

The stromelysin-1 5A/6A promoter polymorphism is a disease marker for the extent of coronary heart disease

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Abstract. *Background.* Matrix metalloproteinases, such as stromelysin-1, are implicated in the pathogenesis of coronary artery disease (CAD) and acute myocardial infarction (MI). A 5A/6A promoter polymorphism can regulate the transcription of the stromelysin-1 gene in an allele-specific manner. Evidence has been presented that the 6A allele is associated with the progression of coronary heart disease (CHD). In contrast, the 5A allele may be linked to the risk of MI.

Results. To analyse the relation of the 5A/6A polymorphism with the risk and severity of CHD and the risk of MI, a case-control study of 515 healthy controls and 1848 participants who underwent coronary angiography for diagnostic purposes was conducted. In the total sample, the mean CHD scores – according to Gensini – were different between 5A/6A genotypes: 5A5A homozygotes had the lowest, 6A6A genotypes the highest and 5A6A heterozygotes intermediate scores. These differences were even more pronounced when the participants were restricted to individuals with a high coronary risk profile (high apoB levels, high Lp(a) levels, high glucose levels, combinations of either high apoB and Lp(a) levels or high apoB, Lp(a) and glucose plasma levels). Mean values were used as cut points for high-risk populations, respectively. In contrast, the 5A allele was not associated with the risk of CHD or MI. Even when angiographically controlled individuals without MI were compared with MI patients in subpopulations of participants with no, single, double and triple vessel disease, the frequencies of the 5A/6A and/or the 5A5A genotypes were not higher in each subgroup, respectively.

Conclusions. The present results do not confirm an association of the 5A allele with the risk of MI, observed in another investigation, but strengthen the hypothesis of earlier studies that the 6A allele is a disease marker for progression of coronary heart disease. Further investigations should evaluate whether 6A allele carriers and especially 6A homozygotes might benefit from a more aggressive therapy against CHD progression.

1. Introduction

Atherosclerosis is directly or indirectly related to nearly one half of all deaths in the Western world [1–3]. Life-threatening complications of coronary atherosclerosis are the acute coronary syndromes including unstable angina pectoris and acute myocardial infarction (MI) [4]. It is well known that plaque rupture with

subsequent thrombosis is a critical event in the pathogenesis of acute MI [4,5].

Matrix metalloproteinases (MMPs), such as stromelysin-1 (MMP-3), can degrade extracellular matrix and are localised extensively in coronary atherosclerotic plaques [6,7]. MMPs have been shown to be implicated in accelerating growth of coronary atheromas by remodelling connective tissue during atherogenesis [8–11]. In addition, MMPs may contribute to weakening of the plaque cap which provokes plaque rupture, thrombosis and consequently acute MI [6].

A bi-allelic single nucleotide polymorphism in the promoter region of the stromelysin-1 gene has been identified by Ye et al. [12]. The 5A allele is charac-

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terised by a cluster of 5 adenosines, the other by six adenosines (6A). The 5A allelic stromelysin-1 promoter has been shown to have greater transcription activity than the 6A allelic promoter [13]. Apparently, this difference is due to preferential binding of a transcription repressor to the 6A allele [14,15]. The impact of this functional polymorphism on coronary heart disease (CHD) has been investigated only in few studies [13, 16–18]. The 6A allele has been found to be associated with accelerated growth of coronary atheromas [13, 16,17] and predisposition to post-angioplasty restenosis [17]. On the other hand, in a Japanese study sample, the 5A allele was associated with an increased risk of MI [18]. However, this observation has not been checked by other investigators. In addition, studies investigating the potential association of the stromelysin-1 promoter 5A/6A polymorphism with the risk of coronary artery disease (CAD) have not been published so far. Therefore, we decided to analyse the impact of this gene polymorphism on the risk of CAD and MI and on the severity of coronary heart disease in a population of 515 healthy controls and 1848 patients who underwent coronary angiography for diagnostic purposes.

2. Materials and methods

2.1. Detection of coronary artery disease and myocardial infarction

2.1.1. Coronary artery disease

Coronary angiography was performed by the Judkins method; coronary vessels with at least 50% stenosis were defined as diseased. By means of coronary angiography, the study population was divided into subjects without any angiographic CAD or with coronary arterial stenoses less than 50% (no vessel disease) and individuals with single, double or triple vessel disease. The severity of CHD was also estimated by calculating the Gensini score [19]; this score is designated “CHD score” in subsequent text.

