Polymorphism of the *CD36* Gene and Cardiovascular Risk Factors in Patients with Coronary Artery Disease Manifested at a Young Age

**Monika Ewa Rać · Janina Suchy · Grzegorz Kurzawski ·
Agnieszka Kurlapska · Krzysztof Safranow · Michał Rać ·
Dagmara Sagasz-Tysiewicz · Andrzej Krzystolik · Wojciech Poncyljusz ·
Katarzyna Jakubowska · Maria Olszewska · Beata Krupa ·
Dariusz Chlubek**

Abstract This study investigates potential associations between *CD36* gene variants and the presence of risk factors in Caucasians with coronary artery disease (CAD) manifested at a young age. The study group consisted of 90 patients; the men were ≤ 50 years old and the women were ≤ 55 years old. Amplicons of exons 4 and 5 including fragments of introns were analyzed by DHPLC. Two polymorphisms were found: IVS3-6 T/C (rs3173798) and IVS4-10 G/A (rs3211892). The C allele of the IVS3-6 T/C polymorphism was associated with higher prevalence of obesity and diabetes, higher hsCRP, lower Lp(a) serum concentrations, and younger

M. E. Rać (✉) · K. Safranow · K. Jakubowska · M. Olszewska · D. Chlubek
Department of Biochemistry and Medical Chemistry, Pomeranian Medical University,
Powstańców Wielkopolskich 72, 70-111 Szczecin, Poland
e-mail: carmon12@gmail.com; carmon@pum.edu.pl

J. Suchy · G. Kurzawski · A. Kurlapska
Department of Genetics and Pathomorphology, Pomeranian Medical University,
Powstańców Wielkopolskich 72, 70-111 Szczecin, Poland

M. Rać
Department of Diagnostic Imaging and Interventional Radiology, Pomeranian Medical University,
Unii Lubelskiej 1, 71-252 Szczecin, Poland

D. Sagasz-Tysiewicz · A. Krzystolik
Department of Cardiology, County Hospital in Szczecin, Arkońska 4, 71-455 Szczecin, Poland

W. Poncyljusz
Department of Interventional Radiology, Pomeranian Medical University,
Powstańców Wielkopolskich 72, 70-111 Szczecin, Poland

B. Krupa
Independent Laboratory of Propedeutics in Pediatrics, Pomeranian Medical University,
Unii Lubelskiej 1, 71-252 Szczecin, Poland

age at myocardial infarction. The A allele of the IVS4-10 G/A polymorphism was associated with older age of myocardial infarction and higher white blood cell count. The functional role of *CD36* polymorphisms in CAD development needs further research.

Keywords   *CD36* gene · Coronary artery disease · Genetic risk factors · Obesity · Myocardial infarction

Introduction

CD36 is a type B scavenger receptor located on the surface of many cell types: platelets, endothelial cells, macrophages, dendrite cells, adipocytes, striated muscle cells, and hematopoietic cells (Greenwalt et al. 1992; Nicholson et al. 2001). The functions of CD36 include removal of oxidized LDL (oxLDL) and fatty acid from plasma by macrophages and monocytes (Park et al. 2009; Rać et al. 2007), induction of apoptosis (Silverstein 2009), and enhancement of cytoadherence of abnormally shaped erythrocytes (Chilongola et al. 2009).

CD36 may play an important role in the pathogenesis of some metabolic diseases. There are reports pointing to increased total and LDL cholesterol serum levels in association with mutations of the *CD36* gene (Yanai et al. 2000). CD36 has been reported to play an important role in atherogenicity (Huszar et al. 2000). There have been suggestions that polymorphisms of the *CD36* gene modulate lipid metabolism and cardiovascular risk in Caucasians (Nozaki et al. 1999; Kintaka et al. 2002; Ma et al. 2004). Some authors have concluded that CD36 mRNA expression in circulating monocytes might be a marker of coronary artery disease (Teupser et al. 2008). There is no clear indication whether mutations of the CD36 receptor gene protect against or increase the risk of hypercholesterolemia, atherosclerosis, and its complications such as vascular dysfunction, progression of arterial hypertension, and ischemic heart disease (Stein et al. 2002).

The objective of this study was to investigate whether there is an association between the sequence changes in the *CD36* gene region encoding the oxLDL- and fatty acid-binding domain and the presence of some known risk factors in Caucasian patients with coronary artery disease (CAD) at a young age.

