Genetics and pathophysiology of arterial stiffness

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Arterial stiffness is a cardiovascular risk factor that is independent of arterial pressure. Clinically, carotid-femoral pulse wave velocity (PWV) is the gold-standard parameter of arterial stiffness. Recent genetic studies have revealed specific genes that contribute to arterial stiffening. Here we review the recent findings on genome-wide linkage analyses and candidate gene polymorphism association studies. We also focus on the latest advances in the identification of gene variants affecting PWV using high density array single nucleotide polymorphism technology in a recent genome-wide association (GWA) study. Linkage and polymorphism studies revealed a first group of genes affecting the renin–angiotensin–aldosterone system, elastic fibre structural components, metalloproteinases, and the NO pathway. A second group of genes, identified by polymorphism association studies and possibly involved in the pathophysiology of arterial stiffness, includes β-adrenergic receptors, endothelin receptors, and inflammatory molecules. The last group of genes, identified by GWA studies and unrelated to currently suspected mechanisms of arterial stiffness, may target transcriptional pathways controlling gene expression, differentiation of vascular smooth muscle cells, apoptosis of endothelial cells, or the immune response within the vascular wall.

KEYWORDS

Genetics; Pulse wave velocity; Arteries; Elasticity

1. Introduction

Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states such as diabetes, atherosclerosis, and chronic renal compromise. Large-artery stiffness is the main determinant of pulse pressure (PP). Aortic stiffness has independent predictive value for total and cardiovascular mortality, coronary morbidity and mortality, and fatal stroke in patients with essential hypertension end-stage renal failure, or diabetes mellitus.1–3

The growing prevalence and associated risk of arterial stiffness provide a major incentive to better understand the underlying molecular, cellular, and genetic causes and the resultant physiological impact of this condition. Initially, genetic studies focused on the association between arterial stiffness parameters and common polymorphisms in single candidate genes, mainly related to the renin–angiotensin–aldosterone system. Then, genome-wide linkage studies, using genetic markers (generally microsatellites) distributed throughout the genome, permitted the identification of chromosomal regions associated with arterial stiffness, without relying on any prior biological hypothesis. The more recent availability of panels of single nucleotide polymorphisms (SNPs) covering the whole genome and their incorporation into high-density genotyping microarrays has led to genome-wide association (GWA) studies to investigate the genetic component of quantitative traits in an unbiased manner. Such a powerful technology has been recently applied to arterial stiffness parameters. However, these techniques are still rapidly evolving, and the current use of SNPs tagging distinct haplotype blocks that encompass the whole human genome, reducing the number of SNPs to be genotyped, should increase the feasibility of large population studies.4 This approach offers great potential for the future discovery of new causes and mechanisms of disease.

Arterial stiffness is defined by a reduction in arterial distensibility and may be quantified by the measurement of different parameters. Clinically, the gold standard parameter is the pulse wave velocity (PWV) which is an estimation of the velocity of the propagation of the forward and backward pressure waves between two points of the arterial tree. This is a direct measure, representing the mean rigidity between the two points of reference along the arterial tree, generally between the carotid and femoral arteries. Other indirect parameters of stiffness are derived from blood pressure signals such as PP, forward and reflected wave amplitude, and augmentation index. Local arterial elasticity is also evaluated by arterial
distensibility and elastic modulus which are mainly used in experimental pathophysiological studies.

The objective of the present review is to summarize results of published genome-wide scans (Table 1) that map arterial stiffness-linked regions of the genome and identify candidate genes (Table 2). We next present candidate and other gene variants associated with PWV (Table 3) and finally discuss the relevance of the genetic variations identified by these different approaches to the pathophysiology of arterial stiffness.

2. Genetics of arterial stiffness

Several studies support a genetic contribution to arterial stiffness. Table 1 indicates that key measures of arterial stiffness were found to have a moderate to substantial heritable component since heritability estimates ranged from 0.21 to 0.66. In addition, existing genome-wide studies have pointed to distinct chromosomal regions of significant or suggestive linkage for PP, carotid-femoral PWV, forward and reflected pressure wave properties, suggesting separate genetic determinants. Genetic association and family-based studies have identified a significant number of candidate genes (Table 2) and gene polymorphisms (Table 3) which could modulate arterial stiffness.