2.1.2. Myocardial infarction

Acute MI was diagnosed according to criteria established by the World Health Organisation. Within the subgroup of angiographic controlled individuals, 16% of patients without vessel disease, 47% of individuals with single vessel disease, 51% of patients with double vessel disease and 62% of patients with triple vessel disease had suffered a MI before recruitment in the study.

2.2. Study sample

The gene polymorphism was analysed in 2363 male Germans. All individuals who agreed to participate in the study were evaluated with a structured questionnaire which provided information about coronary risk factors [20]. The study was approved by the local ethics committee.

For the control group of 515 male individuals without vascular disease, we used the detailed Rose questionnaire [20] to identify disease free controls and to exclude subjects who were suspicious to have any form of vascular disease. Controls had to be (a) without a history of MI or angina, (b) without symptoms, suggesting angina assessed by the Rose questionnaire [20], and (c) without a history of stroke or any other vascular event. Systematic screening of the control participants' families was conducted and subjects with a family history of premature coronary heart disease (presence of symptomatic ischemic heart disease or coronary death in a first-degree relative aged < 55 years) were excluded from the study.

A group of 1848 participants underwent coronary angiography for diagnostic purposes. About 80% of the participants underwent this diagnostic procedure due to presumptive or verified CHD. The remaining part consisted almost completely of patients who underwent coronary angiography for clarification of reduced left ventricular function. In 90% of these patients, CAD was documented; in 10% of this subpopulation (= 2% of the total cohort), reduced left ventricular function was caused by dilated cardiomyopathy or longstanding arterial hypertension.

In the present study, established risk factors and the stromelysin 5A/6A genotypes were compared between (i) healthy controls without vascular disease and CAD patients (verified by coronary angiography), (ii) participants without and with CAD within the subpopulation of individuals with coronary angiography, (iii) subjects with different degrees of CAD (verified by coronary angiography), (iv) healthy controls without vascular disease and MI patients and (v) MI negative and MI positive patients within the subgroup of individuals with coronary angiography.

2.3. Measurements of substrates, definition of variables and genotyping of stromelysin 5A/6A promoter

Triglyceride, total cholesterol, apolipoprotein B (apoB), apolipoprotein AI (apoAI), lipoprotein (a)

(Lp(a)), glucose, fibrinogen and body mass index (BMI) were measured or calculated as described [21]. Diabetes mellitus and hypertension are given as binary variables and not divided into subcategories. Hypertension was defined by either treatment or diastolic blood pressure higher than 95 mm Hg on two consecutive visits for those untreated. Cigarette consumption was given as pack-years (1 pack-year: e.g. 20 cigarettes per day for one year).

The stromelysin 5A/6A promoter polymorphism was analysed according to the method of Dunleavy et al. [22]. In principle, three mismatched nucleotides were introduced in a PCR primer annealed to the proximity of the 5A/6A polymorphism, creating a recognition sequence for restriction endonuclease Xmn1 at the polymorphic site. An Xmn 1 digestion cleaved PCR products deriving from 5A allele but not from 6A allele [22].

2.4. Definition of low and high risk subpopulations

The mean values of coronary risk factors (age, apoAI, apoB, apoAI/apoB ratio, Lp(a), fibrinogen, cigarette smoking) from the study population were used as cut points for definition of low and high risk populations. With respect to hypertension and diabetes, low and high risk groups were defined by the absence or presence of these diseases. All low- and high-risk groups, presented in this study, were considered in our primary hypotheses.

