ORIGINAL ARTICLE

CD36 gene is associated with thickness of atheromatous plaque and ankle-brachial index in patients with early coronary artery disease

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Abstract

Background: CD36 is a multifunctional molecule engaged in the removal of oxidised LDL from plasma. It is unclear whether mutation of the *CD36* gene protects against, or increases, the risk of hypercholesterolaemia, atherosclerosis and its complications.

Aim: To search for associations between the *CD36* gene polymorphisms and radiological markers of atherosclerosis progress in Caucasian patients with coronary artery disease (CAD) diagnosed at a young age.

Methods: The study group comprised 70 patients with early CAD. Doppler ultrasound of carotid and peripheral arteries was carried out and genomic DNA was isolated from each patient.

Results: We found two single nucleotide substitutions in introns (IVS3-6 T/C – rs3173798 and IVS4-10 G/A – rs3211892) and two synonymous polymorphisms in exon 6 (G573A – rs5956 and A591T). The allele frequencies were: 10.7% for the IVS3-6C, 3.6% for the IVS4-10A, 3.6% for the 573A, and 2.1% for the 591T. The 573A allele of *CD36* rs5956 polymorphism is associated with low thickness of atheromatous plaque. The 591T allele is associated with lower ankle–brachial index.

Conclusions: The 573A allele has a protective effect against atherosclerosis development and the 591T allele is a cardiovascular risk factor. Assessment of their functional implications requires further research.

Key words: *CD36* gene, genetic risk factors, atheromatous plaque, ankle–brachial index

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INTRODUCTION

The aetiology and pathogenesis of atherosclerosis is complex; progression is particularly rapid when environmental factors coexist with genetic ones. Features which predispose to atherogenesis depend on genes coding for various proteins which participate in the metabolism of lipoproteins, regulate the equilibrium between coagulation and fibrinolysis, control blood pressure, and catalyse the reactions of homocysteine turnover [1]. Recently, increasing interest has been devoted to growth factors and adhesion proteins which appear to play a very important role in the formation of the atheromatous plaque [2, 3]. This group includes CD36 — a type B scavenger receptor located on the surface of many cell types. One of the functions of CD36 is the removal of oxidised low-density lipoproteins (oxLDLs) from plasma by macrophages and monocytes [4, 5]. It is also a long-chain fatty acid receptor [6]. The *CD36* gene is located on chromosome 7 q11.2 and encoded by 15 exons [7, 8]. The receptor is present on the surface of platelets, endothelial cells, macrophages, dendrite cells, adipocytes, striated muscle cells and haematopoietic cells [9, 10].

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More than 20 mutations in the coding sequence of the *CD36* gene have been described [6, 11, 12]. CD36 deficiency is divided into two subgroups according to the phenotypes. In type I deficiency, neither platelets nor monocytes express CD36, while in type II deficiency (very rare in Caucasians — 0.3% of the population, but more frequent in Asians and Afro-Americans — 3–4% of the population), CD36 is expressed in monocytes but not in platelets [13].

CD36 may play an important role in the pathogenesis of metabolic diseases. In our earlier study, we observed that *CD36* IVS3-6C allele is associated with young age of myocardial infarction [14]. Some other reports have pointed to increased total cholesterol and LDL cholesterol concentrations in serum in association with mutations of the *CD36* gene [15]. Recently, CD36 has been reported to play an important role in atherogenicity [16]. Some authors have suggested that polymorphisms of the *CD36* gene modulate lipid metabolism and cardiovascular risk in Caucasians [17–19]. There has been no clear evidence either way as to whether mutation of the *CD36* gene protects against, or increases, the risk of atherosclerosis and complications.

The aim of this study was to investigate if there is an association between the sequence changes in the *CD36* gene region encoding the oxLDL- and fatty acid-binding domain and radiological markers of atherosclerosis progress in Caucasian patients with coronary artery disease (CAD) diagnosed at a young age.