2.1 Genome-wide linkage studies

In 2001, Atwood et al. found, for the first time in a population-based sample, four distinct chromosomal regions showing suggestive linkage [logarithm of the odds (LOD) scores >1.9] for PP. The concordance between the loci for PP and systolic blood pressure (SBP) and the identification of two candidate genes in the chromosome 8 locus, aldosterone synthase gene (CYP11B2), and the adjacent 11β-hydroxylase (CYP11B1) highly associated with hypertension, suggests that PP and SBP have the same genetic aetiology. Camp et al. in 2003 published linkage signals for PP in chromosome 8, overlapping with and confirming the results of Atwood et al. on PP. In addition, they also found two regions on chromosomes 8 and 12 with superior linkage evidence for PP than for SBP, raising the major hypothesis that genes involved in arterial stiffness and blood pressure could be different. The analysis of DeStefano et al. in the Framingham Heart Study supports this conclusion by showing that only one of the three chromosomal regions with LOD scores >2.0 for PP overlaps with a linkage peak for SBP.

More recently, in the Family Blood Pressure Program, Bielinski et al. show similar global linkage profiles for PP and SBP, although the higher LOD scores for PP than for SBP may be explained by anti-hypertensive treatment and ethnicity. Using multivariate linkage analysis, Turner et al. have identified more statistically significant genetic loci for PP associated with coronary artery calcifications (on chromosomes 1 and 11), brain atrophy (on chromosomes 11 and 16), or serum creatinine (chromosome 5) than for each trait alone, which may represent the pleiotropic effects of a single gene or of nearby genes. These linkage studies were conducted using PP as the quantitative trait, which represents only an approximation of large artery stiffness. Aortic stiffness, as measured by PWV has a higher independent predictive value than PP for both total and cardiovascular deaths, as well as for cardiovascular events.

The demonstration of linkage regions for carotid femoral PWV was given by the Framingham Heart Study, in which four regions of suggestive linkage were identified in chromosomes 2, 7, 13, and 15 (LOD scores >2.0). Potential candidate genes in these regions included the insulin-like growth factor-1 receptor (IGF1R), myocyte-specific enhancer factor 2A (MEF2A), chondroitin synthase (CHSY1), proprotein convertases (PACE4 and FURIN), 1β-adducin (ADD2), neurokinin-1 receptor (TACR1), α2B adrenergic receptor (ADRA2B), and interleukin-6 (IL6). As expected, some of these positional genes (IGF1R, MEF2A, CHSY1, and PACE4) had been postulated as candidate genes for PP in the larger study by DeStefano et al. The influence of age on PP is always important to consider since Franceschini et al. have recently identified a significant locus for PP on chromosome 7 (in close vicinity with peaks for PWV in the Framingham Heart Study) which is attenuated when including the age interaction term.

In conclusion, these genome-wide linkage studies for arterial stiffness are relatively recent, especially those related to PWV. Arterial stiffness is mainly the consequence of various cardiovascular diseases and not the primary event. Thus, the main issue is to determine whether these genetic associations are related to specific molecular determinants of arterial stiffness or to those of underlying diseases. Larger GWA studies across several generations should help in elucidating this question.

2.2 Candidate gene polymorphisms

The contribution of a given gene polymorphism (either a SNP or another variant), commonly occurring in the general population, to the variance of arterial stiffness phenotype has been addressed in many studies. In addition, various analyses have been performed to determine the interactions between aging, genetic variants, and arterial stiffness or between two or more gene polymorphisms.

2.2.1 Renin–angiotensin–aldosterone genes

The first study showed the influence of the 1166 A/C polymorphism of the Angiotensin II type 1 receptor gene (AGTR1) on the regulation of aortic stiffness in hypertensive subjects. The 1166C allele was, in most cases, associated with higher aortic stiffness, even after an adjustment for age and blood pressure. In the presence of the AGTR1 1166C allele, the positive relationship between age and PWV was shifted upwards, i.e. was linked to higher values of aortic stiffness at any age, compared with the 1166AA genotype. Furthermore, the AGTR1 153G allele presented additive effects on aortic stiffness after the age of 55.