2.5. Statistical analysis

Statistical analyses were performed using the SPSS for Windows software (Version 9.0). The χ^2 -test was used to test for deviation of genotype distribution from Hardy-Weinberg equilibrium. In order to compare established risk factors between stromelysin 5A/6A genotypes, the relation of this polymorphism to continuous variables was tested by Kruskal-Wallis 1-Way Anova and to diabetes and hypertension by χ^2 analysis. Established risk factors for CAD and MI were identified by multiple regression analysis (extent of CAD, CHD score) or multiple logistic regression (absence /presence of CAD or MI). The relation of the 5A/6A polymorphism to the extent of CAD was determined by multiple regression analysis with adjustment for coronary risk factors. Odds ratios with 95% confidence intervals as an estimate of relative risk of CAD and MI and two-tailed p-values were calculated by multiple logistic regression after adjustment for coronary risk

factors. A two-sided probability value of less than 0.05 was considered to indicate statistical significance. The analyses were based on a recessive, co-dominant and dominant model of inheritance.

3. Results

3.1. Distribution of the stromelysin 5A/6A genotypes and its effect on physiochemical and clinical variables

A deviation of the stromelysin 5A/6A genotypes from Hardy-Weinberg equilibrium was not observed in the total sample ($p = 0.249$), in healthy controls without vascular disease ($p = 0.753$), in angiographic controlled patients without MI ($p = 0.908$), without CAD ($p = 0.941$), without CAD and also MI ($p = 0.902$), and in patients with CAD ($p = 0.330$) or with MI ($p = 0.253$). Age, total cholesterol, triglycerides, apoAI, apoB, apoAI/apoB ratio, Lp(a), glucose, fibrinogen, prevalence of diabetes and arterial hypertension, BMI and cigarette consumption were almost identical between 5A/6A genotypes (i) of the total study population, (ii) of healthy controls, (iii) of patients without or with single- or multi-vessel disease and (iv) of subjects without and with MI (data not shown). The mean delay between the occurrence of MI and recruitment in this study (5.6 ± 0.24 years) did not differ between 5A/6A genotypes ($p = 0.636$; data not shown).

3.2. Relation of established risk factors to the risk of coronary artery disease and myocardial infarction and the extent of coronary heart disease

3.2.1. Risk of coronary artery disease

A comparison of the control group of healthy individuals without vascular disease with angiographic proven CAD patients revealed apoB ($p = 0.00001$), Lp(a) ($p = 0.00001$), diabetes mellitus ($p = 0.0002$), hypertension ($p = 0.00001$), smoking habit (pack-years, $p = 0.0009$) and age ($p = 0.00001$) as risk factors for CAD, and apoAI ($p = 0.00001$) and consequently high apoAI/apoB ratios ($p = 0.00001$) as protective factors against this disease (Table 1). Within the group of angiographic controlled patients, the same risk factors were identified (Table 1).

Table 1
Distribution of risk factors of coronary artery disease and myocardial infarction.

Risk factor	± Coronary artery disease					± Myocardial infarction				
	- CAD ⁽¹⁾ (n = 515)	- CAD ⁽²⁾ (n = 432)	+ CAD (n = 1416)	2 p ⁽¹⁾	2 p ⁽²⁾	- MI ⁽¹⁾ (n = 515)	- MI ⁽²⁾ (n = 1003)	+ MI (n = 845)	2 p ⁽¹⁾	2 p ⁽²⁾
Age (years)	55.3 ± 10.3	57.7 ± 11.4	62.8 ± 9.4	0.00001	0.00001	55.3 ± 10.3	61.0 ± 10.5	62.4 ± 9.7	0.00001	0.0004
BMI (kg/m ²)	26.3 ± 3.3	27.2 ± 3.9	27.0 ± 3.4	n. s.	n. s.	26.3 ± 3.3	27.1 ± 3.6	27.0 ± 3.5	n. s.	n. s.
Pack-years	16.2 ± 28	20.5 ± 25	23.9 ± 27	0.0009	0.018	16.2 ± 28	20.5 ± 25	26.0 ± 27	0.00001	0.00001
% Diabetes	8	13	21	0.0002	0.0055	8	18	21	0.0002	n. s.
% Hypertension	16	57	68	0.00001	0.002	16	66	65	0.00001	n. s.
Chol (mg/dl)	211 ± 43	202 ± 42	207 ± 43	n. s.	n. s.	211 ± 43	208 ± 43	204 ± 44	n. s.	n. s.
Trig (mg/dl)	139 ± 53	137 ± 83	147 ± 83	n. s.	n. s.	139 ± 53	145 ± 87	145 ± 78	n. s.	n. s.
ApoAI (g/l)	1.46 ± 0.25	1.42 ± 0.27	1.38 ± 0.29	0.00001	0.0003	1.46 ± 0.25	1.41 ± 0.27	1.37 ± 0.30	0.00001	0.0015
ApoB (g/l)	1.11 ± 0.26	1.16 ± 0.27	1.25 ± 0.32	0.00001	0.00001	1.11 ± 0.26	1.22 ± 0.30	1.24 ± 0.32	0.00001	n. s.
ApoAI/ApoB	1.39 ± 0.43	1.29 ± 0.47	1.23 ± 0.31	0.00001	0.00001	1.39 ± 0.43	1.22 ± 0.41	1.17 ± 0.36	0.00001	0.009
Lp(a) (mg/l)	20 ± 25	21 ± 28	30 ± 38	0.00001	0.00001	20 ± 25	26 ± 36	29 ± 36	0.00001	n. s.

