Stromelysin-1 and Interleukin-6 Gene Promoter Polymorphisms Are Determinants of Asymptomatic Carotid Artery Atherosclerosis

Rainer Rauramaa, Sari B. Väisänen, Le-Anh Luong, Arno Schmidt-Trückäss, Ilkka M. Penttilä, Claude Bouchard, Jari Töyry, Steve E. Humphries

Abstract—The functional 5A/6A polymorphism of the stromelysin-1 promoter has been implicated as a potential genetic marker for the progression of angiographically determined atherosclerosis in patients with coronary artery disease. Recently, a novel interleukin-6 (IL-6) gene functional G/C polymorphism at −174 in the promoter has also been reported. In this study, we analyzed the relation of these two polymorphisms with carotid artery atherosclerosis in 109 randomly selected, middle-aged men without exercise-induced ischemia. Atherosclerosis was quantified as intima-media thickness (IMT) by high-resolution ultrasonography. Univariately, stromelysin genotype was significantly (P=0.015) associated with IMT, and this relation remained (P=0.033) after adjustments for age, cardiorespiratory fitness, body mass index, smoking, LDL cholesterol, and systolic blood pressure and for sonographers. The 5A/6A polymorphism independently explained 7% of the variance in carotid bifurcation IMT. The IL-6 polymorphism was also significantly associated (P=0.036) with increased IMT, with men homozygous for the G allele having IMT that was 11% greater than men homozygous for the C allele. Men who were homozygous for both the 6A and G alleles had an covariate adjusted IMT that was 36% greater than men who were homozygous for neither allele (P<0.003). These data suggest that genetic factors that predispose to reduced matrix remodeling (stromelysin 6A allele) and to increased inflammation (IL-6 G allele) combine to increase susceptibility for intima-media thickening in the carotid bifurcation, a predilection site for atherosclerosis. (Arterioscler Thromb Vasc Biol. 2000;20:2657-2662.)

Key Words: stromelysin-1 ■ interleukin-6 ■ DNA polymorphism ■ B-mode ultrasonography ■ carotid atherosclerosis ■ population sample

Vascular remodeling is an essential phenomenon in the development of atherosclerotic changes in the arterial wall. Matrix metalloproteinases and their endogenous tissue inhibitors (eg, tissue inhibitor of metalloproteinase-1) regulate the accumulation of extracellular matrix during tissue injury and thus the growth of the atherosclerotic plaque.1,2 Stromelysin-1 is a key member of the matrix metalloproteinase family and has a wide substrate specificity.3 Stromelysin expression is regulated primarily at the level of transcription, where the promoter of the gene responds to different stimuli including growth factors and cytokines.4

Recently, a common variant in the promoter sequence of the stromelysin-1 gene has been reported.5 The polymorphism is located 600 bp upstream from the start of transcription in which 1 allele has a run of 6 adenosines (6A), whereas the other has only 5 (5A). In vitro studies of promoter strength showed that the 5A allele expressed higher activity than the 6A allele in both cultured fibroblasts and vascular smooth muscle cells,6 and band shift assays showed that a nuclear protein bound more strongly to the 6A than the 5A sequence, suggesting that this protein may be a repressor of transcriptional activity. This suggests that compared with other genotypes, individuals homozygous for the 6A allele would have lower stromelysin levels in the arterial wall because of reduced gene transcription, and this lower level of proteolytic activity might therefore favor deposition of extracellular matrix. This would lead to a more rapid development and progression of an atherosclerotic plaque. In support of this, the 6A allele has been implicated as a potential genetic marker for the progression of angiographically determined atherosclerosis in patients with coronary artery disease.5,7,8

Interleukin-6 (IL-6) is a cytokine derived from diverse tissues including fibroblasts, monocytes, adipocytes, and endothelial cells.9,10 It plays a key role in driving the acute

