International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-1, 2017, 112-120
http://www.bipublication.com

Research Article

Association study of rs1994016 polymorphism on ADAMTS-7 loci with Coronary Artery Disease in the Iranian population

Forough Sargolzaeiaval[1], Hossein Vakili[2], Davood Karimi Hosseini[3], Aliyeh Sargazi[4] and Sayyed Mohamad Hossein Ghaderian[5*]

[1]School of Medicine,
Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Cardiovascular Research Center, Modarres Hospital,
Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Otolaryngology Head and Neck Surgery Department, Stanford University, Palo Alto, CA, USA.
[4]Students research Committee, Zabol University of Medical Sciences, Zabol, Iran.
*[5]Urogenital Stem Cell Research Center,
Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Corresponding email: sghaderian@yahoo.co.uk

ABSTRACT

Coronary artery disease (CAD) is the single greatest cause of death worldwide. Although CAD is highly heritable, the DNA sequence variations that confer cardiovascular risk remain largely unknown. Definition of the genetic architecture of CAD can provide substantial benefits through improved risk prediction and development of novel therapies. Genome-wide association studies of coronary artery disease have recently identified a new susceptibility locus, ADAMTS-7, in subjects of European ancestry. However, the significance of this locus in Iranian populations has not been identified. This study was designed to evaluate the effect of rs1994016, a non-synonymous variant in the prodomain of the ADAMTS-7 protease, on CAD risk and atherosclerosis severity in an Iranian population. Genetic performed association analyses through TaqMan probe real time PCR technique in a case-control cohort, which included a total of 200 participants. Based on angiography test results and biochemical characteristics, participants were divided into two case and control groups (more than 50% stenosis in coronary arteries was considered as case (n=100), and less than 50% stenosis in coronary arteries was considered as control (n=100). Blood samples were collected and DNA was extracted for evaluation of rs1994016. Final results and clinical and biomedical characteristics were analyzed statistically. According to the data, ADAMTS-7 rs1994016 was significantly associated with susceptibility to CAD in the studied population of patients with CAD [odds ratio (OR) = 0.013, 95 % confidence interval (CI) = 0.003-0.059, P < 0.001]. The frequency of the T mutant allele was considerably higher in the case group. (T allele Frequency in cases: 0.81 and in controls: 0.1). These results suggested ADAMTS-7 rs1994016 were associated with susceptibility to CAD in Iranian population.

Keywords: Coronary Artery Disease, Atherosclerosis, ADAMTS-7 gene

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in high-income countries and the second most common contributor to morbidity and mortality in medium to low-income countries (1), and the great majority of its burden stems from atherosclerosis process. Despite undeniable role of environmental and lifestyle factors in development of CAD, Genetic epidemiological assessments of family history and twin concordance studies highly suggest an underlying

multifactorial model of disease susceptibility with a significant polygenic component (2).

However, many mechanisms of this heredity are yet to be identified. Over the past few years, many common susceptibility variants for complex diseases have been mapped in several genome wide association studies (GWASs). In case of CAD, GWASs have identified multiple loci with significant associations with CAD in which the most recent and complete findings come from two global consortia, CARDIOGRAM (3) and C4D (4) that introduce a total of 46 genome-wide significant loci associated with CAD. Several of these studies have shown associations between particular single nucleotide polymorphisms (SNPs) and risk factors of CAD such as dyslipidemia (5) and hypertension (6), as well as risk of atherosclerosis (7, 8) and ischemic heart disease (9) independently of known and traditional risk factors.

Recently in two independent GWASs, ADAMTS-7 gene on 15q25.1 loci has been identified as a novel locus for the development of coronary atherosclerosis (10, 11). The ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family comprises 19 discrete zinc metalloprotease proteins (12) and the linkage of these metalloproteases with the pathogenesis of atherosclerosis has been proved in multiple studies.

The ADAMTS1, ADAMTS-4 and ADAMTS-9 proteins have been observed to be expressed in regions of the vasculature prone to atherosclerotic plaque formation (13) which suggests the association of these proteins with cardiovascular disease (14). The ADAMTS-7 protein cleaves the cartilage oligometric matrix protein (COMP) and contributes to the progression of arthritis (15). According to more recent studies, overexpression of ADAMTS-7 was shown to increase primary vascular smooth muscle cell (VSMC) migration in atherosclerotic plaques as well as increasing postinjury neointimal formation in balloon-injured rat carotid arteries (16).