Values are means ± SD or % of a group. The relation of the risk factors to CAD and to MI was analysed by multiple logistic regression. Abbreviations: n. s., not significant; Chol, cholesterol; Trig, triglycerides; Apo, apolipoprotein; "-CAD⁽¹⁾" and "-MI⁽¹⁾", control group of individuals free of cardiovascular disease; "-CAD⁽²⁾", group of patients with coronary angiography and without vessel disease; "-MI⁽²⁾", patients with coronary angiography and without MI; "2 p⁽¹⁾"; two-tailed p-values for the comparisons of CAD (MI) patients with control individuals ("-CAD⁽¹⁾, -MI⁽¹⁾"); "2 p⁽²⁾", two-tailed p-values for the comparisons between patients who underwent coronary angiography.

3.2.2. Extent of coronary artery disease, CHD score

With respect to the extent of CAD and to the CHD score, apoB ($p = 0.00001$), Lp(a) ($p = 0.00001$), diabetes mellitus ($p = 0.00001$), hypertension ($p = 0.00001$), smoking habit (pack-years, $p = 0.018$) and age ($p = 0.00001$) were identified as risk factors and apoAI ($p = 0.00001$) and high apoAI/apoB ratios ($p = 0.00001$) as protective factors (data not shown).

3.2.3. Risk of myocardial infarction

When the control group of healthy individuals without coronary heart disease was compared with MI patients, apoB ($p = 0.00001$), Lp(a) ($p = 0.00001$), diabetes mellitus ($p = 0.0002$), hypertension ($p = 0.00001$), smoking habit ($p = 0.00001$) and age ($p = 0.00001$) could be demonstrated as risk factors, and apoAI ($p = 0.00001$) and high apoAI/apoB ratios ($p = 0.00001$) as protective factors against MI (Table 1). When the study sample was restricted to angiographic controlled individuals, only smoking habit ($p = 0.00001$) and age ($p = 0.0004$) were found as risk factors and apoAI ($p = 0.0015$) and high apoAI/apoB ratios ($p = 0.009$) as protective factors (Table 1).

3.3. Relation of the stromelysin 5A/6A promoter polymorphism to coronary heart disease

3.3.1. Risk of coronary artery disease

With all models of inheritance, not any association was detected between the stromelysin 5A/6A promoter polymorphism and the risk of CAD. This observation applied not only to the total sample (Table 2), but also to low- and high-risk populations (data not shown).

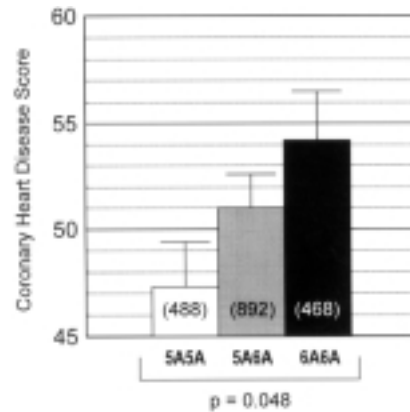


Fig. 1. Comparison of mean coronary heart disease scores between the stromelysin-1 promoter 5A/6A genotypes in the total study sample. The mean CHD scores were compared by multiple regression analysis after adjustment for coronary risk factors between patients who underwent coronary angiography for diagnostic purposes. Values are means ± SEM. Numbers of individuals are given in parentheses. Coronary angiography was performed by the Judkins method. The CHD score was estimated according to Gensini [19]. A two-tailed probability value of < 0.05 was considered to indicate statistical significance.