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inflammatory response and orchestrates the production of acute phase proteins such as C-reactive protein.\textsuperscript{9} IL-6 has been associated with several markers of endothelial dysfunction such as chemokine and adhesion molecule release.\textsuperscript{10} In this respect, it may play a direct role through the induction of endothelial activation\textsuperscript{11} or an indirect role through the stimulation of fibrinogen synthesis,\textsuperscript{12} which may itself be directly pathogenic. IL-6 may thus be pivotal in the putative inflammatory pathology of coronary disease. Inflammatory markers are associated with the development of coronary disease, with disease severity,\textsuperscript{13} and with the occurrence of coronary events.\textsuperscript{14} Data from the Physicians Health Study suggest that this association is still present after an 8-year follow-up period,\textsuperscript{15} implying that progression of atheroma may also be associated with raised inflammatory markers. Unstable angina is associated with activation of systemic circulating neutrophils\textsuperscript{16} and with elevated inflammatory markers such as C-reactive protein and IL-6 levels.\textsuperscript{17–19} The magnitude of this elevation predicts poor outcome and is not merely secondary to the presence of myocardial necrosis or ischemia.\textsuperscript{20}

We have recently detected a functional polymorphism 174 bp upstream from the start of transcription of the IL-6 gene.\textsuperscript{21} The polymorphism is common, with the frequency of the C allele being 0.41 in a group of 944 healthy men from the United Kingdom. Using constructs of the 5′ flanking region of the IL-6 gene in a luciferase reporter vector transiently transfected into HeLa cells, the C construct showed 62% lower expression than the G construct at baseline. However, after stimulation with lipopolysaccharides (LPS) or IL-1, expression from the C construct was not significantly increased, whereas expression from the G construct increased to 235% and 360%, respectively, compared with the unstimulated level. Thus, the G allele appears to be associated with a significant increase in IL-6 response to inflammatory stimuli, at least in vitro. As would be expected from this result, in vivo, individuals with the genotype GG have the highest mean IL-6 levels and CC individuals the lowest.\textsuperscript{21} There is no evidence that IL-6 has a direct effect on stromelysin gene expression, but the upregulation of tissue inhibitor of metalloprotease-1 synthesis by IL-6 may shift the balance in favor of matrix protein deposition, leading to atherothrombosis and the progression of coronary artery disease.\textsuperscript{22,23} Thus, an IL-6 genotype that determines plasma IL-6 levels may have an indirect effect on the vascular wall through this mechanism. The aim of this study was thus to investigate the combined roles of the 5A/6A polymorphism of the stromelysin-1 promoter and of the G-174C polymorphism of the IL-6 promoter in ultrasonographically quantified carotid artery atherosclerosis in a randomly selected sample of asymptomatic, middle-aged men without exercise-induced ischemia. The study protocol was approved by the Ethics Committee of Kuopio University.

**Carotid Ultrasonography**

Carotid artery atherosclerosis was determined by measuring the mean maximum intima-media thickness (IMT)\textsuperscript{26} of the far walls of the carotid artery bifurcations, that is, the distance between the end of the distal common carotid and the tip of the flow diver. The ultrasonic device was equipped with a high-resolution, 10-MHz annular array transducer providing 0.25-mm axial resolution (Bio- sound Phase 2). Two certified sonographers performed the ultrasound scanning from the anterior, lateral, posterior oblique views by using standardized and pretested protocols.\textsuperscript{27} The calibration of the ultrasound unit was routinely checked with the use of an RMI 414B tissue phantom. The examination was recorded on half-inch videotape (Panasonic 7330 SVHS). A sonographer chose from the videotape up to 5 images for digitization (Studio DC10 Plus frame grabber). The measurement of IMT was based on a new automated edge detection software, based on an active contour model, also called snake.\textsuperscript{28,29} Essentially, the snake adapts itself to the intima-media layer by a deformable energy-minimization process. This process uses a combination of gray-level gradient intensity, spatial correlation, and/or certain knowledge-based criteria. It incorporates the assessment of edges by combining the initial estimation, desired edge properties, continuity and the curvature of a contour, and some other constraints into a single dynamic process. This process was tuned by adapting the elasticity and rigidity of the snake to the contour characteristics of the intimal and adventitial layers. This design is appropriate for both intimal and adventitial layer tracking. If noises are present in the subintimal region (this could happen often in thick arterial walls or in the region of the carotid bifurcation), the snake might be trapped by them. To avoid this, the cost values are memorized while passing the subintimal region and a limited subadventitial region. Together with the assumption that the adventitial layer should have the maximum mean gradient value in this region, the snake can detect the optimum shape for the adventitia.

