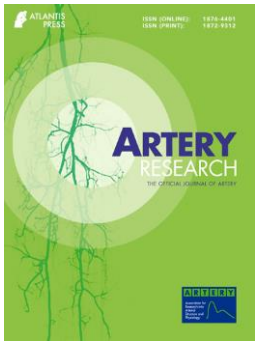

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Genetic determinants of arterial properties and of heart disease

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It has been known for a long time that arterial properties are strongly genetically determined: total heritability of arterial stiffening, independently of other factors, is estimated to be 30–40%.[1,2] It is also interesting that telomeric length, a heritable indicator of biological ageing, has been found to correlate with increased arterial stiffening.[3] Large amount of data on genetics of arterial stiffness has been published and various genetic methods were used including genome-wide association studies; despite these modern genetic technologies, the candidate gene approach gives us up to now the most relevant information. The list of genes potentially involved is long. From pathophysiological point of view, arterial stiffening is the consequence of altered structure and function of extracellular matrix, cellular growth and their interaction in the vascular wall. Therefore, a large group of genes potentially involved are the *genes coding for extracellular matrix components*.[4,5] This group includes genes coding for elastin and fibrillin-1, type 1 collagen, and matrixmetalloproteinase 3 and 9. A number of systems regulating the circulation globally influence vascular wall properties, and therefore, a group of *non-matrix genes* play a role as well. Among them, the genes coding for components of renin–angiotensin–aldosterone system (RAAS) seems to be of primary importance. There are also data on genes coding for sympathetic nervous system (beta 1, 2 and 3 adrenergic receptors), nitric oxide synthase, endothelin and its receptors, guanine nucleotide regulatory proteins (G-proteins), estrogen receptors alpha, adhesion molecules (ICAM1 and VCAM1) and several others. This article cannot give exhaustive information on this very large field. It deals with several genes with common polymorphisms where there are enough data suggesting that they may be important for both arterial properties and heart disease.

Among the RAAS genes, the A1166C polymorphism of *angiotensin II type 1 receptor gene* (AGTR1) has been shown to influence strongly aortic pulse wave velocity (PWV). Although located in the untranslated region of the gene, it has been suggested to be related to modified response of the receptor to angiotensin II. Benetos and colleagues[6] showed in a group of normotensive and untreated hypertensive subjects that this polymorphism accounted for a large proportion of variability in aortic PWV: it was the second most significant determinant just after systolic blood pressure. Its effect was stronger in subjects whose age was above median which was approximately 50 years. We have shown in a population-based sample of 250 subjects that this polymorphism was not associated with aortic PWV, but there was a strong association with femorotibial PWV.[7] This result seems biologically plausible because unlike aortic stiffness, the stiffness of arteries of lower extremities is mainly determined by the degree of smooth muscle cell hypertrophy and collagen production, and therefore, the proliferative effects of angiotensin II may be more pronounced in muscular-type arteries. There are also some data about the associations of angiotensinogen and ACE I/D gene polymorphisms with arterial properties, but they are less consistent than for AGTR1.

Aldosterone synthase gene (CYP11B2) has a common polymorphism C-344T in the promoter region of the gene. The C allele is probably associated with higher aldosterone production. We have shown within the EPOGH cohort (European Project On Genes in Hypertension) that the association of arterial properties, as measured by augmentation index (AIx), with C-344T polymorphism

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depend on salt intake[8]: in subjects above median (i.e., 24-h urinary sodium excretion above 210 mmol), the CC homozygotes had significantly higher AIx than heterozygotes or TT homozygotes. This effect did not exist when salt intake was not taken into account.

Endothelial nitric oxide synthase gene has two common polymorphisms, one in the promoter region (T-786C) and another one in exon 7 (Glu298Asp). Whereas the former is probably linked to the amount of nitric oxide production, the latter may be related to the speed of nitric oxide degradation. So far, the data about their relationships to arterial properties have been equivocal. We have shown that T-786C polymorphism was associated with femorotibial, but not aortic PWV.[7] Similarly as for AGTR1, the strong relationship with stiffness of muscular-type artery can be explained by the ability of eNOS to influence vascular smooth muscle cell function, which in the long run leads probably to structural changes. We further studied haplotypes: when the AGTR1 and eNOS polymorphisms were combined, their effects were found to be synergistic: the subjects who were simultaneously variant homozygotes in one polymorphism and heterozygotes or variant homozygotes in the second polymorphism, had their peripheral PWV about 15 m/s, while other groups had the mean PWV around 12 m/s. Mourad and colleagues[9] showed that the increase of brachial pulse pressure with age is higher when the variant allele of either Glu298Asp of eNOS, or A1166C of AGTR1 is present, however, when variant alleles of both polymorphisms were present simultaneously, the slope with age was significantly steeper. In fact, brachial pulse pressure is dependent on stiffness of peripheral muscular-type arteries, and therefore, our results are in line with those of Mourad and colleagues.

