T-CADHERIN GENE POLYMORPHISM IS ASSOCIATED WITH CORONARY HEART DISEASE MANIFESTATIONS

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A number of studies have shown that a *CDH13*-encoded T-cadherin protein, which is a receptor for low density lipoproteins and adiponectin, an adipocyte hormone, is associated with atherosclerosis and coronary heart disease (CHD) development. Some single nucleotide polymorphisms in *CDH13* gene affect the expression of T-cadherin and the levels of adiponectin and blood plasma lipids, but the connection between these polymorphisms and CHD development has not been studied yet. In this work the role of *rs12051272, rs4783244*, *rs12444338* and *rs11646213* single nucleotide polymorphisms in CHD development and its manifestations was investigated. The study enrolled men under 55 years of age: 79 patients with stable effort angina with no prior myocardial infarction, 107 patients with prior myocardial infarction being the first manifestation of CHD, and 99 healthy subjects. All subjects were clinically examined; laboratory tests and genotyping were conducted. The results of genotyping were evaluated using SNPStats on-line software. This study has not found a connection between *CDH13* gene polymorphisms and CHD development. However, it was shown that *rs12051272* polymorphism is associated with the specifics of the disease onset: GT genotype was detected in 13 (16.5 %) patients with stabile effort angina and only in 3 (2.8 %) patients with myocardial infarction (odd ratio of 7.54; 95 % confidence interval of 2.01–28.35). Thus, the study demonstrates that *CDH13* gene polymorphism can affect atherogenesis and CHD manifestations.

Keywords: T-cadherin, *CDH13*, gene polymorphism, low density lipoproteins, adiponectin, coronary heart disease, myocardial infarction

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ПОЛИМОРФИЗМ ГЕНА Т-КАДГЕРИНА (*CDH13*) АССОЦИИРОВАН С ХАРАКТЕРОМ МАНИФЕСТАЦИИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА

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Ряд исследований показал, что белок Т-кадгерин, кодируемый геном *CDH13* и являющийся одновременно рецептором липопротеидов низкой плотности и адипоцитарного гормона адипонектина, играет роль в развитии атеросклероза и ишемической болезни сердца (ИБС). Некоторые однонуклеотидные замены в гене *CDH13* влияют на экспрессию Т-кадгерина, уровни адипонектина и липидов плазмы крови, однако связь между данными заменами и развитием ИБС не исследована. В настоящей работе изучали роль однонуклеотидных замен *rs12051272*, *rs4783244*, *rs12444338* и *rs11646213* в развитии ИБС и характере ее манифестации. В исследование включили мужчин в возрасте до 55 лет: 79 пациентов со стабильной стенокардией напряжения без инфаркта миокарда, 107 человек, перенесших инфаркт миокарда как дебют ИБС, и 99 здоровых лиц. Всем исследуемым проводили клинико-лабораторное обследование и генотипирование. Результаты генотипирования оценивали с помощью онлайн-программы SNPStats. В настоящей работе взаимосвязи полиморфизма гена *CDH13* с развитием ИБС не выявлено, однако показано, что замена *rs12051272* ассоциирована с характером дебюта заболевания: генотип GT выявили у 13 (16,5 %) пациентов со стабильной стенокардией напряжения и только у 3 (2,8 %) человек с инфарктом миокарда (отношение шансов — 7,54; 95 % доверительный интервал — 2,01–28,35). Таким образом, показано, что полиморфизм гена *CDH13* может влиять на процессы атерогенеза и характер манифестации ИБС.

Ключевые слова: Т-кадгерин, *CDH13*, генетический полиморфизм, липопротеиды низкой плотности, адипонектин, ишемическая болезнь сердца, инфаркт миокарда

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Coronary heart disease (CHD) is an extremely important medical and social issue. This disease is currently one of the leading causes of death and disability worldwide [1].

Acute coronary syndrome is often the first symptom of CHD. Intravascular thrombi are formed on the surface of a damaged atherosclerotic plaque, which leads to the development of myocardial infarction (MI) [2]. The median percent stenosis of the infarct-related artery is 48% [3]. Thus, patients with unstable plaques can be spared angina and other myocardial ischemia symptoms, but are very likely to develop acute MI. In case the atherosclerotic plaque and CHD develop gradually, stable effort angina (SEA) often becomes the first manifestation of the disease.