METHODS

The study group comprised 70 patients (18 women and 52 men) with early CAD (i.e. diagnosed at no more than 50 years for men and 55 years for women). The patients were all Polish residents hospitalised in the Department of Cardiology of the County Hospital in Szczecin in north western Poland, and then referred to the outpatient clinic between 2008 and 2011. Clinically stable patients with optimal pharmacological treatment and no acute coronary syndrome or revascularisation procedures within the previous month were included in the study. Patients with haemodynamically significant congenital or acquired valvular heart disease, symptomatic heart failure (NYHA class > 1), renal failure (serum creatinine > 3 mg/dL), type 1 diabetes mellitus, thyroid dysfunction (current hypo- or hyperthyroidism), or malignancy were excluded from the study. The criteria for early CAD diagnosis included angiographically documented presence of at least one coronary lesion (≥ 40% diameter stenosis of the left main coronary artery or ≥ 50% stenosis of one of the three major epicardial arteries, or ≥ 70% stenosis of a branch) or a history of revascularisation procedure, or evidence of past myocardial infarction [20].

Doppler ultrasound of carotid and peripheral arteries was carried out in each patient using a Doppler ultrasound unit (Technos, Esaote) by the same experienced radiologist. Intima-media complex thickness (IMC) of common carotid (CCA) and brachial arteries, density and thickness of atheromatous plaque at CCA bifurcation were measured using a M'Ath program [21]. The quality of IMC automatic measurement in each patient was assessed by quality index (QI). Since QI value was > 50% in each case, all measurements were included in further statistical analyses. Density measurement was based on the intensity of reflection from the plaque dependent on calcium deposits. Ankle–brachial index (ABI) was calculated by dividing the systolic blood pressure in the arteries at the left and right ankle (posterior tibial artery) or foot (anterior tibial artery) by the higher of the two systolic blood pressures in the arms.

Each patient's weight, height, waist and hip circumference, systolic and diastolic blood pressure were measured, and the body mass index, waist-to-hip ratio and mean arterial pressure were calculated.

Genomic DNA was extracted from 5 mL EDTA-anticoagulated blood as described [22]. Amplicons of exons 4, 5 and 6 including fragments of introns were studied using the denaturing high-performance liquid chromatography (DHPLC) technique as previously described [23].

This study conformed with the principles outlined in the Declaration of Helsinki and was approved by our institutional Ethics Committee. Informed consent was obtained from each patient.

Statistical analysis

Differences between subgroups of patients classified according to the *CD36* genotype were tested with the Mann-Whitney test for quantitative variables and the Fisher's exact test for qualitative variables. The consistency of genotype distribution with the Hardy-Weinberg equilibrium was assessed with the use of the exact test.

RESULTS

The clinical data, morphometric parameters and pharmacological treatment of patients are presented in Table 1.

Changes detected by DHPLC comprised two single nucleotide substitutions in introns (IVS3-6 T/C – rs3173798 and IVS4-10 G/A – rs3211892) and two synonymous polymorphisms in exon 6 (G573A – rs5956 and A591T) as set out in Table 2. The A591T (Thr197Thr) alteration has been previously described by us in Caucasian newborns [23]. Genotype distributions were consistent with the Hardy-Weinberg equilibrium for all sequence changes ($p = 1$).

The radiological parameters of patients stratified by the *CD36* genotype are presented in Table 3. IVS3-6 TC and IVS4-10 GA heterozygotes did not significantly differ from the wild-type homozygotes in terms of any of the analysed parameters. The exon 6 573GA genotype was associated with significantly lower thickness of plaque of left common carotid artery and bifurcation, as well as with a borderline lower density of plaque of right common carotid artery than wild-type

Table 1. Characteristics of the study group (n = 70)

Parameter	Value
Gender (% males)	74%
SBP [mm Hg]	128 ± 15.0
DBP [mm Hg]	77.6 ± 8.6
MAP [mm Hg]	94.3 ± 9.3
WHR	0.97 ± 0.10
BMI [kg/m^2]	28.4 ± 4.2
History of hypertension	66%
Diabetes (type 2)	13%
Past MI	66%
Age of the first MI [years]	44.0 ± 6.0
Current smoking	11%
Past smoking	93%
Past PTCA	71%
Past CABG	33%
ACEI	80%
ARB	16%
Beta-blockers	86%
Diuretics	27%
CCB	19%
Statins	93%

Data are given as mean ± SD or percentage of patients with the indicated genotype. SBP — systolic blood pressure; DBP — diastolic blood pressure; MAP — mean arterial pressure; WHR — waist-to-hip ratio; BMI — body mass index; MI — myocardial infarction; PTCA — percutaneous transluminal coronary angioplasty; CABG — coronary artery bypass grafting; ACEI — angiotensin 1 converting enzyme inhibitors; ARB — angiotensin 2 receptor blockers; CCB — calcium channel blockers

573GG genotype. The ABI was significantly lower in the exon 6 591AT heterozygotes than in the AA patients. The exon 6 591AT heterozygotes were characterised also by higher prevalence of ABI < 0.9 and a borderline lower prevalence of higher density of plaque (> 70 arbitrary units) than wild-type 591AA homozygotes. The thickness and density of plaque were significantly lower when eight patients with exon 6 G573A or A591T alterations were combined as variant heterozygotes and compared to 62 patients with 573GG and 591AA genotypes (Table 3).