3.3.2. Extent of coronary artery disease, CHD score

In the total population, the 5A/6A promoter polymorphism was not associated with the extent of CAD defined by the number of diseased vessels (Table 2). However, in the total sample the mean CHD scores were significantly different between 5A/6A genotypes: 5A5A homozygotes had the lowest, 6A6A genotypes the highest and 5A6A heterozygotes intermediate Gensini scores (Fig. 1; $p = 0.048$). These differences were even more pronounced when the study participants were re-

Table 2

Distribution of the stromelysin 5A/6A genotypes in subjects without or with coronary artery disease and individuals without or with acute myocardial infarction

Controls/Cases	Mean age (\pm SD)	n	5A/6A Genotypes			5A/6A Alleles	
			n (5A5A)	n (5A6A)	n (6A6A)	5A (95% CI)	6A (95% CI)
\pm CAD							
<i>Subjects without coronary angiography</i>							
No CAD (healthy controls)	55.3 \pm 10.2	515	139	249	127	0.51 (0.48–0.54)	0.49 (0.46–0.52)
<i>Subjects with coronary angiography</i>							
No vessel disease	57.7 \pm 11.4	432	122	212	98	0.53 (0.49–0.56)	0.47 (0.44–0.51)
Single vessel disease	60.7 \pm 9.8	359	101	162	96	0.51 (0.47–0.55)	0.49 (0.46–0.53)
Double vessel disease	62.9 \pm 9.8	396	101	189	106	0.49 (0.46–0.53)	0.51 (0.47–0.54)
Triple vessel disease	64.0 \pm 8.9	661	164	329	168	0.50 (0.47–0.52)	0.50 (0.48–0.53)
\pm MI							
<i>Subjects without coronary angiography</i>							
No MI (healthy controls)	55.3 \pm 10.2	515	139	249	127	0.51 (0.48–0.54)	0.49 (0.46–0.52)
<i>Subjects with coronary angiography</i>							
No MI	61.4 \pm 10.2	1003	282	494	227	0.53 (0.51–0.55)	0.47 (0.45–0.50)
≥ 1 MI	62.2 \pm 9.6	845	206	398	241	0.48 (0.46–0.50)	0.52 (0.50–0.55)

Coronary angiography was performed by the Judkins method. Vessels were defined as diseased if at least 50% stenosis were demonstrated. Acute myocardial infarction were diagnosed according to criteria by the World Health Organisation. No vessel disease: Persons without any detectable stenosis of coronary arteries or patients with less than 50% stenosis of coronary arteries.

stricted to individuals with a high coronary risk profile (Fig. 2). This observation applies to individuals (i) with high apoB levels (≥ 1.2 g/l; mean value), (ii) with high Lp(a) levels (≥ 26 mg/l, mean value), (iii) with high glucose levels (> 108 mg/dl, mean value), (ii) with a combination of high apoB and Lp(a) levels (mean values, respectively), and (iv) with a combination of high apoB, Lp(a) and glucose plasma levels (mean values, respectively) (Fig. 2).

3.3.3. Risk of myocardial infarction

In the total sample and also in low and high risk populations, the stromelysin 5A/6A promoter polymorphism was not associated with the risk of MI (Table 2). This observation was made when healthy individuals and also angiographically controlled subjects without MI were compared with MI patients (Table 2). In addition, no significant differences for the 5A and 6A allele frequencies were calculated when angiographically controlled individuals without MI were compared with MI patients in subgroups of participants with no, single, double and triple vessel disease (Table 3).

4. Discussion

In their Editorial [23], Libby and Lee stressed that "... far from being mere structural cement that surrounds cells, the extracellular matrix is a dynamic, interactive milieu that sends signals that influence such critical cell functions as reproduction, life, and death". The extracellular matrix breakdown is strictly con-

trolled by matrix metalloproteinases (MMPs) and their inhibitors TIMPs (tissue inhibitors of MMPs). MMPs and TIMPs are under tight transcriptional control; in addition, MMPs are first synthesized as inactive zymogene precursors [24,25]. Thus, the actual activity of MMPs depends on the rate of synthesis, activation, and the balance between active enzyme and inhibitors [23].