The mechanism of unstable atherosclerotic plaque formation has not been fully studied. Some studies have shown that T-cadherin has an important role in the development of atherosclerosis and CHD [4-7]. T-cadherin is a glycosylphosphatidylinositol-anchored protein; it belongs to the cadherin superfamily and is a receptor for low density lipoproteins (LDL) [8] and high molecular weight adiponectin, a hormone secreted by adipose tissue [9]. Many works describe the antiatherosclerotic effects of adiponectin resulting from the increased synthesis of high density lipoproteins in the liver, the reduction of cholesterol concentration in the atherosclerotic plaque [10-12] and the suppression of macrophage-to-foam-cell transformation [13]. M.M.Joosten et al. showed that low adiponectin was associated with atherosclerosis development: reduced adiponectin levels in blood serum correlated with the presence of multiple atherosclerotic vascular lesions [14, 15]. By contrast, X.J.Cai et al. demonstrated that adiponectin suppresses proliferation, migration and transformation of adventitial fibroblasts [16], which possibly causes cap thinning and increases the risk of MI. T-cadherin also functions as an LDL receptor [8,17] and thus contributes to the build-up of an unstable atherosclerotic plaque independently of adiponectin.

Some studies showed that single nucleotide polymorphisms in T-cadherin gene (*CDH13*) can affect a diponectin concentrations in blood and thus be a part of the mechanism of cardiovascular disorder development. However, there are almost zero data on the *CDH13* polymorphism association with CHD and MI. For this work we have selected four single nucleotide polymorphisms in *CDH13* gene and investigated the connection between them and both CHD development and symptoms indicative of the disease onset. It was established that *rs12051272* (G→T) and *rs4783244* (G→T) polymorphisms [18, 19] are associated with the adiponectin level changes in blood serum. The single nucleotide polymorphism *rs12444338* (G→T) is related to the changes in T-cadherin gene promoter activity [20] and to the carotid intima-media thickness [21], which indicates its possible impact on the atherogenesis. No similar data were obtained in relation to *rs11646213* (A→T) polymorphism [19, 22]; however, allele A is associated with the reduced risk of arterial hypertension (AH) and the increased risk of metabolic syndrome development [22, 23]. All polymorphisms studied in this work are associated with blood serum lipid levels [22, 24-26].

METHODS

The study enrolled 285 men aged 26 to 55. Blood samples and clinical data were obtained from the biobank of the Faculty of Fundamental Medicine of Lomonosov Moscow State University. All patients signed the informed consent as required by the Declaration of Helsinki. The control group consisted of 99 individuals: military air forces pilots without arterial hypertension, dyslipidemia and CHD signs according to cardiac stress test results. The group of patients with CHD included 186 individuals, with the age of onset being below 55. Based on the symptoms accompanying the disease onset, two subgroups were formed. For the first subgroup (n=79), the inclusion criteria was SEA without MI confirmed by cardiac stress test or coronary angiography. The second subgroup (n=107) included men in whom CHD first manifested itself as a clinically, laboratorially (elevated levels of myocardial necrosis markers) and instrumentally (electrocardiography, echocardiography, radionuclide diagnostics) confirmed MI without prior effort angina. Coronary angiography data were not used as a criterion for MI diagnosis; however, coronary angiography was performed on the patients with MI for deciding on the further treatment when the connection between MI and coronary atherosclerosis was not certain. Glucose tolerance defects and diabetes mellitus were exclusion criteria for all groups.

Patients were diagnosed with AH if their systolic blood pressure was higher than 140 mmHg and diastolic blood pressure was higher than 90 mmHg, or if they were undergoing the antihypertensive therapy. Patients were diagnosed with dyslipidemia if total blood cholesterol was over 5.3 mmol/l, LDL was over 3.0 mmol/l, or if patients were undergoing the antihyperlipidemic therapy at the time of CHD onset. Patients with body mass index over 30 were considered obese. For this study we used the data obtained from the first medical examination at the time of CHD diagnosis.

Genomic DNA was extracted using QIAamp DNA Blood Mini Kit (QIAGEN, Germany) and QIAcube robotic workstation (QIAGEN, Germany) for sample preparation of venous blood stabilized by EDTA. Genotyping was performed using TaqMan SNP Genotyping Assays (Applied Biosystems, USA).

For qualitative characteristics, the significance of differences between the groups was assessed by Yates chi-squared test. Distribution of qualitative characteristics was evaluated by Shapiro-Wilk test. Characteristics with near normal distribution were assessed using Student's t-test; other qualitative characteristics were assessed by Mann-Whitney U-test. In all cases the difference was interpreted as statistically significant with $p<0.05$. Genotyping data were analyzed using SNPStats software. To assess the probability of disease development with different genotypes, odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated. Akaike information criterion (AIC) was used to detect the inheritance pattern (codominant, dominant, recessive, superdominant and log-additive) that best matched the obtained results [27].