A certified sonographer performed the measurement of IMT along segments of the far walls of the carotid bifurcation up to the level of the flow divider. Every pixel along the traced regions served as a measurement point (pixel size, 0.0038 mm). The traced regions were as long as both layers could be detected by the active contour program so that on the average, 413 measurement points were performed at each measurement site. The measurement results and the tracing lines were stored and could be reloaded, together with the image for visual control of the tracing lines. The capability for manual correction was not installed to avoid a reduction in the precision of the IMT measurements by manual outlining. Instead, a cut function for incorrectly traced sections was established to exclude them from analysis.

**Exercise ECG and Cardiorespiratory Fitness**

The detailed description of the cardiopulmonary exercise stress test has been published elsewhere.\textsuperscript{24} The ECG was continuously monitored and recorded every minute during exercise and up to 7 minutes after exercise with standard and Mason-Likar leads. ST-segment change 80 ms after the QRS complex was assessed automatically to the nearest 0.01 mV at the highest ergometer work load (Case 12, Marquette Electronics, Inc). The ischemic waveform potential was classified as the 8% to 11% cumulative frequency of ST-segment changes in each ECG lead in the study population, including all subjects who underwent the exercise stress test. For the assessment of the greatest ECG signal amplitude (ie, ST-segment change) with equally spaced lead vectors, leads V\textsubscript{1} and aVR were not used. Spatial distribution of ischemia was classified by combining any ischemic waveform potential in leads V\textsubscript{4} through V\textsubscript{6} (cutoff limits for the ST change: increase of 0.04, V\textsubscript{4} to decrease of up to 0.18 mV, V\textsubscript{6}), leads I through III (decrease of 0.04 mV, lead I, up to 0.2 mV, leads II through III), and leads aVL or aVF (decrease of 0.04 and 0.18 mV). Subjects were classified into the ischemic group by any ischemic waveform potential. The nonischemic group consisted of no ST-segment potential changes in the respective ECG leads. Subjects with either left (n = 1) or right (n = 4) bundle-branch block, ventric-
promoter polymorphisms was carried out as described.\textsuperscript{7,21} Genomic DNA was isolated from white blood cells by digestion with proteinase K and SDS followed by the phenol/chloroform extraction procedure and dialysis.\textsuperscript{31} Genotyping for the stromelysin and IL-6 proteinase K and SDS followed by the phenol/chloroform extraction procedure and dialysis.\textsuperscript{31} Genotyping for the stromelysin and IL-6 polymorphisms was carried out as described.\textsuperscript{7,21}

The method for assessing cardiorespiratory fitness has been described elsewhere.\textsuperscript{30} An exercise physiologist defined aerobic threshold visually as the first nonlinear increase of ventilation by means of breath-by-breath respiratory gas analyses during the exercise test.

DNA Analyses

Genomic DNA was isolated from white blood cells by digestion with proteinase K and SDS followed by the phenol/chloroform extraction procedure and dialysis.\textsuperscript{31} Genotyping for the stromelysin and IL-6 promoter polymorphisms was carried out as described.\textsuperscript{7,21}

Other Methods

Venous blood samples were drawn, without stasis, between 7:30 and 10:00 AM after a 12-hour fast and 30 minutes of rest in a supine position. Serum IL-6 concentrations were analyzed with the Pelikine tool set (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam) and stromelysin by the Biotrak Matrix metallproteinase-3 human ELISA system (Amersham International plc). The methodology for the lipoprotein cholesterol assays has been described earlier.\textsuperscript{24} Blood pressure was measured with a random zero device with a cuff size of 52×14 cm, as described previously.\textsuperscript{24} Smoking habits were evaluated by asking the subject the number of cigarettes smoked daily. Waist-to-hip ratio was defined as the ratio of waist girth at the umbilicus to the hip girth, measured at the trochanteric level.