Materials and Methods

The study group comprised 90 patients with CAD. The 66 men were no older than 50 years and the 24 women no older than 55 years. The patients were all Polish residents treated in the Department of Cardiology of the County Hospital in Szczecin (northwestern Poland) in 2007–2010. Clinically stable patients with optimal pharmacological treatment and no acute coronary syndrome or revascularization procedures within the previous month were included in the study. Patients with hemodynamically significant congenital or acquired valvular heart disease, symptomatic heart failure (NYHA class > 1), renal failure (creatinine > 3 mg/dl),

type 1 diabetes mellitus, thyroid dysfunction (current hypo- or hyperthyroidism), or malignancy were excluded from the study. The criteria for CAD diagnosis included angiographically documented presence of at least one coronary lesion ($\geq 40\%$ diameter stenosis of the left main coronary artery or $\geq 50\%$ stenosis of one of the three major epicardial arteries, or $\geq 70\%$ stenosis of a branch) or a history of revascularization procedure, or evidence of past myocardial infarction. The fasting blood sample was taken for DNA extraction, complete blood count, and measurements of serum glucose, high-sensitivity C-reactive protein (hsCRP), lipid profile (total, high- and low-density lipoprotein cholesterol, and triacylglycerols), ApoA1, ApoB, and Lp(a). Each patient's weight, height, waist and hip circumference, and 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 isolated as previously described (Lahiri and Schnabel 1993). Amplicons of exons 4 and 5 including fragments of introns were studied using the denaturing high-performance liquid chromatography (DHPLC) technique as previously described (Rać et al. 2010). PCR products with alterations detected by DHPLC were bidirectionally sequenced using the Applied Biosystems Dye-terminator Cycle Sequencing Ready Reaction kit, according to the manufacturer's protocol. Semi-automated sequence analysis was performed using a 373A DNA fragment analyzer (Applied Biosystems, Foster City, CA).

The study complies with the principles outlined in the Declaration of Helsinki and was approved by our institutional ethics committee. Informed consent was obtained from each patient.

Differences between subgroups of patients classified according to the *CD36* genotype were tested with the Mann–Whitney U test for quantitative variables and Fisher's exact test for qualitative variables. Odds ratio (OR) and its 95% confidence interval (95% CI) were calculated for statistically significant associations between genotype and qualitative variables. The consistency of genotype distribution with Hardy–Weinberg equilibrium was assessed using the exact test.

Results

Changes detected by DHPLC included two single nucleotide substitutions in introns, IVS3-6 T/C (rs3173798) and IVS4-10 G/A (rs3211892) (Table 1). No sequence alterations were found in exons. Genotype distributions were consistent with Hardy–Weinberg equilibrium for both sequence changes ($P = 1$).

Table 1 *CD36* sequence alterations in 90 patients with coronary artery disease

CD36 region	DNA sequence alteration[a]	Genotype frequency	Minor allele frequency (%)
Intron 3	IVS3-6 T/C (rs3173798)	81.1% TT, 18.9% TC	9.4
Intron 4	IVS4-10 G/A (rs3211892)	92.2% GG, 7.8% GA	3.9

[a] Detected initially by DHPLC and then confirmed by direct sequencing

The clinical data and morphometric parameters of patients showed differences between the *CD36* genotypes (Table 2). Body mass index was slightly higher ($P = 0.08$) and obesity (BMI $\geq$ 30 kg/m^2) was slightly more frequent in the IVS3-6 TC heterozygotes than in the TT patients (OR = 2.93, 95% CI 0.98–8.76, $P = 0.07$). TC heterozygotes were also characterized by a higher prevalence of diabetes (OR = 6.09, 95% CI 1.66–22.32, $P = 0.009$), and they received calcium channel blockers more frequently than TT homozygotes (OR = 4.98, 95% CI 1.51–16.39, $P = 0.01$). In the subgroup of patients with past myocardial infarction, the TC genotype was associated with a slightly younger age at this event ($P = 0.057$). On the contrary, IVS4-10 GA heterozygotes had a significantly older age at the first myocardial infarction than wild-type GG homozygotes ($P = 0.003$).

The blood count and biochemical data also revealed differences between the *CD36* genotypes (Table 3). The mean corpuscular hemoglobin concentration was slightly higher ($P = 0.06$) and basophil percentage of the white blood cells was significantly lower ($P = 0.03$) in the IVS3-6 TC heterozygotes than in the TT patients. The IVS3-6 TC genotype was also associated with significantly higher hsCRP ($P = 0.02$) but with lower Lp(a) ($P = 0.01$). The IVS4-10 GA genotype was associated only with significantly higher white blood cell count ($P = 0.03$).