Three GWASs up to now have revealed the significant association of SNPs on ADAMTS-7 gene with CAD. The lead SNPs in two studies were rs3825807 in the prodomain of ADAMTS-7 (3) and rs4380028 at 7.6 kb upstream of the gene (4), respectively.

In the other study, rs1994016 was the lead SNP significantly associated with CAD (P= 0.0174); this SNP, a cysteine (C) to thymine (T) polymorphism, resides in intron 8 of ADAMTS-7 gene and it is shown to cause a 19% increase in the risk of developing atherosclerotic CAD in patients carrying this polymorphism (10). There is some degree of variation in different populations' gene pools and the genetic architecture of complex diseases must be studied and understood separately in each population in order to provide improved risk prediction models and development of effective therapies. Here we assessed whether or not the well validated CAD related SNP in subjects of European ancestry, rs1994016 on ADAMTS-7 gene, is also associated with this disease in an Iranian population. In addition, we assessed the relationship between rs1994016 polymorphism and known risk factors of CAD.

MATERIAL & METHODS

Subjects and clinical data

This was a case-control study conducted in Human Genetics research center of Shahid Beheshti University of Medical Sciences.

Based on the world health organization (WHO) guideline for assessment and management of cardiovascular disease (CVD) risk (17), a total of 200 subjects who had at least 10-20% 10-years risk of developing a cardiovascular event and were indicated candidates for coronary angiography (18), were recruited in this study; comprising 100 CAD cases (male, female), as ascertained by coronary angiographic phenotyping as follows: men and women over 40 years old with at least one coronary artery with stenosis of 50% or more; and 100 normal controls (male, female) who had no family history of CAD and their coronary angiography and left

ventriculography results were negative for evidences of CAD. Subjects were excluded in case of pregnancy or lactation, previous history of coronary angiography, systemic inflammatory diseases, chronic renal or liver diseases and genetic disorders influencing the heart. Blood samples were taken for DNA extraction and laboratory measurements.

For further evaluation and comparison between the case and control groups, some cardiovascular risk factors were selected which their impression on onset and development of CAD had been proven in former studies.

Demographic information (including age, gender, weight and height) was collected by means of a questionnaire. BMI was cal¬culated as weight (kilograms) divided by height (me¬ters) squared. Fasting blood sugar, lipid profile (total cholesterol, triglyceride, LDL and HDL) values were measured by valid clinical laboratories. Systolic and diastolic blood pressure and waist and hip circumferences were measured using standard procedures. All subjects gave their written informed consent to participate.

DNA isolation and SNP genotyping

By utilizing the DNA isolation kit (High pure PCR template preparation kit, Roche company), Genomic DNA was extracted from blood samples. The final extracted DNA was checked and qualified using agarose gel-electrophoresis and quantitated by NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA).

Rs1994016 located on ADAMTS-7 gene with minor allele frequency (MAF) of 0.22 were selected based on previous studies and NCBI dbSNP database (http://www.ncbi.nlm.nih. gov/) and the typing of this SNP was determined by means of predesigned TaqMan SNP genotyping assays (Real time PCR, Light cycler 96, Roche company, Germany).

The reaction was performed in 25 µL final volume with real-time polymerase chain reaction using 96-well plates on Real time PCR, Light cycler 96, (Roche Company). The polymerase chain reaction conditions were done as follows: initial denaturation at 95 °C for 10 minutes and 40 cycles of denaturation at 92 °C for 15 seconds and annealing and elongation at 60 °C for 1 minute.

SDS software version 1.3 (Applied Biosystems) was used for Individual genotype identification according to the manufacturer's standard protocols, in which the genotyping success rate was greater than 95% for the selected SNP. In order to recheck the genotyping quality, 10 per cent of the samples were run in duplicate without any inconsistencies. Nuclease-free water was used as negative control.

Statistical analysis

SPSS19.0 (SPSS Inc., Chicago, Illinois, USA) software was used for general statistical analysis. One-way ANOVA analysis and linear regression were performed to assess the correlations between risk factors and the genotyped SNP. $P< 0.05$ was considered significant in the main analysis.