The effect of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism is more controversial and depends on the vascular territory and on the interactions with other genes. The presence of the I allele was associated with increased stiffness in healthy subjects and hypertensives or in patients with type 2 diabetes, whereas older adults with the D allele exhibited higher carotid distensibility in the Rotterdam Study. In contrast, in another study of normal subjects, D allele carriers had lower PWV. In a multigene analysis, femoral artery distensibility was lower in ACE DD white subjects also homozygous for α-adducin Gly460, whereas there was a decreased distensibility of the common carotid artery in ACE DD homozygotes who also carried the aldosterone synthase –344T
<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Number of genotyped individuals</th>
<th>Age (years)</th>
<th>Parameter measured</th>
<th>Heritability</th>
<th>Location with evidence of linkage (chromosome, cM)</th>
<th>Type of evidence</th>
</tr>
</thead>
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<tr>
<td>Atwood et al.⁵</td>
<td>Mexican Americans</td>
<td>441 (10 families)</td>
<td>40–60</td>
<td>PP</td>
<td>0.21</td>
<td>4–114, 8–154, 8–116, 21–46</td>
<td>Suggestive</td>
</tr>
<tr>
<td>Camp et al.⁶</td>
<td>Utahns</td>
<td>1454 (26 pedigrees)</td>
<td>27.8 ± 18.2</td>
<td>PP</td>
<td>0.25</td>
<td>8–54, 12–109</td>
<td>Suggestive</td>
</tr>
<tr>
<td>DeStefano et al.⁷</td>
<td>Framingham Heart Study</td>
<td>1584 (345 pedigrees)</td>
<td>47.5 ± 8.8</td>
<td>PP</td>
<td>0.51</td>
<td>15–122, 5–53, 7–71, 7–152, 8–140, 10–81, 22–36</td>
<td>Suggestive</td>
</tr>
<tr>
<td>Bielinski et al.⁸</td>
<td>Family blood pressure program (FBPP)</td>
<td>10 798 (3320 families)</td>
<td>13 to 93</td>
<td>PP</td>
<td>0.29</td>
<td>18–75, 1–200, 21–25</td>
<td>Suggestive</td>
</tr>
<tr>
<td>Mitchell et al.¹²</td>
<td>Framingham Offspring Study</td>
<td>1480 (heritability)</td>
<td>60 ± 10</td>
<td>CFPWV</td>
<td>0.40 0.35</td>
<td>2–94, 7–29, 13–108, 15–108</td>
<td>Suggestive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>590 (linkage)</td>
<td>58 ± 10</td>
<td>Central PP</td>
<td>0.21 0.28</td>
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<td>Suggestive</td>
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<tr>
<td></td>
<td></td>
<td>(204 families)</td>
<td></td>
<td>FWA</td>
<td>0.48 0.33</td>
<td>7–174</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RWA</td>
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<td>Significant</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RWTT</td>
<td></td>
<td>8–33, 1–27, 9–22, 9–164</td>
<td>Significant</td>
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<tr>
<td></td>
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<td>MAP</td>
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<td>1–192</td>
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<td>PP</td>
<td>0.294</td>
<td>7–79, 11–17</td>
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<td>Turner et al.¹⁰</td>
<td>Genetic Epidemiology Network of</td>
<td>488 (223 families)</td>
<td>64.7 ± 7.5</td>
<td>PP</td>
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<td>Arteriopathy (GENOA) of the FBPP</td>
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<td>7–37</td>
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<td>FWA</td>
<td>0.43</td>
<td>19–92</td>
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<tr>
<td>Franceschini et al.¹³</td>
<td>Strong Heart Family Study</td>
<td>948 (393 families)</td>
<td>59.6 ± 9.9</td>
<td>CFPWV</td>
<td>0.43</td>
<td>2–74, 18–40, 15–100, 4–12</td>
<td>Suggestive</td>
</tr>
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<td></td>
<td></td>
<td>1892 (14 pedigrees)</td>
<td>14–93</td>
<td>PW</td>
<td>0.22</td>
<td>3–60</td>
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<td></td>
<td></td>
<td>RW</td>
<td>0.66</td>
<td>8–19, 9–10, 4–169, 15–100, 1–12</td>
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<td>Levy et al.⁵⁰</td>
<td>Framingham Offspring Study</td>
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<td>28–62</td>
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<td>0.43</td>
<td>4–169</td>
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PP, pulse pressure; CFPWV, carotid-femoral pulse wave velocity; FWA, forward wave amplitude; RWA, reflected wave amplitude; RWTT, reflected wave transit time; MAP, mean arterial pressure.
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<thead>
<tr>
<th>Chr.</th>
<th>Marker, cM</th>
<th>LOD score</th>
<th>Candidate gene in the region</th>
<th>Published study</th>
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<td>Carotid-femoral pulse wave velocity</td>
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<td>40</td>
<td>2.68</td>
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<td>Myocyte-specific enhancer factor 2A (MEF2A)</td>
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<td>Chondroitin synthase (CHSY1)</td>
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<td>Proprotein convertases (PACE4 and FURIN)</td>
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<td>108</td>
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<td>Interleukin-6 (IL6)</td>
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<td>Integrin β3 (IGTB8)</td>
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<td>Neuropeptide Y (NPY)</td>
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<td>β-adducin (ADD2)</td>
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<td>α-2B adrenergic receptor (ADRA2B)</td>
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<td>12</td>
<td>2.17</td>
<td>Reflected wave properties</td>
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<td>2</td>
<td>94</td>
<td>2.46</td>
<td>Lipoprotein lipase (LPL)</td>
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<td>α-1A adrenergic receptor (ADRA1A)</td>
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<td>Calcineurin A γ-subunit (PPP3CC)</td>
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<td>22</td>
<td>1.78</td>
<td>Protein tyrosine phosphatase, non-receptor type 2 (PTPN2)</td>
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<td>100</td>
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<td>9</td>
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<td>Microfibrillar-associated protein 2 (MFAP2)</td>
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<td>10</td>
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<td>8</td>
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<td>4.93</td>
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<td>2.34</td>
<td>Forward wave properties</td>
<td>Mitchell et al.</td>
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<td>Endothelial nitric oxide synthase (NOS3)</td>
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<td>Kallikrein 1 (KLK1)</td>
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<td>D8S1100, 154</td>
<td>1.98</td>
<td>Calcitonin gene-related peptide</td>
<td>Bielinski et al.</td>
</tr>
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<td>D8S1048, 54</td>
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<td>Adrenomedullin (ADM)</td>
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<td>2.61</td>
<td>Aldosterone synthase (CYP11B2) and 11 β-hydroxylase (CYP11B1)</td>
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<tr>
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<td>140</td>
<td>1.56</td>
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<td>160</td>
<td>2.72</td>
<td>Aldosterone synthase (CYP11B2) and 11 β-hydroxylase (CYP11B1)</td>
<td>Camp et al.</td>
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</table>
allele. It was also demonstrated that, in the presence of the AGT1 1166C allele, ACE inhibitors were able to decrease stiffness to a greater degree than calcium antagonists.21 Interestingly, the opposite was observed in AA homozygotes for the 1166A/C polymorphism, in which calcium antagonists were more effective in decreasing aortic stiffness. These results suggest that the AGT1 A1166C genotype should be taken into consideration in anti-hypertensive drug strategy in patients with increased arterial stiffness at very high cardiovascular risk.