RESULTS

Major risk factors and their prevalence in the individuals enrolled in the study are presented in tables 1 and 2. Differences between the group of patients with CHD and the controls based on the prevalence of major risk factors and age were accounted for in the mathematical models describing the obtained results. At the same time, no significant differences were observed in the prevalence of major risk factors of cardiovascular diseases between the subgroups of patients.

No statistically significant difference was found in the frequencies of different genotypes while comparing the controls with the group of patients who had CHD, and while comparing the controls with each of subgroups of patients who had stable effort angina and prior myocardial infarction.

However, while comparing the controls with the subgroup of patients with SEA disregarding such traditional risk factors as age, obesity, smoking, dyslipidemia and AH, differences in the

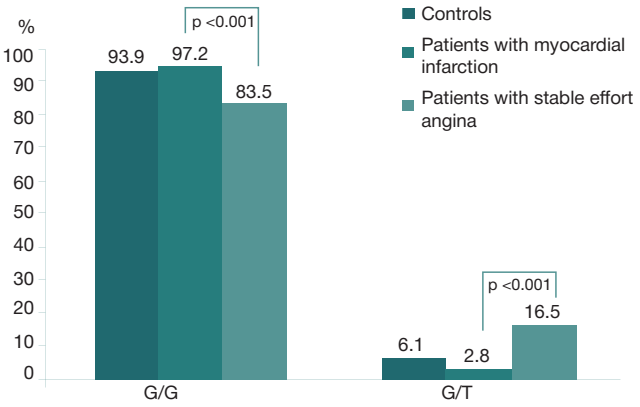
frequencies of *rs12051272* and *rs11646213* polymorphisms were detected (see tables 3, 4).

To clarify the role of these polymorphic markers, subgroups of patients with MI and SEA were compared. When introducing traditional risk factors to the model, statistically significant differences were obtained for *rs12051272* polymorphism only; for G/T genotype the OR (95% CI) of stable effort angina development was 7.54 (2.01-28.35) (see table 5). For *rs11646213* polymorphism no statistically significant difference was found.

Thus, no statistically significant differences were found between the controls and each of the studied subgroups; however, the association of *rs12051272* polymorphism with CHD manifestation pattern (MI or SEA) was shown . *rs12051272* genotype frequency data are presented in the chart below.

DISCUSSION

Reduced T-cadherin level in blood plasma is associated with the severity of atherosclerotic damage of coronary arteries and acute coronary syndrome development [7], which indicates a possible connection between *CDH13* gene polymorphism that affects protein levels and the development of CHD and its manifestation patterns. It is known that *rs12444338* (G/T) polymorphism is associated with both adiponectin level and *CDH13* promoter activity [20], that is why we expected that this marker would be associated with CHD development.



Frequency of *rs12051272* polymorphism genotypes of *CDH13* gene in the studied groups

However, no data indicated the correlation of *rs12444338*, *rs4783244* and *rs11646213* polymorphisms with CHD development and its manifestation patterns. Similar results were presented by H. Morisaki et al. for *rs12444338*; they did not find any effect of that polymorphism on MI development and the levels of LDP and adiponectin [19].

Mathematical models applied in this study accounted for the traditional factors of cardiovascular risk (age, AH, smoking, obesity and dyslipidemia), but the specifics of the controls did not allow for the demonstration of *CDH13* polymorphism association with CHD development. Still, the association of *CDH13* polymorphism with the disease manifestation pattern was shown: the frequency of G/T genotype of *rs12051272* polymorphism was significantly higher in the group of patients with SEA and without MI (16.5 and 2.8 %, respectively); OR was 7.54; 95 % CI was 2.01–28.35. The obtained data can indicate the possible protective role of T allele, which is a paradox, because this allele is associated with a lower level of adiponectin in blood plasma [19].

There are a number of possible explanations for the association discovered in this work. First, it should be noted that detecting the level of circulating adiponectin in patients with MI is hindered: it binds to T-cadherin and accumulates in the zone of myocardial damage [28], thus the reduced adeponectin level in patients with MI can be merely a result of this process [29]. Besides, adiponectin is likely to induce a number of various effects on the build-up of atherosclerotic plaques and MI development. On the one hand, high levels of adiponectin prevent the development of MI by normalizing the lipid profile [10] and suppressing macrophage transformation to foam cells [13]. On the other hand, some works have shown that adiponectin suppresses the migration of fibroblasts and their transformation to miofibroblasts [16]. As a part of this

Table 1. Prevalence of risk factors in the studied groups

Risk factors	Controls, n=99	Patients with CHD, n=186
Age, years*	36.0 (32.0; 39.0)	47.0 (44,0; 51.0)#
Dyslipidemia	0 (0)	52 (27.96 %)#
Obesity	7 (7.07 %)	57 (30.65 %)#
Smoking	27 (27.27 %)	93 (50.00 %)#
AH	0 (0)	116 (62.37 %)#

For patients with CHD, the age of the disease onset is shown; the median (interquartile range) # is presented; # — p<0.001 when compared with the corresponding figure in the controls.