Discussion

In intron fragments adjacent to the tested exons, we found IVS3-6 T/C (rs3173798) and IVS4-10 G/A (rs3211892) polymorphisms. The IVS3-6C allele frequency (9.4%) was similar to that described earlier in Caucasian populations (6.2–11.2%), according to the NCBI dbSNP database. The IVS4-10A allele frequency (3.9%) was slightly higher than that described in Caucasians (1.6–2.6%) according to the dbSNP.

The IVS3-6 T/C polymorphism is located at a conserved splice site (Fry et al. 2009). The functional effects of both polymorphisms have not been elucidated so far.

The effect of both single nucleotide polymorphisms (rs3173798 and rs3211892) of *CD36* on initial clinical presentation of coronary artery disease as myocardial infarction or stable angina was analyzed in the American population, where more than half of the subjects studied were Caucasians (Knowles et al. 2007). It was shown that neither of the two alterations is significantly associated with myocardial infarction. Patients with myocardial infarction as an initial presentation of CAD, however, had a significantly higher frequency of the minor allele of another polymorphism in intron 14 (rs3211956), which is not known to have functional effects. In our study, we observed a trend ($P = 0.057$) or significant association ($P = 0.003$) between the IVS3-6 TC and IVS4-10 GA genotypes, respectively, and age at myocardial infarction, but the direction of the association was reversed: the age at the first myocardial infarction was younger for TC but older for GA heterozygotes.

In our study, the IVS3-6 TC heterozygous genotype was associated with three cardiovascular risk factors: elevated hsCRP, higher prevalence of obesity, and

Table 2 Clinical and morphometric characteristics of 90 patients stratified by *CD36* genotypes

Characteristic	CD36 genotype					
	IVS3-6 T/C (rs3173798)			IVS4-10 G/A (rs3211892)		
	TT	TC	*P*-value	GG	GA	*P*-value
Number of patients	73	17		83	7	
Gender (% male)	70%	88%	0.14	79%	86%	0.67
Blood pressure (mmHg)						
Systolic	130.0 ± 14.0	120.0 ± 18.0	0.92	128.0 ± 15.0	130.0 ± 16.0	0.59
Diastolic	80.0 ± 9.0	80.0 ± 11.0	0.83	80.0 ± 9.0	80.0 ± 10.0	0.81
Mean arterial pressure	93.3 ± 9.4	96.7 ± 10.9	1.00	93.3 ± 9.5	96.7 ± 11.2	0.61
Heart rate (1/min)	70.0 ± 7.0	72.0 ± 6.0	0.22	70.0 ± 6.4	64.0 ± 13.0	0.20
Obesity						
Weight (kg)	84.0 ± 16.8	88.0 ± 18.6	0.21	84.0 ± 17.5	76.0 ± 13.3	0.45
Body mass index (kg/m^2)	27.5 ± 3.7	29.7 ± 4.9	0.08	27.8 ± 4.0	27.4 ± 3.9	0.37
≥ 25 kg/m^2	73%	82%	0.55	76%	71%	1.00
≥ 30 kg/m^2	23%	47%	0.07	28%	29%	1.00
Waist (cm)	98.0 ± 4.2	103.0 ± 14.0	0.35	100.0 ± 12.4	93.0 ± 9.9	0.31
Hip (cm)	103.0 ± 7.9	104.0 ± 11.2	0.67	104.0 ± 8.9	101.0 ± 4.9	0.36
Waist-to-hip ratio	0.96 ± 0.10	0.98 ± 0.11	0.39	0.96 ± 0.10	0.94 ± 0.07	0.45
History of hypertension	59%	71%	0.42	61%	57%	1.00
Age at diagnosis of hypertension (years)	43.5 ± 8.5	42.1 ± 9.7	0.99	42.9 ± 8.9	43.5 ± 5.3	0.82
Diabetes, type 2	8%	35%	0.009	13%	14%	1.00
Oral hypoglycemic drugs (% of patients with diabetes)	83%	67%	1.00	82%	0%	0.25
Insulin (% of patients with diabetes)	17%	0%	1.00	0%	100%	0.08
Past myocardial infarction	60%	65%	0.79	60%	71%	0.70
Age at first myocardial infarction (years)	45.7 ± 5.8	42.2 ± 5.1	0.057	44.2 ± 5.6	51.0 ± 4.1	0.003
Current smoking	8%	24%	0.10	11%	14%	0.57
Past smoking	81%	100%	0.34	90%	100%	1.00
Treatment						
Past percutaneous transluminal coronary angioplasty	78%	65%	0.35	64%	100%	0.18
Past coronary artery bypass grafting	42%	35%	0.79	36%	0%	0.09