The concentration of angiotensinogen is a rate-limiting factor in the generation of angiotensin II. The molecular variant (M235T) of the angiotensinogen gene has been found to be correlated with the plasma concentration of angiotensinogen and to be associated with the degree of intima-media thickness in hypertension.22 Patients homozygous for the T allele had a reduced carotid distensibility and an increased stiffness of the carotid wall material (Young’s elastic modulus), independent of blood pressure, compared with patients homozygous for the M allele. Although the plasma concentration of angiotensinogen was not measured in this study, the favoured hypothesis was an increased AT1 receptor stimulation in patients with the 235TT genotype.

In the same way, a codominant association between plasma aldosterone levels and the −344 T/C polymorphism, located in the promoter region of the aldosterone synthase (CYP11B2) gene has been demonstrated in essential hypertension.23 The C allele was associated with an increase in PWV and aldosterone levels but no relationship between plasma aldosterone and PWV levels was observed. Sodium intake seems to modulate this genetic effect since the −344 C allele occurred in patients with a high sodium excretion (210 mmol/day).24

2.2.2 Matrix and metalloproteinase genes
Genotype–phenotype studies have also focused on matrix proteins, mainly polymorphisms of the elastin (ELN) and fibrillin-1 genes, and matrix metalloproteinase (MMP) genes. ELN is a major component of the vascular wall and disorders of elastic fibres may cause arterial stiffness.1,25 Among three ELN polymorphisms (Nos 145, 158, and 160), the ELN 3’-untranslated region (−1A) polymorphism (160) was significantly associated with hypertension, blood pressure values, and PWV in a Japanese population, supporting the notion that this polymorphism is associated with blood pressure levels through its influence on large vessel stiffness.26 Fibrillin-1 is the gene affected in Marfan syndrome, in which large-artery stiffness and elevated PP play an important role in aortic dilation.27 Fibrillin-1 genotype was tested on VNTR polymorphism (number of TAAAA repeats in intron 28) corresponding to the major genotypes 2–2, 2–3, and 2–4, accounting for 86% of the population. Patients with the 2–3 genotype had stiffer large arteries, higher PP, and more severe coronary artery disease than other genotypes, suggesting an important role for fibrillin-1 genotype in cardiovascular risk associated with large-artery stiffening.

Polymorphisms occurring in MMP genes have been associated with age-related arterial stiffening.28 Specifically, large arteries were reported to be stiffer in older (>60 years) but not in young subjects homozygotic (5A or 6A) for the MMP-3 5A/6A polymorphism compared with heterozygotes.29 For the MMP-9 genotype (−1562 C/T and R279Q polymorphisms), the T and Q alleles were independently linked with arterial stiffness in healthy subjects.30 The T allele was also found to be associated with arterial stiffness in patients with coronary artery disease31 and in never-treated hypertensive patients with no significant increase in the augmentation index.32 The possible causal involvement of genetic variations in MMP genes is supported by their association with increased PWV, and their occurrence in regulatory regions that affect the level of gene expression and active protein levels.