Table 2. Prevalence of risk factors in the controls and the subgroups of patients

Risk factors	Controls, n=99	Patients with SEA, n=79	Patients with MI, n=107	p^{1-2}	p^{1-3}	p^{2-3}
Age, years*	36.0 (32.0; 39.0)	48.0 (43.0; 51.0)	47.0 (44.0; 52.0)	<0.001	<0.001	0.971
Dyslipidemia	0 (0)	24 (30.38 %)	28 (26.17 %)	<0.001	<0.001	0.64
Obesity	7 (7.07 %)	29 (36.71 %)	28 (26.17 %)	<0.001	<0.001	0.167
Smoking	27 (27.27 %)	35 (44.30 %)	58 (54.21 %)	<0.05	<0.001	0.235
AH	0 (0)	53 (67.09 %)	63 (58.88 %)	<0.001	<0.001	0.322

* — for the subgroups of patients, the age at the time of the disease onset is shown; the median (interquartile range) is presented; p^{1-2} —statistically significant differences between the controls and the subgroup of patients with SEA; p^{1-3} — statistically significant differences between the controls and the subgroup of patients with MI; p^{2-3} — statistically significant differences between the subgroups of patients.

Table 3. Frequency of *rs12051272* polymorphism genotypes of *CDH13* in healthy subjects and patients with stable effort angina without consideration of risk factors

Genotype	Controls, n (%)	Patients with SEA, n (%)	OR (95% CI)	p	AIC
G/G	93 (93.9)	66 (83.5)	1	< 0.05	243.5
G/T	6 (6.1)	13 (16.5)	**3.05 (1.10–8.45)**		

Table 4. Frequency of *rs11646213* polymorphism genotypes of *CDH13* in healthy subjects and patients with stable effort angina without consideration of risk factors

Inheritance pattern	Genotype	Controls, n (%)	Patients with SEA, n (%)	OR (95% CI)	p	AIC
Codominant	T/T	36 (36.4)	35 (44.3)	1	0,07	245.2
	A/T	44 (44.4)	38 (48.1)	0.89 (0,47–1.68)		
	A/A	19 (19.2)	6 (7.6)	**0.32 (0.12–0.91)**		
Dominant	T/T	36 (36.4)	35 (44.3)	1	0,28	247.4
	A/T-A/A	63 (63.6)	44 (55.7)	0.72 (0.39–1.31)		
Recessive	T/T-A/T	80 (80.8)	73 (92.4)	1	0,023	243.3
	A/A	19 (19.2)	6 (7.6)	**0.35 (0.13–0.91)**		
Superdominant	T/T-A/A	55 (55.6)	41 (51.9)	1	0,63	248.3
	A/T	44 (44.4)	38 (48.1)	1.16 (0.64–2.10)		
Log-additive	–	–	–	0.66 (0.42–1.02)	0,058	244.9

Table 5. Frequency of *rs12051272* polymorphism genotypes of *CDH13* in patients with stable effort angina and myocardial infarction with the consideration of all risk factors of interest

Genotype	Patients with MI, n (%)	Patients with SEA, n (%)	OR (95% CI)	p	AIC
G/G	104 (97.2)	66 (83.5)	1	< 0.001	251.1
G/T	3 (2.8)	13 (16.5)	**7.54 (2.01–28.35)**		

mechanism, adiponectin can cause thinning of fibrous cap of the already formed atherosclerotic plaque, which eventually causes its rupture, atherothrombosis and MI. It should be noted that changes in T-cadherin level can affect sensitivity to insulin, activity of endothelial nitric oxide synthase, endothelial cells migration and angiogenesis [30], contractile activity of vascular smooth muscle cells and organization of extracellular matrix [31]. All these factors can change the pattern of atherosclerosis development.

There is some evidence that T-cadherin level (at least in blood plasma) negatively correlates with the level of adiponectin in young males, while in females this correlation is positive [32]. The inclusion of only male individuals was a limitation of this study.

CONSLUSIONS

It has been shown that genetically determined variations in T-cadherin expression are associated with the pattern of CHD onset: myocardial infarction or stable effort angina. This indicates T-cadherin participation in atherogenesis and its effect on the stability of atherosclerotic lesions. The mechanism of this effect can be associated with adiponectin or LDP activity and requires further examination. The obtained results can be useful for the assessment of the myocardial infarction risk and for the prediction of how the initial atherosclerotic changes will progress.

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