Table 2 continued

Characteristic	CD36 genotype					
	IVS3-6 T/C (rs3173798)			IVS4-10 G/A (rs3211892)		
	TT	TC	P-value	GG	GA	P-value
Angiotensin 1 converting enzyme inhibitors	81%	76%	0.47	77%	86%	1.00
Angiotensin 2 receptor blockers	17%	24%	0.47	14%	29%	0.34
Beta-blockers	82%	88%	1.00	82%	100%	0.59
Diuretics	24%	41%	0.37	30%	0%	0.17
Calcium channel blockers	12%	41%	0.01	18%	14%	1.00
Statins	99%	88%	0.10	99%	86%	0.22

Unless otherwise noted, values are the mean $\pm$ SD or the percentage of patients with the indicated genotype

diabetes. No data to suggest an association between the CD36 variants and anthropometric parameters or hsCRP levels in the Caucasian population have been published so far. Leprêtre et al. (2004) demonstrated a lack of association between the IVS4-10 G/A alteration and adiponectin levels in the Caucasian population. On the other hand, it was demonstrated that all of the CD36 sequence alterations studied by Love-Gregory et al. (2008) (rs3211850 located in intron 3; rs3173804 located in intron 9; nonsense mutation rs3211938 located in exon 10; rs7755, rs13246513, and rs13230419 located in the 3′ UTR) in African Americans with hypertension were associated with such anthropometric parameters as body mass index above 30 kg/ m^2 and waist circumference above 100 cm.

It has been demonstrated that rs1527479 CD36 promoter polymorphism is associated with insulin resistance and type 2 diabetes in Caucasians (Corpeleijn et al. 2006). On the other hand, no association has been described so far between CD36 variants investigated in our study and the prevalence of type 2 diabetes. Type 2 diabetes was diagnosed more frequently in IVS3-6 TC heterozygotes than in wild-type homozygotes. The fasting serum glucose concentration, however, did not differ between the groups, which may be because most of the TC heterozygotes with diabetes took oral hypoglycemic agents or insulin. IVS4-10 GA heterozygotes did not differ from wild-type homozygotes in the prevalence of type 2 diabetes. A similar result was published in the study by Leprêtre et al. (2004), where no association was found between the IVS4-10 G/A alteration and type 2 diabetes in the Caucasian population.

Some authors have reported that some promoter (rs10499859, rs109654) and intron (rs1358337) CD36 polymorphisms in African Americans may contribute to an increase in HDL plasma concentrations (Love-Gregory et al. 2008). Other authors (Goyenechea et al. 2008) have shown an association between the CD36 promoter rs2151916 polymorphism and LDL levels in the St. Thomas UK Adult Twin Registry cohort: LDL cholesterol concentrations were significantly lower in minor allele homozygotes. IVS3-6 T/C and IVS4-10 G/A polymorphisms were not analyzed in that study. Ma et al. (2004) reported a correlation of two polymorphisms

Table 3 Blood count and biochemical data for 90 patients stratified by *CD36* genotypes