RESULTS

Our study was performed on 100 CAD cases and 100 controls. The demographic characteristics of patients are shown in Table 1 according to the case and control groups. There were significant differences between two groups in the following parameters: systolic and diastolic blood pressure, FBS, TG, TC, HDL and LDL. The genotyping results for ADAMTS7 gene, rs1994016, are shown in Table 2 and the observed frequencies of the SNP were consistent with Hardy-Weinberg equilibrium.

The rate of genotyping success was greater than 95% for the selected SNP. As it is shown in Table 3, the CT and TT genotypes of rs1994016 in a codominant model ($p<0.001$), CT+TT genotype in a dominant model ($p<0.001$), TT genotype in a recessive model ($p<0.001$) and CT genotype in an overdominant model ($p = 0.01$) were all found to be significantly associated with a higher risk of CAD.

Table 1. Characteristics of 200 study subjects in case and control groups.

Base line characteristic	Case (n=100)	Control (n=100)	P-value
Age(years)	58.65±6.46	48.15±9.83	0.14
BMI (kg/m²)	27.46±3.63	25.26±7.17	0.116
SBP (mm Hg)	135.8±11.72	114.92±27.22	<0.001
DBP (mm Hg)	83.5±7.55	75.95±13.48	<0.001
Hip Circumstance	102.12±8.04	99.77±9.52	0.218
Waist Circumstance	96.75±9.98	87.73±12.05	0.086
TG(mg/dl)	155.8±60.94	115.12±62.94	0.002
FBS (mg/dl)	139.05±64.49	86.77±39.62	0.001
HDL(mg/dl)	39.15±12.72	48.61±13.77	<0.001
LDL(mg/dl)	102.04±28.31	93.66±28.87	<0.001
TC(mg/dl)	173.56±38.42	174.42±26.12	0.825

The data are presented as the mean ± s.d.. The p-value was calculated using Student's t-test or the $\chi 2$-test. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol.

Table 2. Results of genotyping in case and control groups.

Genotype	CAD (N=100)	Control (N=100)	Total (N=200)
CC	2	81	83
CT	34	18	52
TT	64	1	65
Total	100	100	200

Table 3. Association analysis of rs1994016 with CAD assuming different genetic models.

Model	Genotype	Case (n=100)	Control (n=100)	OR(95%CI)	P-Value
Codominant	CC	2(2%)	81(81%)	1	<0.001
	CT	34(34%)	18(18%)	0.013(0.003-0.059)	
	TT	64(64%)	1(1%)	<0.001(<0.001-0.004)	
Dominant	CC	2(2%)	81(81%)	1	<0.001
	CT-TT	98(98%)	19(19%)	0.005(0.001-0.021)	
Recessive	CC-CT	36(36%)	99(99%)	1	<0.001
	TT	64(64%)	1(1%)	0.006(0.001-0.042)	
Overdominant	CC-TT	66(66%)	82(82%)	1	0.010
	CT	34(34%)	18(18%)	0.426(0.221-0.822)	

DISCUSSION

In this present study we investigated the association between rs1994016 on ADAMTS-7 gene and the incidence of CAD in a case-control study of 200 Iranian subjects. The results showed a significant association between this polymorphism and susceptibility of developing CAD. The ADAMTS-7 gene has been previously

replicated in several studies across populations from Europeans to East Asians (3, 4, 10). The fact that ADAMTS-7 has been identified as a novel locus for CAD might have been facilitated by use of coronary angiography confirmed cases in different studies as well as our current study, because an angiographic CAD label, besides the clinical definition, requires a specified impression of coronary atherosclerosis simultaneously. It has been observed that members of ADAMTS genes family have a similar domain structure, consisting of a preproregion, a reprolysin-type catalytic domain, a disintegrin-like domain, a thrombospondin type-1 module, a cysteine-rich domain, a spacer domain, and a COOH-terminal thrombospondin type-1 module. ADAMTS-7 derived protein degrades cartilage oligomeric matrix protein and has been implicated in bone growth and inflammatory arthritis. In 2009, Wang et al. reported that polymorphisms and mutations that lead to overexpression or up-regulation of ADAMTS-7 gene greatly accelerated VSMC migration and contributed to neointimal thickening and progression of atherosclerotic plaques (15) which is considered to be through degradation of COMP (19). These findings suggest that ADAMTS-7 has a considerable role in the proliferative response to vascular injury, which is a known phase of progression of atherosclerosis (20).