2.2.3 Endothelial cell-related genes
The first studies of nitric oxide synthase gene (NOS3) polymorphisms (G023T and Glu298Asp) did not show any significant association with arterial stiffness either in hypertensive or normotensive subjects.33 In the Framingham heart study, Mitchell et al.34 found that the G allele genotype of the Glu298Asp SNP was associated with increased central PP and wave reflections, mainly in women. This association was not significant for PWV, indicating a modest role for the NOS3 Glu298Asp in increased arterial stiffness, in agreement with the Bogalusa heart study in young black adults showing that the presence of the T allele of the same polymorphism was associated with a lower Peterson’s elastic modulus.35 Increased arterial stiffness evaluated by radial
<table>
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<th>Gene</th>
<th>Candidate gene from linkage studies</th>
<th>Polymorphism and protein domain</th>
<th>Impact on RNA and protein expression</th>
<th>Arterial stiffness phenotype</th>
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<tr>
<td>Angiotensin II type 1 receptor (AGTR1)</td>
<td>chromosome 3; location 3q21–q25</td>
<td>rs5186: 1166 A/C (5' end of the 3' untranslated region); rs275653: −153 A/G (promoter region); rs4340: I/D (insertion in intron 16)</td>
<td>Unknown</td>
<td>C allele: increased PWV; G allele: additive effect</td>
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<tr>
<td>Angiotensin-converting enzyme (ACE)</td>
<td>chromosome 17; location 17q23.3</td>
<td>No</td>
<td>D allele: increased plasma ACE activity</td>
<td>C allele: reduced carotid distensibility</td>
</tr>
<tr>
<td>Angiotensinogen (AGT)</td>
<td>chromosome 1; location 1q42–q43</td>
<td>No</td>
<td>C allele: increased AGT plasma level</td>
<td>C allele: increased PWV</td>
</tr>
<tr>
<td>Aldosterone synthase (CYP11B2)</td>
<td>chromosome 8; location 8q21–q22</td>
<td>rs699: 704 T/C (exon 2, Met235Thr), localized at the outside of the protein solvent accessible region</td>
<td>C allele: increased aldosterone plasma level</td>
<td>C allele: increased PWV</td>
</tr>
<tr>
<td>a1-adducin (ADD1)</td>
<td>chromosome 4; location 4p16.3</td>
<td>No</td>
<td>Unknown</td>
<td>No association alone with distensibility; ACE DD and ADD1 GG: lower distensibility</td>
</tr>
<tr>
<td>Elastin (ELN)</td>
<td>chromosome 7; location 7q11.23</td>
<td>No</td>
<td>Unknown</td>
<td>A allele: increased PWV</td>
</tr>
<tr>
<td>Fibrillin-1 (FBN1)</td>
<td>chromosome 15; location 15q21.1</td>
<td>VNTR (TAAAA in intron 28)</td>
<td>Unknown</td>
<td>Haplotype 2–3: higher input and characteristic impedance</td>
</tr>
<tr>
<td>Matrix metalloproteinase 3 (MMP3)</td>
<td>chromosome 11; location 11q22.3</td>
<td>No</td>
<td>5A: higher expression of MMP3 in vascular tissues</td>
<td>5A/5A and 6A/6A: higher input impedance</td>
</tr>
<tr>
<td>Matrix metalloproteinase 9 (MMP9)</td>
<td>chromosome 20; location 20q11.2–q13.1</td>
<td>No</td>
<td>T and A alleles: higher expression of serum and aortic MMP9</td>
<td>T and A alleles: increased PWV</td>
</tr>
<tr>
<td>Endothelial nitric oxide synthase (NOS3)</td>
<td>chromosome 7; location 7q36</td>
<td>rs207074: −786 T/C (promoter region); rs1808593: 10 G/T (intron 23); rs1799983: 894 G/T (exon 7, Glu298Asp), in the chain B</td>
<td>Unknown</td>
<td>C allele (−786 T/C): increased A; 10 G/T and 894 G/T genotypes: no association with PWV; T allele (894 G/T): lower Peterson’s elastic modulus</td>
</tr>
<tr>
<td>Lysyl oxidase-like 2 (LOXL2)</td>
<td>chromosome 8; location 8p21.3–p21.1</td>
<td>No</td>
<td>Unknown</td>
<td>Not tested</td>
</tr>
<tr>
<td>b1-adrenergic receptor (ADRB1)</td>
<td>chromosome 10; location 10q24–q26</td>
<td>No</td>
<td>No difference in β-adrenergic receptor expression in heart</td>
<td>G allele (145 A/G): increased PWV; G allele (1165 C/G): increased af-PWV</td>
</tr>
<tr>
<td>b2-adrenergic receptor (ADRB2)</td>
<td>chromosome 5; location 5q31–q32</td>
<td>No</td>
<td>No difference in β-adrenergic receptor expression in heart</td>