Parameter	*CD36* genotype					
	IVS3-6 T/C (rs3173798)			IVS4-10 G/A (rs3211892)		
	TT	TC	*P*-value	GG	GA	*P*-value
Number of patients	73	17		83	7	
Blood count						
White blood cells (G/L)	6.7 ± 2.2	7.5 ± 1.5	0.17	6.8 ± 2.1	8.6 ± 2.1	0.03
Red blood cells (T/L)	4.9 ± 0.4	4.9 ± 0.4	0.53	5.0 ± 0.4	4.8 ± 0.5	0.29
Hemoglobin (g/dL)	15.0 ± 1.2	15.0 ± 1.2	0.90	15.0 ± 1.2	14.9 ± 1.3	0.89
Hematocrit (%)	44.3 ± 3.3	43.6 ± 3.1	0.59	44.2 ± 3.3	43.9 ± 3.3	0.96
Mean corpuscular (MC) volume (fL)	90.2 ± 4.5	88.6 ± 4.1	0.50	89.8 ± 4.4	92.4 ± 4.4	0.17
MC hemoglobin (pg/erythrocyte)	30.0 ± 1.7	34.1 ± 1.8	0.60	30.1 ± 1.7	30.7 ± 2.3	0.43
MC hemoglobin concentration (g/dL)	33.5 ± 0.8	34.1 ± 0.9	0.06	33.7 ± 0.8	33.5 ± 1.0	0.99
Platelets (G/L)	215.5 ± 43.8	228.0 ± 47.1	0.10	220.0 ± 44.3	223.0 ± 57.0	0.77
Neutrophils (% white blood cells)	55.0 ± 8.8	51.4 ± 9.8	0.34	54.5 ± 8.7	47.3 ± 12.0	0.62
Lymphocytes (%)	33.9 ± 8.7	37.1 ± 8.3	0.36	33.4 ± 7.8	38.4 ± 10.3	0.64
Monocytes (%)	9.1 ± 2.0	9.8 ± 1.9	0.60	9.1 ± 1.9	10.0 ± 2.3	0.46
Eosinophils (%)	2.1 ± 1.9	2.2 ± 1.9	0.66	2.2 ± 1.9	1.4 ± 1.0	0.30
Basophils (%)	0.37 ± 0.20	0.25 ± 0.15	0.03	0.34 ± 0.20	0.30 ± 0.20	0.39
High-sensitivity C-reactive protein (mg/L)	1.1 ± 1.8	1.9 ± 2.9	0.02	1.2 ± 2.1	1.3 ± 2.7	0.73
Glucose (mg/dL)	100.5 ± 23.4	102.2 ± 18.8	0.64	100.3 ± 20.8	107.0 ± 38.3	0.55
Lipid profile (mg/dL)						
Total cholesterol	163.5 ± 37.8	159.0 ± 26.4	0.52	161.0 ± 36.9	167.0 ± 22.5	0.52
HDL cholesterol	47.5 ± 11.6	41.0 ± 12.9	0.17	47.0 ± 11.6	45.0 ± 15.6	0.87
LDL cholesterol	90.5 ± 33.3	88.0 ± 26.7	0.39	90.0 ± 33.3	96.0 ± 17.2	0.59
Triacylglycerols	126.5 ± 52.4	149.0 ± 69.8	0.43	128.0 ± 57.2	137.0 ± 45.1	0.99
Lp(a) (mg/dL)	23.1 ± 54.4	10.3 ± 29.0	0.01	20.7 ± 53.1	10.8 ± 19.6	0.22
ApoA1 (mg/dL)	148.0 ± 42.0	144.0 ± 29.0	0.42	148.5 ± 41.1	139.0 ± 22.0	0.64
ApoB (mg/dL)	74.5 ± 20.4	74.0 ± 16.2	0.41	73.0 ± 20.4	77.0 ± 6.4	0.47

Unless otherwise noted, values are the mean ± SD of patients with the indicated genotype

(rs1984112, rs1761667) at alternative transcription start sites (exons 1A and 1B), one polymorphism (rs1527483) in intron 11, and two polymorphisms (rs3840546, rs1049673) in an alternative 3′ UTR region (exons 14 and 15) with plasma free fatty acid metabolism in Caucasians. The authors investigated patients with type 2 diabetes stratified into CAD-positive cases and CAD-negative controls. Their results suggest that all of those alterations in *CD36* may be associated with an increased risk of CAD, but the IVS3-6 T/C and IVS4-10 G/A polymorphisms were not investigated in their study. In our study, we did not observe any statistically

significant differences in serum lipid concentrations between genotype groups. It is worth noting that almost all of our study subjects, while being under constant cardiologic monitoring, took statins, which could affect the results concerning lipids. On the other hand, we observed that the IVS3-6 TC genotype was associated with lower Lp(a), which is identified as a putative risk factor for atherosclerotic diseases such as coronary heart disease and stroke. Such association could potentially be beneficial for carriers of the variant C allele.

It has been demonstrated (Chilongola et al. 2009) that a homozygous nonsense mutation in exon 10 (rs3211938) is associated with high blood hemoglobin concentration in Africans. In our study, we did not observe any statistically significant differences in blood hemoglobin concentration between the genotype groups. We found in turn that the mean corpuscular hemoglobin concentration in erythrocytes is borderline higher and basophil percentage is significantly lower in IVS3-6 TC heterozygotes, and the white blood cell count is higher in IVS4-10 GA heterozygotes than in wild-type homozygotes. No such associations have been reported so far.

In conclusion, the IVS3-6C allele of *CD36* is associated with cardiovascular risk factors such as high hsCRP, body mass index, and type 2 diabetes. On the other hand, this variant is associated with low Lp(a), suggesting its protective effect in terms of development of atherosclerosis. The IVS3-6C allele is associated with a younger age at myocardial infarction and IVS4-10A with an older age. Further research is necessary to assess their functional implications for the risk and clinical course of coronary artery disease.

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