There are data supporting the evidence that all these three genes, coding for AGTR1, CYP11B2 and eNOS, may also be related to *heart disease*. AGTR1 polymorphism was found to influence the response of coronary arteries to vasoconstrictive agent: homozygous subjects with CC genotype had significantly more vasoconstriction.[10] This phenomenon may lead to greater tendency to coronary heart disease. Indeed, some studies, though not all, found higher prevalence of CC genotype among patients after myocardial infarction (MI).[11] Interestingly, C allele of this polymorphism has recently been found to be more frequent in patients with hypertrophic cardiomyopathy than in controls, and more frequent in patients from affected families than in sporadic cases.[12] These findings show that there may be a common mechanism, caused by this gene, of both vascular smooth muscle cell hypertrophy and hypertrophy of myocardium. CYP11B2 gene was studied in numerous studies in context with left ventricular structure. A meta-analysis published recently[13] included 2157 patients from 14 studies and did not find any relationship of the gene polymorphism to left ventricular mass or dimensions. The value of such meta-analysis is limited by the fact that no other factors like salt intake or classic cardiovascular risk factors are taken into account. A case—control study of post-MI patients, based on the Helsinki Heart Study, showed that this polymorphism had no effect on the risk of MI when the whole groups of MI patients and controls were compared.[14] However, when the groups were divided according to the smoking status, the smokers with CC genotype had more than threefold risk of having MI than the subjects with TT genotype; in non-smokers no such association existed. Similarly as for smoking, the presence of low HDL cholesterol level and high systolic blood pressure resulted in significant effect of CYP11B2 gene polymorphism on the risk of MI. As regards eNOS gene polymorphisms and their relationship to coronary heart disease, a high number of studies were published. A meta-analysis of 26 studies with more than 23,000 subjects showed that the homozygous Asp/Asp subjects in the Glu298Asp polymorphism have increased risk of coronary heart disease by more than 30%.[15] The results for T-786C polymorphism are not so consistent; a study of Rossi et al.,[16] however, showed that C allele carriers have an increased risk of multiple coronary artery disease among patients undergoing coronary angiography with odds ratio of 1.67.

In summary, there are data suggesting that AGTR1, CYP11B2 and eNOS gene polymorphisms may play a role in both arterial stiffness and heart disease. All these gene polymorphisms are common, with the variant allele prevalences ranging from 20 to 50%, and therefore, they may have impact on cardiovascular health in populations at large. For studying arterial stiffness, more data are necessary about peripheral stiffness of muscular-type arteries. Although it is not associated with cardiovascular prognosis, this phenotype can be extremely important for elucidating the mechanisms of arterial disease and its genetic background. There are potential common mechanisms for both arterial stiffness and heart disease: (1) altered structure and function of both aorta and coronary arteries (as suggested for AGTR1 and eNOS gene polymorphisms), (2) simultaneous collagen proliferation in the vessel wall and cardiac fibrosis (CYP11B2), and (3) simultaneous hypertrophy of vascular smooth muscle cells and myocardium (AGTR1). Therefore, further studies involving both cardiac and arterial phenotypes are necessary. It is of utmost importance that genes are studied in their large context, predefined on the basis of pathophysiological mechanisms of the disease. Gene—gene interactions should be tested and non-genetic factors, such as age, blood pressure, smoking, sex, salt intake, etc, must be taken into account. A particular gene polymorphism may be important only in special situation, or at least its role is amplified in some circumstances: AGTR1 gene polymorphism acts more on arterial stiffness in the elderly, CYP11B2 becomes important in subjects with high sodium intake or in subjects with high cardiovascular risk, etc. So far, this context, has often been neglected in genome-wide association studies, and this may be one of the reasons why their contribution to understanding heritability of cardiovascular diseases has not been very high, yet.

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