<td>A allele: increased af-PWV only in blacks</td>
</tr>
<tr>
<td>p3-adrenergic receptor (ADRB3)</td>
<td>chromosome 8; location 8p12–p11.2</td>
<td>No</td>
<td>Unknown</td>
<td>C allele: increased af-PWV</td>
</tr>
<tr>
<td>G-protein β3 subunit (GNB3)</td>
<td>chromosome 12; location 12p13</td>
<td>No</td>
<td>Unknown</td>
<td>T allele: increased PWV</td>
</tr>
<tr>
<td>Endothelin-A receptor (EDNRA)</td>
<td>chromosome 4; location 4q31.23</td>
<td>No</td>
<td>Unknown</td>
<td>G allele (−231 A/G): increased PWV in women only</td>
</tr>
<tr>
<td>Gene/Protein</td>
<td>Chromosome/Location</td>
<td>rs ID</td>
<td>Description</td>
<td>Association</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Endothelin-B receptor (EDNRB)</td>
<td>13; 13q22</td>
<td>No</td>
<td>rs5351: 831 A/G (exon 5, Leu277Leu), in the fifth transmembrane domain</td>
<td>Unknown</td>
</tr>
<tr>
<td>C-reactive protein receptor (CRP)</td>
<td>1; 1q21–q23</td>
<td>No</td>
<td>rs1130864: 1444 C/T (exon 2, 3’ untranslated region)</td>
<td>T allele: increased basal and stimulated C-reactive protein levels</td>
</tr>
<tr>
<td>Tumour necrosis factor-α (TNF)</td>
<td>6; 6p21.3</td>
<td>No</td>
<td>rs1800629: −308 A/G (promoter region)</td>
<td>Increased TNF-α production on stimulation</td>
</tr>
<tr>
<td>P-selectin (SELP)</td>
<td>1; 1q22–q25</td>
<td>No</td>
<td>rs2244529: C/T (intron 2); rs6131: 1087 G/A (exon 7, Ser331Asn), in the complement binding-like repeat 3</td>
<td>A allele (1087 G/A): lower soluble P-selectin concentration</td>
</tr>
<tr>
<td>Intercellular adhesion molecules-1 (ICAM1)</td>
<td>19; 19p13.3–p13.2</td>
<td>No</td>
<td>rs1799969: 13014 G/A (exon 4, Gly241Arg), in the protein Ig-like domain 3 (Mac-1 binding domain)</td>
<td>A allele: lower soluble ICAM1 concentration</td>
</tr>
<tr>
<td>Vascular cell adhesion molecules-1 (VCAM1)</td>
<td>1; 1q22–q25</td>
<td>No</td>
<td>rs3176878: 2079 C/T (exon 9, Asp693Asp), in the transmembrane domain</td>
<td>Unknown</td>
</tr>
<tr>
<td>Transforming growth factor β1 (TGFB1)</td>
<td>19; 19q13.1</td>
<td>No</td>
<td>rs11466314: −800 G/A (promoter region); rs1800469: −509 C/T (promoter region); rs1800470: 869 T/C (exon 1, Leu10Pro), in the signal sequence; rs1800471: 915 G/C (exon 1, Arg25Pro), in the signal sequence</td>
<td>T allele (−509 C/T): higher transcriptional activity; G allele (915 G/C): higher TGFβ1 level</td>
</tr>
<tr>
<td>Estrogen receptor α (ESR1)</td>
<td>6; 6q25.1</td>
<td>No</td>
<td>rs2234693: −401 T/C (intron 1) rs2077647: 30 T/C (exon 1, Ser3Ser), in the N-terminal domain</td>
<td>C allele (−401): enhanced activation of the B-myb binding site, the transcriptional activator</td>
</tr>
<tr>
<td>TNF receptor superfamily, member 6 (FAS)</td>
<td>10; 10q24.1</td>
<td>Yes²⁴</td>
<td>rs10509561: A/T (intron 1)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1)</td>
<td>6; 6q22–q23</td>
<td>No</td>
<td>rs1044498: A/C (exon 4, Lys121Gln), in the first somatomedin B-like extracellular domain</td>
<td>Unknown</td>
</tr>
<tr>
<td>Myocyte enhancer factor 2C (MEF2C)</td>
<td>5; 5q14</td>
<td>Yes⁵⁰</td>
<td>rs770189: G/C (intron 3)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Spectrin repeat containing, nuclear envelope 1 (SYNE1)</td>
<td>6; 6q25</td>
<td>Yes⁵⁰</td>
<td>rs1322512: G/T</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tumour necrosis factor ligand superfamily, member 11 (TNFSF11)</td>
<td>13; 13q11</td>
<td>Yes⁵⁰</td>
<td>rs10507514: A/G</td>
<td>Unknown</td>
</tr>
<tr>
<td>Collagen, type VIII, α1(COL8A1)</td>
<td>3; 3q12.3</td>
<td>Yes⁵⁰</td>
<td>rs792833: G/A (intron 3)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Transforming growth factor II (TGFB2R)</td>
<td>32; 3p22</td>
<td>Yes⁵⁰</td>
<td>rs3773643: A/G (intron 4)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Methylenetetrahydrofolate reductase (MTHFR)</td>
<td>1; 1p36.3</td>
<td>Yes¹²</td>
<td>rs1801133: 677 C/T (exon 5, Ala222Val), in the catalytic domain</td>
<td>T allele: reduced enzyme activity</td>
</tr>
</tbody>
</table>