Reilly et al. conducted a meta-analysis study of CAD associated SNPs on 15,810 European subjects, mainly from the PennCath and MedStar study cohorts. Among more than 2.4 million primarily genotyped and imputed SNPs, rs1994016 showed a highly significant association with CAD (P-value: $4•98\times10^{-13}$) throughout a four stage criteria of SNP selection based on the approach of Kathiresan and colleagues (10). With respect to this result, ADAMTS-7 locus was reported as a novel locus for coronary atherosclerosis. The finding of our study that rs1994016 polymorphism was significantly associated with an increased risk of CAD is in line with that of the epidemiological study by Reilly et al. Moreover, it has been discussed in Reilly et al. study that this locus does not predict the incidence or prevalence of myocardial infarction (MI) in patients with CAD (21); however, this locus and other determined loci for CAD may relate to MI indirectly via atherosclerosis process rather than showing a certain contribution to vulnerable plaque and MI.

Rs1994016 is in linkage disequilibrium (LD) with the other lead CAD-related SNPs, rs3825807 and rs4380028, identified in two recent GWASs ($r2 > 0.8$ with rs3825807 and > 0.4 with rs4380028, based on data from HapMap and the 1000 Genomes Project). Considering the physical location of this SNP in intron 8 of ADAMTS-7, it might have an influence on its expression or act as a proxy marker for other functional SNPs like rs3825807; even though no supporting evidence has been reported up to now. ADAMTS-7 is present in human coronary and carotid atherosclerotic plaques in which VSMCs with accumulated ADAMTS-7 are mostly located near the intima-media border and the fibrous cap (22). Furthermore, in a general population cohort study ($n = 787$), we detected an association between the presence of carotid atherosclerosis and the minor allele (G) of the ADAMTS-7 SNP rs3825807, with the G/G genotype having a protective effect (22).

Results suggest that the rs3825807 polymorphism leading to a Ser-to-Pro substitution in the prodomain, influences ADAMTS-7 maturation, COMP degradation and VSMC migration and is associated with subclinical atherosclerosis (22). Animal models and cell and molecular studies implicated ADAMTS-7 in the pathogenesis of atherosclerosis. The totality of evidence indicates that ADAMTS-7 can facilitate VSMC migration in the arterial intima and promote vascular calcification through degradation of COMP, thereby leading to atherosclerotic plaque development. This raises the intriguing possibility that therapeutic blockade of ADAMTS-7 directly or indirectly by interfering with its substrates may protect against atherosclerosis (22). Interestingly,

in available expression quantitative trait loci (eQTL) data sets with large sample sizes,189 the lead SNPs from the PennCath (rs1994016), CARDIoGRAM (rs3825807), and C4D (rs4380028) GWAS studies demonstrate a significant association with ADAMTS-7 expression and match the directionality and causality of in vivo data using mouse model, with the CAD risk alleles being associated with higher ADAMTS-7 expression. However, currently there are no large eQTL or RNA-Seq-based ASE data that provide adequate power to determine eQTL directionality in the most pertinent human vascular cells and tissues (23). The GWAS studies, variants rs4380028, rs1994016, and rs3825807 in the ADAMTS-7 gene were associated with human CAD but not acute myocardial infarction (24). The rs3825807G/G genotype in the ADAMTS-7 locus was associated with lower atherosclerosis prevalence and severity (24). However, the direct report of circulation ADAMTS-7 levels in stable CHD patients is still lacking (24). To the best of our knowledge, the present study is the first study to investigate the associations between plasma ADAMTS-7 and severity of CAD in Iranian population.