The presence of stromelysin-1, a MMP with a broad substrate specificity [26], was originally demonstrated by in situ mRNA hybridisation [11]. A common polymorphism in the stromelysin promoter, located about 600 bp upstream from the start of transcription and defined by the presence of either six (6A) or five (5A) adenosines, has been identified by Ye et al. [12]. The about two-fold higher transcription activity of the 5A allelic stromelysin-1 promoter [13] is apparently caused by a preferential binding of a transcription repressor to the 6A allele [14,15]. It can be concluded that 6A allele carriers might have lower stromelysin-1 levels and thus a lower proteolytic activity which favours deposition of extracellular matrix in the atherosclerotic lesion, development of an atherosclerotic plaque and consequently a more rapid progression of coronary stenosis. Not only three earlier studies [13,16,17] but also the present investigation support this hypothesis since we were able to detect an association of the 6A allele with the severity of coronary heart disease defined by the Gensini score [19]. Obviously, the 6A allele influence the degree of CHD in a dose-dependent manner: 6A homozygotes had highest, 6A heterozygotes intermediate and 5A5A genotypes lowest CHD scores in the total study sample (Fig. 1) and in subgroups of

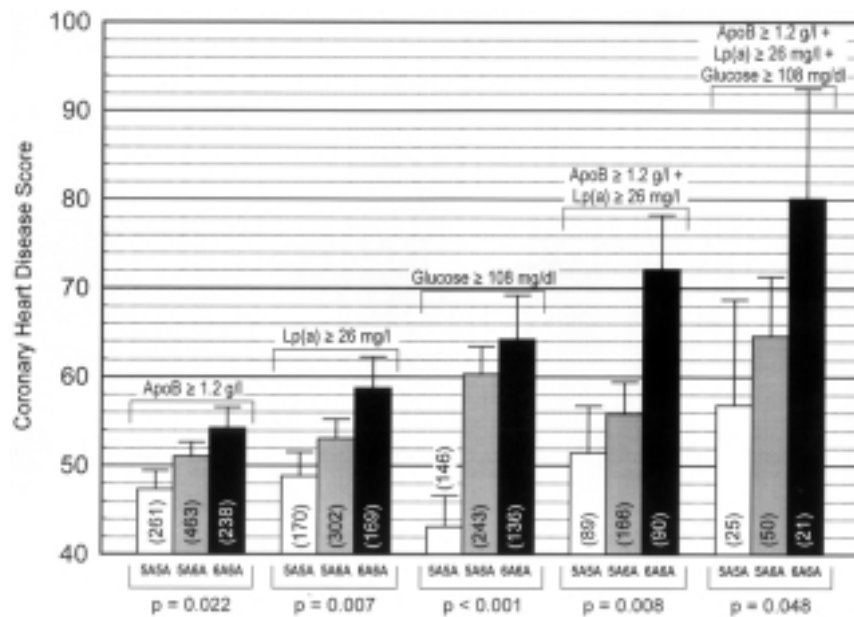


Fig. 2. Comparisons of mean coronary heart disease scores between the stromelysin-1 promoter 5A/6A genotypes in subgroups of patients with coronary high-risk profiles. The mean CHD scores were compared by multiple regression analysis after adjustment for coronary risk factors between patients who underwent coronary angiography for diagnostic purposes. Values are means \pm SEM. Numbers of individuals are given in parentheses. The mean values of coronary risk factors were used as cut points for definition of high risk populations. Coronary angiography was performed by the Judkins method. The CHD score was estimated according to Gensini [19]. A two-tailed probability value of < 0.05 was considered to indicate statistical significance.