DISCUSSION

No data published to date has suggested an association between variation in the *CD36* gene and radiological indicators of atherosclerosis in any population. We studied an early CAD group to obtain high prevalence of atheromatous plaque presence. It has been demonstrated [24] that CD36 can be detected in the atherosclerotic plaque, and its level increases with the progress of atherosclerosis. Handberg et al. [25] examined Caucasian patients with high-grade internal carotid stenosis (> 70%) treated with carotid endarterectomy or carotid angioplasty with stenting. The plaques were classified as echolucent or echogenic/heterogeneous, depending on plaque echogenicity on ultrasound examination. Plasma concentration of soluble CD36 was measured by enzyme-linked immunoassay. The patients with echolucent carotid plaques tended to have higher soluble CD36 levels compared to those with echogenic/heterogenic plaques. Higher plasma CD36 concentration was also associated with plaque instability and symptomatic carotid atherosclerosis.

In our study, exon 6 591AT heterozygous genotype was significantly associated with lower ABI. We also observed that exon 6 573GA genotype was associated with slightly lower thickness and density of plaque CCA and bifurcation. Furthermore, the thickness and density of plaque were significantly lower in eight patients with exon 6 G573A or A591T alterations combined as variant heterozygotes. This may suggest that these two exon 6 variants have similar functional implications for plaque formation.

It is known that increased risk of atherosclerosis is associated with lower ABI and higher thickness of IMC [26, 27]. Density of plaque reflects its calcification and lower plaque calcification is associated with plaque instability [28, 29]. On the other hand, high plaque calcification is associated with a predisposition to thrombosis and may be consistent with a moderate to high risk of a cardiovascular event within the next two to five years [30]. In our study, 591T allele may be associated with higher cardiovascular risk due to higher proportion of CAD patients with low ABI, and the 573A allele may be regarded as protective since it is associated with lower plaque thickness. *CD36* 591T allele is associated with disadvantageous lower ABI, but its effect on plaque thickness and density seems to be similar to 573A. These results should be confirmed in a larger group due to the low frequency of the A591T variant.

Table 2. *CD36* sequence alterations detected initially by denaturing high-performance liquid chromatography and then confirmed by direct sequencing in a group of 70 patients with coronary artery disease

CD36 exon/intron	DNA sequence alteration	RefSNP(rs) number	Deduced protein sequence alteration	Genotype frequency	Minor allele frequency
Intron 3	IVS3-6 T/C	rs3173798	–	78.6% TT, 21.4% TC	10.7%
Intron 4	IVS4-10 G/A	rs3211892	–	92.7% GG, 7.1% GA	3.6%
Exon 6	G573A	rs5956	Pro191Pro	92.7% GG, 7.1% GA	3.6%
Exon 6	A591T	–	Thr197Thr	95.7% AA, 4.3% AT	2.1%

Table 3. Radiological parameters of 70 patients stratified by IVS3-6 T/C, IVS4-10 G/A, G573A and A591T *CD36* genotypes