It is plausible that ADAMTS-7 plays a key role in mediating VSMC responses to inflammatory stresses in atherosclerosis and facilitates VSMC phenotype transition and localized matrix remodeling (25). ADAMTS-7 plays a key role in the regulation of VSMC phenotype switching and the development of atherosclerosis (25). Atherosclerotic lesions as well as early lesions suggest that therapeutic inhibition of ADAMTS-7 even in established and advanced human disease might translate to clinical benefit (25). Similar to rs3825807, the other rs1994016 and rs4380028, exhibited genotypic effects on VSMC migration in our experiments, which could be due to LD between these three SNPs as discussed earlier. The finding from our study that in atherosclerotic plaques, ADAMTS-7 positive VSMCs were predominantly located near the intima-media border is in line with the notion that ADAMTS-7 may play a role in VSMC migration during atherogenesis (26). It is reported, ADAMTS-7 and SNPs rs1994016 and rs4380028 which respectively reside in intron 8 and 7.6 kb upstream of the ADAMTS-7 gene. However the mechanisms underlying disease association have remained unclear (27).

In conclusion, overexpression of ADAMTS-7 accelerates migration of vascular smooth muscle cells in vitro and exacerbates neointimal thickening after carotid artery injury in vivo, perhaps through degradation of cartilage oligomeric matrix protein. These data implicate ADAMTS-7 in the proliferative response to vascular injury, a process that has parallels to the progressive phase of atherosclerosis. These mechanistic findings coincide with the lack of association of ADAMTS-7 SNPs with early-onset myocardial infarction (28). These results suggested ADAMTS-7 rs1994016 were associated with susceptibility to CAD in Iranian population. Recently over 40 genomic loci have been identified by GWAS to be correlated with genetic susceptibility to CAD. However, for many of these loci, the functional mechanisms leading to the observed effect remain unknown. It is worth mentioning that allelic frequencies of different genetic variants and polymorphisms may differ in genetic pools and populations. Therefore, functional characterization of these genetic variants and their diversity in different populations can help understanding the underlying biological mechanisms and may facilitate the translation of the genetic discoveries to effective therapeutic developments. The results of our current study on ADAMTS-7 are pertinent in this context.

REFERENCES

1. World Health Organization (2008) The 10 leading causes of death by broad income group (2004) Fact sheet no. 310.
2. Zdravkovic, S., Wienke, A., Pedersen, N.L., Marenberg, M.E., Yashin, A.I. and de Faire, U. Genetic influences on CHD-death and the impact of known risk factors: comparison of

two frailty models. Behav. Genet. 2004; 34, 585–592.

3. Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet. 2011;43(4):333–338.
4. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. Nat Genet. 2011;43(4):339–344.
5. Kathiresan S,WillerCJ, PelosoGMet al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet 2009; 41: 56–65.
6. Newton-Cheh C,JohnsonT,GatevaV et al. Genome-wide association study identifies eight loci associated with blood pressure. NatGenet2009;41:666–76.
7. PatelRS, SuS,NeelandIJ et al. The chromosome 9p21 risklocus is associated with angiographic severity and progression of coronary artery disease.EurHeart J2010;31:3017–23.
8. Muendlein A, Saely CH, Rhomberg S et al. Evaluation of the association of genetic variants on the chromosomal loci 9p21.3, 6q25.1, and 2q36.3 with angiographically characterized coronary artery disease. Atherosclerosis2009;205:174–80.
9. Kathiresan S,MelanderO,AnevskiDet al. Polymorphisms associated with cholesterol and risk of cardiovascular events. N Engl JMed2008;358:1240–9.
10. Reilly MP, Li M, He J, Ferguson JF, Stylianou IM, Mehta NN, Burnett MS, Devaney JM, Knouff CW, Thompson JR, Horne BD, Stewart AF, Assimes TL, Wild PS, Allayee H, Nitschke PL, Patel RS, Martinelli N, Girelli D, Quyyumi AA, Anderson JL, Erdmann J, Hall AS, Schunkert H, Quertermous T, Blankenberg S, Hazen SL, Roberts R, Kathiresan S, Samani NJ, Epstein SE, Rader DJ. Identification of ADAMTS7 as a novel locus for coronary

atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies. Lancet. 2011;vol. 377:383–392.
11. Peden, J.F. & Farrall, M. Thirty-five common variants for coronary artery disease: the fruits of much collaborative labour. Hum. Mol. Genet. 20, R198–R205 (2011).
12. Somerville RP, Longpre JM, Apel ED, Lewis RM, Wang LW, Sanes JR, Leduc R, Apte SS. ADAMTS7B, the full-length product of the ADAMTS7 gene, is a chondroitin sulfate proteoglycan containing a mucin domain. J. Biol. Chem. 2004;vol. 279:35159–35175.
13. Wight TN, Merrilees MJ. Proteoglycans in atherosclerosis and restenosis: key roles for versican. Circ Res. 2004;94(9):1158–1167.
14. Wight TN. Arterial remodeling in vascular disease: a key role for hyaluronan and versican. Front Biosci. 2008;13:4933–4937.
15. Liu CJ, Kong W, Ilalov K, Yu S, Xu K, Prazak L, Fajardo M, Sehgal B, Di Cesare PE. ADAMTS-7: a metalloproteinase that directly binds to and degrades cartilage oligomeric matrix protein. FASEB J. 2006;20(7):988–990.
16. Wang L, Zheng J, Bai X, Liu B, Liu CJ, Xu Q, Zhu Y, Wang N, Kong W, Wang X. ADAMTS-7 mediates vascular smooth muscle cell migration and neointima formation in balloon-injured rat arteries. Circ Res. 2009;104(5):688–698.
17. World Health Organization. Prevention of cardiovascular disease. Guidelines for assessment and management of cardiovascular risk. Geneva, 2007.
18. Scanlon PJ, Faxon DP, Audet AM, et al. Acc/aha guidelines for coronary angiography: executive summary and recommendations. A report of the American college of cardiology/American heart association task force on practice guidelines (committee on coronary angiography) developed in collaboration with the society for cardiac angiography and interventions. Circulation 1999;99:2345–57.
19. Riessen R., Fenchel M., Chen H., Axel D.I., Karsch K.R., Lawler J. Cartilage oligomeric matrix protein (thrombospondin-5) is expressed by human vascular smooth muscle cells. Arterioscler. Thromb. Vasc. Biol. 2001;21:47–54.
20. Hansson GK. Infl ammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685–95.
21. Horne BD, Carlquist JF, Muhlestein JB, et al. Association of variation in the chromosome 9p21 locus with myocardial infarction versus chronic coronary artery disease. Circ Cardiovasc Genet 2008; 1: 85–92.
22. Patel RS, Ye S, PathFRC. ADAMTS7: a promising new therapeutic target in coronary heart disease, Expert Opinion Ther Targets 2013; 17:8, 863-867, DOI: 10.1517/14728222.2013.816287.
23. Nurnberg ST, Zhang H, Hand NJ, Bauer RC, Saleheen D, Reilly MP, Rader DJ. From loci to biology functional genomics of genome-wide association for coronary disease. Circ Res. 2016; 118:586-606.
24. Yu J, Zhou B, Yu H, Han J, Cui M, Zhang F, Wang G, Guo L, Gao W. Association between plasma ADAMTS-7 levels and severity of disease in patients with stable obstructive coronary artery disease. Medicine2016; 95:48(e5523.
25. Bauer RC, Tohyama J, Cui J, Cheng L, Yang J, Zhang X, Ou K, Paschos GK, Long Z, Parmacek MS, Rader DJ, Reilly MP. Knockout of Adamts7, a Novel CAD locus in humans, reduces atherosclerosis in mice. Circulation. 2015 March 31; 131(13): 1202–1213.
26. Pu, X., Q. Xiao, S. Kiechl, K. Chan, F. L. Ng, S. Gor, R. N. Poston, C. Fang, A. Patel, E. C. Senver, S. Shaw-Hawkins, J. Willeit, C. Liu, J. Zhu, A. T. Tucker, Q. Xu, M. J. Caulfield and S. Ye. ADAMTS7 cleavage and vascular smooth muscle cell migration is affected by a

coronary-artery-disease-associated variant. Am J Hum Genet 2013; 92(3): 366-374.
27. Somerville RP, Longpre JM, Apel ED, et al. ADAMTS7B, the full-length product of the ADAMTS7 gene, is a chondroitin sulfate proteoglycan containing a mucin domain. J Biol Chem 2004; 279: 35159–75.
28. Wang L, Zheng J, Bai X, et al. ADAMTS-7 mediates vascular smooth muscle cell migration and neointima formation in balloon-injured rat arteries. Circ Res 2009; 104: 688–98.