Statistical Methods

Conformance of the allele frequencies to Hardy-Weinberg equilibrium proportions were tested by use of a \( \chi^2 \) test.\textsuperscript{32} Serum levels of stromelysin and IL-6 were nonnormally distributed. Although logarithmic transformation could be used for stromelysin analysis, the relatively high number of IL-6 concentrations below the detection limit did not normalize the distribution after square root transformation. Therefore, the median levels and approximate standard deviations have been presented. ANCOVA (general linear model) with Bonferroni correction was used to test the relation of the polymorphisms to IMT. Statistical analyses were performed with SPSS for Windows software package version 9.0.

Results

The characteristics of the men are shown in Table 1 and did not differ by genotype. For both polymorphisms, the distribution of genotypes was in Hardy-Weinberg equilibrium. The frequency of the stromelysin 6A allele 0.58 (95% CI, 0.51 to 0.65) and of the IL-6 G allele was 0.44 (95% CI, 0.37 to 0.60). As shown in Table 2, the stromelysin-1 genotype was significantly (\( P=0\text{.015} \)) associated with IMT, with the heterozygotes having 16% lower IMT compared with other men. Univariately, the stromelysin genotype explained 6.7% of the variance in IMT. The association remained (\( P=0\text{.033} \)) after adjustments for age, cardiorespiratory fitness, body mass index, smoking, LDL cholesterol, and systolic blood pressure and for the sonographer, with the whole adjusted model explaining 13% of the variation in IMT. The IL-6 polymorphism was significantly (\( P=0\text{.036} \)) associated with IMT.

**Table 1. Characteristics of Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.8±3.0</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.98±0.05</td>
</tr>
<tr>
<td>Aerobic threshold, L/min</td>
<td>1.39±0.30</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±17</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88±10</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.5±0.9</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.7±0.9</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.20±0.26</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>25</td>
</tr>
<tr>
<td>Drug treatment for cardiovascular disease, n</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 2. Mean (±SD) of Mean Maximum IMT in Carotid Bifurcation, Geometric Mean of Serum Stromelysin, and Median of IL-6 Levels in Men With Different Stromelysin-1 and IL-6 Genotypes and Their Combinations**

<table>
<thead>
<tr>
<th>Gene and Polymorphism</th>
<th>Carotid IMT, mm</th>
<th>S-Stromelysin, ng/mL</th>
<th>S-IL-6, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromelysin-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A5A (n=19)</td>
<td>1.24±0.35</td>
<td>70.1±17.0</td>
<td>1.00±0.75</td>
</tr>
<tr>
<td>5A6A (n=47)</td>
<td>1.08±0.21</td>
<td>68.4±19.0</td>
<td>1.10±1.51</td>
</tr>
<tr>
<td>6A6A (n=30)</td>
<td>1.30±0.44</td>
<td>68.5±18.7</td>
<td>1.20±1.30</td>
</tr>
<tr>
<td></td>
<td>( P=0.014 )  for trend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG (n=19)</td>
<td>1.30±0.42</td>
<td>71.8±18.9</td>
<td>1.10±1.69</td>
</tr>
<tr>
<td>GC (n=38)</td>
<td>1.09±0.25</td>
<td>69.1±17.9</td>
<td>1.20±0.91</td>
</tr>
<tr>
<td>CC (n=35)</td>
<td>1.17±0.24</td>
<td>66.7±19.7</td>
<td>1.05±1.59</td>
</tr>
<tr>
<td></td>
<td>( P=0.036 )  for trend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A5A/5A6A+CC/CG (n=53)</td>
<td>1.13±0.28*</td>
<td>68.0±20.1</td>
<td>1.10±1.34</td>
</tr>
<tr>
<td>5A5A/5A6A+GG (n=9)</td>
<td>1.14±0.26\†</td>
<td>73.0±7.6</td>
<td>0.90±1.55</td>
</tr>
<tr>
<td>6A6A+CC/CG (n=17)</td>
<td>1.11±0.21\‡</td>
<td>68.1±14.2</td>
<td>1.15±0.99</td>
</tr>
<tr>
<td>6A6A+GG (n=8)</td>
<td>1.54±0.48</td>
<td>70.3±28.7</td>
<td>1.20±1.84</td>
</tr>
</tbody>
</table>