CD36 genotype	IVS3-6 T/C			IVS4-10 G/A			Exon 6 G573A			Exon 6 A591T		
	TT (n = 55)	TC (n = 15)	P	GG (n = 65)	GA (n = 5)	P	GG (n = 65)	GA (n = 5)	P	AA (n = 67)	AT (n = 3)	P
ABI right	1.19 ± 0.22	1.14 ± 0.17	0.74	1.19 ± 0.22	1.13 ± 0.04	0.42	1.17 ± 0.21	1.28 ± 0.27	0.36	1.19 ± 0.21	0.83 ± 0.05	0.005
ABI left	1.22 ± 0.26	1.15 ± 0.15	0.28	1.21 ± 0.25	1.13 ± 0.10	0.31	1.19 ± 0.24	1.32 ± 0.34	0.57	1.21 ± 0.24	0.94 ± 0.21	0.078
ABI mean	1.20 ± 0.24	1.14 ± 0.15	0.37	1.19 ± 0.23	1.13 ± 0.06	0.37	1.18 ± 0.22	1.30 ± 0.30	0.46	1.20 ± 0.22	0.88 ± 0.12	0.011
IMC cca right	0.81 ± 0.14	0.81 ± 0.12	0.94	0.81 ± 0.14	0.80 ± 0.07	0.80	0.81 ± 0.14	0.82 ± 0.12	0.87	0.81 ± 0.14	0.86 ± 0.06	0.53
IMC cca left	0.84 ± 0.15	0.80 ± 0.12	0.28	0.83 ± 0.15	0.80 ± 0.10	0.66	0.84 ± 0.14	0.74 ± 0.14	0.24	0.83 ± 0.15	0.84 ± 0.10	0.73
IMC cca mean	0.82 ± 0.12	0.80 ± 0.10	0.87	0.81 ± 0.12	0.80 ± 0.07	0.83	0.82 ± 0.12	0.78 ± 0.11	0.52	0.81 ± 0.12	0.85 ± 0.05	0.42
PLA thickness right	2.02 ± 0.62	1.75 ± 0.34	0.44	1.89 ± 0.53	2.40 ± 0.76	0.19	1.96 ± 0.57	1.78 ± 0.62	0.41	1.94 ± 0.58	1.95 ± 0.55	0.85
PLA length right	8.65 ± 2.77	8.02 ± 2.79	0.42	8.45 ± 2.86	8.62 ± 1.85	0.63	8.70 ± 2.72	6.07 ± 2.02	0.08	8.58 ± 2.83	7.34 ± 1.40	0.56
PLA density right	73.6 ± 20.9	61.5 ± 14.0	0.10	69.1 ± 15.7	78.0 ± 43.2	0.90	72.0 ± 19.3	50.7 ± 15.4	0.084*	71.5 ± 19.9	55.7 ± 12.1	0.16*
PLA thickness left	2.22 ± 0.73	2.31 ± 0.50	0.59	2.29 ± 0.71	1.84 ± 0.42	0.27	2.30 ± 0.68	1.53 ± 0.09	0.027**	2.26 ± 0.69	1.60	–**
PLA length left	7.19 ± 1.48	6.28 ± 1.82	0.37	6.84 ± 1.39	8.54 ± 2.05	0.18	7.07 ± 1.57	6.81 ± 1.58	0.81	7.16 ± 1.46	4.37	–
PLA density left	75.5 ± 30.8	83.0 ± 19.9	0.30	75.9 ± 27.6	83.0 ± 45.9	0.78	74.6 ± 27.5	101.0 ± 49.5	0.43	75.9 ± 29.5	96.0	–
PLA thickness mean	2.09 ± 0.61	1.81 ± 0.32	0.26	2.01 ± 0.57	2.07 ± 0.55	0.77	2.05 ± 0.56	1.63 ± 0.33	0.19	2.04 ± 0.57	1.78 ± 0.27	0.56
PLA length mean	7.83 ± 1.94	7.72 ± 2.88	0.48	7.75 ± 2.23	8.30 ± 1.79	0.46	7.96 ± 2.14	5.97 ± 1.98	0.17	7.87 ± 2.21	7.04 ± 1.81	0.56
PLA density mean	76.2 ± 23.3	68.0 ± 11.0	0.30	73.8 ± 21.6	76.5 ± 17.6	0.41	74.5 ± 21.7	69.2 ± 13.3	0.78	74.8 ± 21.7	64.7 ± 4.51	0.27
IMC ba right	0.58 ± 0.11	0.54 ± 0.10	0.25	0.57 ± 0.11	0.61 ± 0.09	0.45	0.57 ± 0.11	0.53 ± 0.09	0.37	0.57 ± 0.11	0.54 ± 0.07	0.62
IMC ba left	0.57 ± 0.11	0.56 ± 0.13	0.67	0.57 ± 0.11	0.58 ± 0.07	0.83	0.57 ± 0.11	0.50 ± 0.09	0.19	0.57±0.11	0.64±0.20	0.77
IMC ba mean	0.58 ± 0.10	0.55 ± 0.10	0.34	0.57 ± 0.10	0.60 ± 0.08	0.67	0.57 ± 0.10	0.51 ± 0.09	0.20	0.57±0.11	0.59±0.13	0.95
ABI < 0.9 (right or left side)	5.5%	13.3%	0.28	7.7%	0%	1.00	7.7%	0%	1.00	4.5%	100%	0.005
IMC cca mean > 0.9 mm	23.6%	26.7%	0.54	26.2%	0%	0.32	24.6%	20.0%	1.00	23.9%	33.3%	1.00
PLA present (right or left side)	52.3%	66.7%	0.39	53.9%	80.0%	0.37	53.4%	60.0%	1.00	53.7%	100%	0.25
PLA length mean > 6.0 mm	75.9%	80.0%	1.00	74.3%	75.0%	0.65	80.6%	33.3%	0.13	77.8%	66.7%	0.56
PLA density mean > 70 AU	68.6%	40.0%	0.46	74.3%	100%	0.55	55.6%	33.3%	0.58	58.3%	0%	0.09
IMC ba mean > 0.6 mm	45.5%	26.7%	0.24	51.4%	75.0%	0.61	43.1%	25.0%	0.62	41.8%	33.3%	1.00