PWV, pulse wave velocity; af-PWV, arterial-femoral PWV; ba: brachial-ankle PWV.
tonometry measurement of the augmentation index was associated with the C allele of the -786T/C SNP in children with type 1 diabetes, raising the possibility that other NOS3 polymorphisms may contribute to arterial stiffness.36

Other endothelial gene polymorphisms, -401 T/C and 30 T/C of the estrogen receptor α, have been reported to correlate with arterial stiffness in women only. The CC genotype of these two polymorphisms was associated with lower brachial ankle PWV and this may contribute to the gender difference in arterial stiffness.37 In addition, the reduction in brachial-ankle PWV induced by increased daily physical activity in women with the TC+CC genotype suggests that the impact of this genetic influence can be modified by external factors.38 Elevation of endothelin 1 (ET-1) has been observed in hypertensive patients and its receptors (endothelin A and B) act in the vascular wall as important modulators of vascular tone. Among polymorphisms of the endothelin system genes, the G allele of the ETA receptor variant −231 A/G and the G allele of the ETB receptor variant 30G/A were associated with increased PWV in women only, suggesting that there is no correlation with endothelin levels.39

2.2.4 Inflammatory genes

Regarding inflammatory involvement, several studies have reported that C-reactive protein, interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) concentrations are related to PWV and arterial elasticity. In patients with a history of Kawasaki disease, a synergistic effect of the T allele for the 1444 C/T polymorphism in the C-reactive protein gene and of the A allele for the −308 A/G polymorphism in the TNF gene on the carotid arterial stiffness index has been reported.40 However, such an association between polymorphisms in inflammatory molecule genes has not been found in the control population, suggesting a modest effect of these rare genetic variations. In contrast, the genetic contributions of adhesion molecules, which play a key role in inflammatory processes in arterial stiffening, have been recently reported in healthy youth.41 Young individuals with the Ser290Asn or Asn290Asn genotype or TT homozygotes of rs2244529 (P-selectin) had an increased PWV. For the Asp693Asp (C to T) polymorphism (vascular cell adhesion molecules-1, VCAM1), carriers of the CC genotype had higher PWV while the 241Arg allele (intercellular adhesion molecules-1 - ICAM1) was associated with a decreased PWV. The epistatic interaction between Ser290Asn, Gly241Arg, and Asp693Asp on PWV underlines the interest of exploring systems of genes. Regarding the main circulating inflammatory markers tested in 2409 Framingham Heart Study participants, FAS rs10509561 was among the SNPs showing the strongest association with central PP, and individuals carrying the haplotype of Gly49Gly with Arg389Arg for the β1-AR polymorphisms showed higher PWV compared with those carrying the other haplotypes, demonstrating the interest of combination analysis for these genes.42 In addition, the association between higher PWV in young healthy adults and the T allele of the B25 C/T polymorphism in the gene encoding their signalling protein, the G-protein β3 subunit,43 suggests a role of this pathway in arterial stiffness.

Arterial calcifications, responsible for stiffening of the arteries, are regulated by several physiological inhibitors such as osteopontin, fetuin-A, or ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1). Patients with end-stage renal failure heterozygous for the ENPP1 K121Q variant had significantly higher PWV than matched controls with wild-type ENPP1 K121K genotype.44

Arterial stiffness is a trait with a multifactorial pathogenesis and this has led to the exploration of numerous genes potentially contributing to this phenotype. In this way, the C677T polymorphism of the 5,10-methylenetetrahydrofolate reductase gene (MTHFR) was investigated but showed no association with arterial distension.45 Similarly, polymorphisms in the transforming growth factor β1 gene (−800 G/A, −509 C/T, codon 10Leu/Pro, and codon 25Arg/Pro) were not associated with variations in PWV in the Rotterdam Study,46 questioning the relevance of single genes in complex diseases.