\*\(P=0.003\) vs GG+66; \†\(P=0.021\) vs GG+66; \‡\(P=0.004\) vs GG+66.
univariately but no more after covariate adjustment (Table 2). The IL-6 genotype was neither associated with plasma levels of lipoproteins, IL-6, fibrinogen, or plasminogen activator inhibitor-1, although for the latter three, levels were moderately lower in the CC compared with the GG men (data not shown). There were no differences in the distribution of plaques within the genotypes separately or combined. Serum concentrations of stromelysin or IL-6 differed between genotypes neither separately nor combined (Table 2). No correlation was found between serum stromelysin or IL-6 and IMT.

To test whether there were additive effects of these two gene variants on IMT, genotypes for the 5A/6A and G/C polymorphisms were combined in 4 groups as follows: (1) no homozygotes for the alleles associated with the high IMT: 5A5A or 5A6A and CC or CG (n = 53), (2) 5A5A or 5A6A and GG (n = 9), (3) 6A6A and CC or CG (n = 17), and (4) homozygotes for both alleles associated with the high IMT: 6A6A and GG (n = 8). As shown in the Figure, the combined genotype at both loci was significantly associated with IMT (P = 0.003), with the IMT of the group 4 differing from that of groups 1 (P = 0.003), 2 (P = 0.021), and 3 (P = 0.004). The combined genotype explained 11% of the variance in IMT. This relation remained significant (P = 0.004) after adjustments for age, cardiorespiratory fitness, body mass index, smoking, LDL cholesterol, and systolic blood pressure and for sonographers, with the whole adjusted model accounting for 24% of the variance in IMT.

**Discussion**

The novel finding of this study is the demonstration of the additive effects of the 5A/6A and G/C promoter polymorphisms of the stromelysin-1 and in the IL-6 and genes, respectively, on asymptomatic atherosclerosis in the carotid bifurcation, a predilection site for the development of the disease.33

Stromelysin-1 is a key regulator of matrix remodeling,34–36 and in situations of atherosclerotic development in which extracellular matrix deposition is occurring, individuals who are genetically predisposed to produce less stromelysin-1 would have a lower ability to remodel and degrade the matrix components. In vitro, the 6A allele shows lower promoter activity than the 5A allele,6 and assuming this pattern of transcription also holds in vivo, individuals with 1 or more 6A alleles in the cells within a developing carotid atherosclerotic lesion would be capable of producing less stromelysin-1 mRNA and hence would have a lower enzyme activity. This would result in faster plaque growth and would be seen with carotid ultrasound as a greater IMT. In this sample, there was no difference in stromelysin levels between subjects with different 5A/6A genotypes. This lack of association may be explained in part by the small sample size but may also reflect that serum stromelysin levels will be determined by secretion of stromelysin from many cell types and cells located at a number of different sites within the body, and serum levels may therefore not show a strong association with stromelysin levels within the atherosclerotic plaque or vessel wall.