Data are given as mean ± SD or percentage of patients with the indicated genotype; ABI — ankle-brachial index; IMC cca — intima-media complex of common carotid arteries; PLA — plaque of common carotid arteries and bifurcation; IMC ba — intima-media complex of brachial arteries; mean — value calculated as mean of measurements of the right and left arteries; IMC, plaque length and thickness are expressed in mm; *p = 0.014 for difference between 8 patients with (573GA or 591AT) and 62 with (573GG and 591AA) genotypes (53.2 ± 12.7 vs. 73.7 ± 19.2 arbitrary units — AU); **p = 0.010 for difference between 8 patients with (573GA or 591AT) and 62 with (573GG and 591AA) genotypes (1.55 ± 0.04 vs. 2.33 ± 0.68 mm)

CONCLUSIONS

The 573A allele of *CD36* rs5956 polymorphism is associated with low thickness of atheromatous plaque, suggesting its protective effect against atherosclerosis development. On the other hand, the 591T allele is associated with low ABI which is a cardiovascular risk factor. No association between IVS3-6 T/C and IVS4-10 G/A polymorphisms and radiological markers of atherosclerosis progress was found. Further research is necessary to assess the functional implications of synonymous polymorphisms in exon 6 of *CD36* gene for the risk and clinical course of coronary and peripheral artery disease.

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Związek genu *CD36* z grubością blaszki miażdżycowej i wskaźnikiem kostka–ramię u pacjentów z chorobą wieńcową rozpoznaną w młodym wieku

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Streszczenie

Wstęp: CD36 jest wielofunkcyjną cząsteczką zaangażowaną w usuwanie utlenionych LDL z osocza. Nie ma jednoznacznych dowodów, czy mutacja genu *CD36* ma działanie ochronne, czy też zwiększa ryzyko wystąpienia hipercholesterolemii, miażdżycy i jej powikłań.

Cel: Celem niniejszej pracy było poszukiwanie związku polimorfizmu genu *CD36* z radiologicznymi markerami rozwoju miażdżycy u pacjentów rasy białej z chorobą wieńcową rozpoznaną w młodym wieku.

Metody: Grupę badaną stanowiło 70 pacjentów z chorobą wieńcową rozpoznaną w młodym wieku. U każdego chorego wykonano doplerowskie badanie USG tętnic szyjnych i obwodowych. Od każdego pacjenta pobrano krew w celu izolacji genomowego DNA.

Wyniki: Wykryto 2 substytucje pojedynczych nukleotydów w intronach (IVS3-6 T/C – rs3173798 i IVS4-10 G/A – rs3211892) oraz 2 synonimiczne polimorfizmy w eksonie 6 (G573A – rs5956 i A591T). Częstości alleli wynosiły: 10,7% dla IVS3-6C, 3,6% dla IVS4-10A, 3,6% dla 573A i 2,1% dla 591T. Allel 573A polimorfizmu rs5956 genu *CD36* ma związek z mniejszą grubością blaszki miażdżycowej. Allel 591T ma związek z niższą wartością wskaźnika kostka–ramię.

Wnioski: Allel 573A wykazuje efekt ochronny przed rozwojem miażdżycy, natomiast allel 591T jest czynnikiem ryzyka chorób sercowo-naczyniowych. Ocena wpływu badanych polimorfizmów na funkcje białka CD36 wymaga przeprowadzenia dalszych badań.

Słowa kluczowe: gen *CD36*, genetyczne czynniki ryzyka, grubość blaszki miażdżycowej, wskaźnik kostka–ramię

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