1091-1095.

[11] Nawrocki AR, Hofmann SM, Teupser D, Basford JE, Durand JL, Jelicks LA, Woo CW, Kuriakose G, Factor SM, Tanowitz HB, Hui DY, Tabas I and Scherer PE. Lack of association between adiponectin levels and atherosclerosis in mice. Arterioscler Thromb Vasc Biol 2010; 30: 1159-1165.

[12] Okamoto Y, Folco EJ, Minami M, Wara AK, Feinberg MW, Sukhova GK, Colvin RA, Kihara S, Funahashi T, Luster AD and Libby P. Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. Circ Res 2008; 102: 218-225.

[13] Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, Hotta K, Muraguchi M, Ohmoto Y, Yamashita S, Funahashi T and Matsuzawa Y. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 2001; 103: 1057-1063.

[14] Ho DY, Cook NR, Britton KA, Kim E, Creager MA, Ridker PM and Pradhan AD. High-molecular-weight and total adiponectin levels and incident symptomatic peripheral artery disease in women: a prospective investigation. Circulation 2011; 124: 2303-2311.

[15] Joosten MM, Joshipura KJ, Pai JK, Bertoia ML, Rimm EB, Mittleman MA and Mukamal KJ. Total adiponectin and risk of symptomatic lower extremity peripheral artery disease in men. Arterioscler Thromb Vasc Biol 2013; 33: 1092-1097.

[16] Cai XJ, Chen L, Li L, Feng M, Li X, Zhang K, Rong YY, Hu XB, Zhang MX, Zhang Y and Zhang M. Adiponectin inhibits lipopolysaccharide-induced adventitial fibroblast migration and transition to myofibroblasts via AdipoR1-AMPK-iNOS pathway. Mol Endocrinol 2010; 24: 218-228.

[17] Kuzmenko YS, Stambolsky D, Kern F, Bochkov VN, Tkachuk VA and Resink TJ. Characteristics of smooth muscle cell lipoprotein binding proteins p105/p130) as T-cadherin and regulation by positive and negative growth regulators. Biochem Biophys Res Commun 1998; 246: 489-494.

[18] Chung CM, Lin TH, Chen JW, Leu HB, Yang HC, Ho HY, Ting CT, Sheu SH, Tsai WC, Chen JH, Lin SJ, Chen YT and Pan WH. A genome-wide association study reveals a quantitative trait locus of adiponectin on CDH13 that predicts cardiometabolic outcomes. Diabetes 2011; 60: 2417-2423.

[19] Morisaki H, Yamanaka I, Iwai N, Miyamoto Y, Kokubo Y, Okamura T, Okayama A and Morisaki

T. CDH13 gene coding T-cadherin influences variations in plasma adiponectin levels in the Japanese population. Hum Mutat 2012; 33: 402-410.

[20] Jee SH, Sull JW, Lee JE, Shin C, Park J, Kimm H, Cho EY, Shin ES, Yun JE, Park JW, Kim SY, Lee SJ, Jee EJ, Baik I, Kao L, Yoon SK, Jang Y and Beaty TH. Adiponectin concentrations: a genome-wide association study. Am J Hum Genet 2010; 87: 545-552.

[21] Fava C, Danese E, Montagnana M, Sjogren M, Almgren P, Guidi GC, Hedblad B, Engstrom G, Lechi A, Minuz P and Melander O. A variant upstream of the CDH13 adiponectin receptor gene and metabolic syndrome in Swedes. Am J Cardiol 2011; 108: 1432-1437.

[22] Org E, Eyheramendy S, Juhanson P, Gieger C, Lichtner P, Klopp N, Veldre G, Doring A, Viigimaa M, Sober S, Tomberg K, Eckstein G, Kelgo P, Rebane T, Shaw-Hawkins S, Howard P, Onipinla A, Dobson RJ, Newhouse SJ, Brown M, Dominiczak A, Connell J, Samani N, Farrall M, Caulfield MJ, Munroe PB, Illig T, Wichmann HE, Meitinger T and Laan M. Genome-wide scan identifies CDH13 as a novel susceptibility locus contributing to blood pressure determination in two European populations. Hum Mol Genet 2009; 18: 2288-2296.

[23] Putku M, Kals M, Inno R, Kasela S, Org E, Kozich V, Milani L and Laan M. CDH13 promoter SNPs with pleiotropic effect on cardiometabolic parameters represent methylation QTLs. Hum Genet 2015; 134: 291-303.

[24] Gao H, Kim YM, Chen P, Igase M, Kawamoto R, Kim MK, Kohara K, Lee J, Miki T, Ong RT, Onuma H, Osawa H, Sim X, Teo YY, Tabara Y, Tai ES and van Dam RM. Genetic variation in CDH13 is associated with lower plasma adiponectin levels but greater adiponectin sensitivity in East Asian populations. Diabetes 2013; 62: 4277-4283.