In vitro, the G allele of the IL-6 gene has roughly twice the promoter strength, at least in situations of inflammatory stress such as in the presence of IL-1 and LPS.31 Whereas in vivo the G allele has been associated with higher plasma levels of IL-6,21 the present data failed to show such a relation, although IL-6 levels showed the expected trend of being highest in GG subjects and lower in those with 1 or more C allele. The lack of a statistically significant effect may be explained by the relatively small sample size studied here. Immunohistochemistry of the human arterial atherosclerotic wall has shown IL-6 mRNA expression localized to cellular and extracellular deposits in the connective tissue matrix, with the fibrous plaque having statistically significantly higher level of IL-6 than the intima and media.37 Studies in apoE knockout mice that develop atherosclerotic plaques in the aorta also show that elevated levels of IL-6 mRNA predominate in the plaque area compared with normal mice.38 Thus, IL-6 may damage the endothelium and lead to the initiation of atherosclerosis, especially in areas of the vascular system that are predisposed to atherosclerosis because of decreased shear stress with turbulent blood flow such as the carotid bifurcation.

High-resolution B-mode ultrasonography together with the sophisticated automated analyzing software enabled us to detect early changes in the arterial intima-media layer of the carotid bifurcation. The subjects were asymptomatic healthy men randomly selected from the general population, but the present results agree with recent findings on the stromelysin-1 gene and the progression of atherosclerosis in patients with established atherosclerotic coronary artery disease5 on the progression of angiographically determined coronary atherosclerosis in men after coronary bypass surgery7 and in subjects with coronary artery disease.8 Subjects with the 6A6A genotype and less advanced arterial narrowing in coronary angiography showed more rapid disease progression compared with those already having advanced atherosclerosis. Moreover, in patients whose lipid levels were lowered and who had less progression of disease, the stromelysin-1 genotype was not associated with differences in progression, whereas in those whose lipid levels remained high, the 5A allele was associated with low progression and the 6A allele with high progression of angiographic stenosis. There is now evidence to support the view that besides having a major lipid-lowering effect, statins also have an anti-inflammatory effect,39 probably acting through modulation of NF-κ-B activity.40,41 Thus, part of the reduced influence of the stromelysin genotype on disease progression in treated...
patients may be through this mechanism. Although there are few data available about the biological and clinical associations of the IL-6 G/C polymorphism, no data are available on healthy asymptomatic subjects. In a small study, preliminary data have been obtained that the GG genotype was associated with increased risk of myocardial infarction at a young age (<45 years), whereas the CC genotype was protective. Moreover, the C allele was associated with lower levels of markers of endothelial damage such as E-selectin. The association observed in the present study of greater IMT in healthy men with the genotype GG is supportive of these findings.

The clinical relevance of the 5A/6A and G/C polymorphisms is further emphasized by the high population frequency of the 6A and G alleles, with 29% of subjects in this sample being 6A6A homozygotes, 22% being GG homozygotes, and 10% being homozygous for both. From a population point of view, it is also relevant to note that the frequency of the 6A “risk-predisposing” allele is significantly higher in these healthy men from eastern Finland, a geographic area with a high prevalence of atherosclerotic cardiovascular diseases, than reported in healthy men from the United Kingdom, where the risk of coronary heart disease is lower (frequency for the 6A allele 0.55 versus 0.48, P<0.05). By contrast, the frequency of the “high-risk” G allele in these Finnish men is significantly lower than reported in the United Kingdom (0.44 versus 0.59, P=0.01).

The present results show for the first time the combined contribution of genetic variation in the genes coding for a key cytokine of the inflammatory processes and for a matrix metalloproteinase in the evolution of asymptomatic atherosclerosis, as assessed noninvasively by the measurement of arterial wall thickening in a randomly selected population sample. Homozygotes for both the G and 6A alleles, who, based on their allele frequency should represent roughly 10% of the Finnish population, appear to be predisposed to arterial wall thickening compared with other genotypes. The present data are potentially valuable for the primary prevention, and together with recent observations on patients with advanced atherosclerosis, should help in identifying individuals with inherited high risk for coronary heart disease. Given the strength of the present findings, it is important that studies be undertaken in different ethnic populations to confirm these observations.

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