Table 3
Comparison of stromelysin-1 5A and 6A genotypes between individuals without MI and MI patients

n	- MI						+ MI						2p		
	5A5A		5A6A		6A6A		5A (- MI)		5A (+ MI)		6A (- MI)			6A (+ MI)	
	n	n	n	n	n	n	5A (- MI)	5A (+ MI)	6A (- MI)	6A (+ MI)	6A (- MI)	6A (+ MI)			
NVD 432	100	177	86	22	35	12	0.52 (0.48–0.56)	0.57 (0.49–0.66)	0.48 (0.44–0.52)	0.43 (0.35–0.51)	0.260				
SVD 359	62	87	43	39	75	53	0.55 (0.50–0.60)	0.46 (0.40–0.52)	0.45 (0.40–0.50)	0.54 (0.48–0.60)	0.121				
DVD 396	56	94	45	45	95	61	0.53 (0.48–0.58)	0.46 (0.41–0.51)	0.47 (0.42–0.52)	0.54 (0.49–0.59)	0.095				
TVD 661	64	136	53	100	329	168	0.52 (0.48–0.56)	0.48 (0.45–0.52)	0.48 (0.44–0.52)	0.52 (0.48–0.55)	0.274				

Stromelysin-1 5A/6A genotypes were compared between angiographically controlled individuals without MI and MI patients in subgroups of participants with no, single, double and triple vessel disease. Coronary angiography was performed by the Judkins method. Vessels were defined as diseased if at least 50% stenosis were demonstrated. Acute myocardial infarction were diagnosed according to criteria by the World Health Organisation. No vessel disease: Persons without any detectable stenosis of coronary arteries or patients with less than 50% stenosis of coronary arteries. Abbreviations: NVD, no vessel disease; SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease; 2p, two-tailed p-values for the comparisons between individuals without MI and MI patients by multiple logistic regression.

high risk patients (Fig. 2). Humphries et al. [16] stated that – since measurements of the stromelysin-1 expression level in atherosclerotic plaques are essentially impossible – the stromelysin-1 5A/6A promoter polymorphism may act as a disease marker for coronary heart disease and add information to measurable plasma risk factors for estimating the severity and prognosis of this disease. The potential link of the gene variation to the risk of CAD has not been studied so far. Obviously, both alleles have no impact on the risk of coronary artery disease, since the allele frequencies of 5A and

6A were essentially the same in healthy controls and patients with coronary heart disease (see Table 2). This observation applied to the total sample and to subpopulations of individuals with low- and high coronary risk profile.

In contrast and due to the about two-fold higher transcription activity of the 5A allelic stromelysin-1 promoter which leads to a higher rate of remodelling and degradation of matrix components, it was hypothesized that 5A/5A homozygotes may have an increased risk of plaque rupture and subsequent myocardial infar-

tion [18]. The identification of such functional gene variations would achieve a great advantage in the prevention of MI by distinguishing patients who have genetically increased susceptibility to plaque rupture. Indeed – in a Japanese population – Terashima et al. identified the 5A allele as an independent risk indicator of myocardial infarction [18]. To our knowledge, other studies analysing the relation of the 5A/6A promoter polymorphism to MI have not been studied so far. The results of the present study clearly indicate that the 5A allele carriers were not over-represented in the group of MI patients (Table 2). This conclusion could be drawn for the comparison of healthy controls to MI patients and of angiographically controlled subjects without and with MI when univariate (data not shown) or multivariate (Table 2) statistical procedures were applied. Regarding the functional characteristics of the 5A allele and the strong association of the established coronary risk factors with MI (Table 1), we speculated that the functional importance of the 5A allele or of the 5A5A genotype may only become apparent in subgroups of study participants with similar degree of vessel disease. Therefore, we compared the 5A/6A allele frequencies between angiographically controlled patients without and with MI in subpopulations of individuals with zero-, single-, double or triple vessel disease. Also these comparisons did not reveal any significant association of the 5A allele with the risk of MI (Table 3). In consequence, the results of our study strengthen the hypothesis that – in a German population – the 5A allele and/or the 5A5A genotype has no significant impact on the risk of MI. Further studies are warranted to add information to the important question whether the 5A allele or the 5A5A genotype might act as disease marker for an increased susceptibility for MI caused by plaque rupture.

5. Conclusions

Although the present results do not confirm an association of the 5A allele with the risk of MI, they strengthen the hypothesis of earlier investigations that the 6A allele is a disease marker for progression of coronary heart disease. Further studies should evaluate whether 5A6A heterozygotes and 6A6A homozygotes – especially with a coronary high-risk profile – might benefit from a more aggressive therapy against CHD progression.

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