[25] Teng MS, Hsu LA, Wu S, Sun YC, Juan SH and Ko YL. Association of CDH13 Genotypes/Haplotypes with Circulating Adiponectin Levels, Metabolic Syndrome, and Related Metabolic Phenotypes: The Role of the Suppression Effect. PLoS One 2015; 10: e0122664.

[26] Sole X, Guino E, Valls J, Iniesta R and Moreno V. SNPStats: a web tool for the analysis of association studies. Bioinformatics 2006; 22: 1928-1929.

[27] Denzel MS, Scimia MC, Zumstein PM, Walsh K, Ruiz-Lozano P and Ranscht B. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. J Clin Invest 2010; 120: 4342-4352.

[28] Shibata R, Sato K, Kumada M, Izumiya Y, Sonoda M, Kihara S, Ouchi N and Walsh K. Adiponectin accumulates in myocardial tissue that has been damaged by ischemia-reperfusion injury via leakage from the vascular compartment. Cardiovasc Res 2007; 74: 471-479.

[29] Lee JH, Shin DJ, Park S, Kang SM, Jang Y and Lee SH. Association between CDH13 variants and cardiometabolic and vascular phenotypes in a Korean population. Yonsei Med J 2013; 54: 1305-1312.

Table S1. Effects of rs11646213 genotype on type of CHD onset (adjusted by AH + obesity + dyslipidaemia + smoking)

Model	Genotype	SAP, n (%)	MI, n (%)	OR (95% CI)	*P*-value	AIC
Codominant	T/T	35 (44.3%)	43 (39.8%)	1.00	0.33	262.3
	A/T	38 (48.1%)	50 (46.3%)	0.98 (0.53-1.84)		
	A/A	6 (7.6%)	15 (13.9%)	2.07 (0.72-5.99)		
Dominant	T/T	35 (44.3%)	43 (39.8%)	1.00	0.69	262.3
	A/T-A/A	44 (55.7%)	65 (60.2%)	1.13 (0.62-2.05)		
Recessive	T/T-A/T	73 (92.4%)	93 (86.1%)	1.00	0.14	260.3
	A/A	6 (7.6%)	15 (13.9%)	2.09 (0.76-5.75)		
Overdominant	T/T-A/A	41 (51.9%)	58 (53.7%)	1.00	0.6	262.2
	A/T	38 (48.1%)	50 (46.3%)	0.85 (0.47-1.55)		
Log-additive	-	-	-	1.25 (0.80-1.96)	0.32	261.5

Table S2. Effects of rs12444338 genotype on type of CHD onset (adjusted by AH + obesity + dyslipidaemia + smoking)

Model	Genotype	SAP, n (%)	MI, n (%)	OR (95% CI)	*P*-value	AIC
Codominant	T/T	21 (26.6%)	27 (25%)	1.00	0.8	264.1
	G/T	45 (57%)	59 (54.6%)	1.05 (0.52-2.12)		
	G/G	13 (16.5%)	22 (20.4%)	1.33 (0.54-3.28)		
Dominant	T/T	21 (26.6%)	27 (25%)	1.00	0.75	262.4
	G/T-G/G	58 (73.4%)	81 (75%)	1.12 (0.57-2.19)		
Recessive	T/T-G/T	66 (83.5%)	86 (79.6%)	1.00	0.52	262.1
	G/G	13 (16.5%)	22 (20.4%)	1.28 (0.60-2.76)		
Overdominant	T/T-G/G	34 (43%)	49 (45.4%)	1.00	0.82	262.5
	G/T	45 (57%)	59 (54.6%)	0.93 (0.52-1.69)		
Log-additive	-	-	-	1.14 (0.73-1.79)	0.56	262.2

Table S3. Effects of rs4783244 genotype on type of CHD onset (adjusted by AH + obesity + dyslipidaemia + smoking)

Model	Genotype	SAP, n (%)	MI, n (%)	OR (95% CI)	*P*-value	AIC
Codominant	G/G	17 (21.5%)	27 (25%)	1.00	0.88	264.2
	G/T	44 (55.7%)	57 (52.8%)	0.85 (0.41-1.76)		
	T/T	18 (22.8%)	24 (22.2%)	0.81 (0.34-1.95)		
Dominant	G/G	17 (21.5%)	27 (25%)	1.00	0.62	262.3
	G/T-T/T	62 (78.5%)	81 (75%)	0.84 (0.42-1.69)		
Recessive	G/G-G/T	61 (77.2%)	84 (77.8%)	1.00	0.8	262.4
	T/T	18 (22.8%)	24 (22.2%)	0.91 (0.45-1.85)		
Overdominant	G/G-T/T	35 (44.3%)	51 (47.2%)	1.00	0.83	262.5
	G/T	44 (55.7%)	57 (52.8%)	0.94 (0.52-1.70)		
Log-additive	-	-	-	0.90 (0.58-1.39)	0.64	262.3