In conclusion, analysis of common polymorphisms in candidate genes has the advantage of being based on prior pathophysiological knowledge of arterial stiffness. This strategy has provided many interesting results but, to date, only CYP11B2 and NOS3 have been confirmed by genome-wide linkage studies as being associated with arterial stiffness. It is indeed puzzling that none of the other genes whose polymorphisms (see Table 3) have been reported to be linked to arterial stiffness came up as candidate genes in linkage studies, as they are not positioned within the loci identified. This observation, together with the lack of consistency in loci identification between studies (Table 2), illustrates the complexity of the genetic regulation of arterial stiffness in the general population.

There are many reasons for the apparent lack of concordance between genome-wide linkage and candidate-gene association studies, which have been discussed elsewhere,47 and are out of the scope of this review. Many of the linkage studies were conducted in selected populations or were family-based. The limitations of linkage studies probably lie mainly in the existence of multiple weak associations due to small phenotypic effects associated with individual alleles, complex epistatic interactions, lack of statistical power, incomplete marker coverage of the genome, unknown confounders, etc. On the other hand, candidate gene association studies may also suffer from insufficient statistical power because they are based on a single hypothesis and often concern smaller sample sizes.48

For methodological reasons, candidate gene studies related to arterial stiffness were started several years before genome-wide linkage studies. Contemporary studies are now focusing on analysis of genome-wide SNP associations (GWAS), using dense panels of common SNPs, as recently published by Levy et al.49 in the Framingham Heart Study. First, in this study, linkage analysis was performed for carotid-femoral PWV or other individual arterial
stiffness phenotypes (carotid-brachial PWV, forward and reflected pressure waves, and mean arterial pressure). Although linkage signals were fairly low, not reaching genome-wide significance and as such, requiring confirmation, some interesting likely candidate genes came up: myocyte enhancer factor 2C (MEF2C), spectrin repeat containing, nuclear envelope 1 (SYNE1), tumour necrosis factor ligand superfamily, member 11 (TNFSF11), collagen type VIII α1 (COL8A1), and transforming growth factor β receptor II (TGFBRII). Then, joint analysis of the five phenotypes identified lysyl oxidase-like 2 (LOXL2), SYNE1, and MEF2C as attractive genes in arterial stiffness. SNPs in the renin–angiotensin–aldosterone pathway genes were only weakly related to each arterial stiffness parameter, suggesting a small contribution of these genetic variants.

2.3 Gene expression profiling

Using microarray technology to identify novel transcriptional biomarkers of arterial stiffening, Durier et al. found that 151 probe sets were differentially expressed between stiff and distensible aortas from patients with coronary heart disease, and that 32 of these probe sets were significantly positively or negatively associated with PWV. Most of the genes identified were related to the cytoskeleton, with the remainder being distributed between matrix and membrane. Differentially expressed genes involved in the mechanical regulation of vascular structure included integrins (α2b, α6, β3, and β5), proteoglycans (decorin, osteomodulin, etc.), fibulin-1, and fascin. Changes in the profiles of signalling molecules may be involved in the regulation of cell cytoskeletal organization, cell-matrix interactions, or the contractile state of the cell.

Using chips specific for 25,000 human genes, the same group also found 101 genes differentially expressed between patients with and without chronic renal failure (CRF). CRF is considered as a model of accelerated arterial stiffness. Ninety-seven transcripts were increased in CRF patients, including genes involved in the regulation of actin filament polymerization (adenylyl cyclase-associated protein 1–CAP1, capping protein muscle Z-line α 1–CAP2A1, actin-related protein 2/3 complex–ARP3C, and moesin–MSN), in migration (apolipoprotein D–APOD and ornithine decarboxylase 1–ODC) and in organization of vascular smooth muscle cells (lumican–LUM). Until now, the contribution of these genes to arterial stiffness has not been tested.

3. Pathophysiology

In recent years, genetic studies have largely modified our understanding of the pathophysiology of arterial stiffness. However, they have not yet identified a novel molecular determinant or a new signalling pathway, mainly because arterial stiffness is a multifactorial phenotype. Arterial stiffness is generally considered to represent the sum of the passive stiffness, corresponding to the contribution of the inert structural components, mainly elastic and collagen fibres, and the active stiffness provided by the smooth muscle tone. More recently, other matrix determinants have been proposed, such as fibronectin and their integrin membrane receptors.

Taken together, the different genetic studies published to date have focused on three categories of candidate genes, those already widely known as determinants of arterial stiffness, those likely to be involved considering their biological role, and the last set of genes representing genetic markers since they are apparently unrelated to any currently known mechanisms of arterial stiffness.

The first group of genes affecting arterial elasticity naturally integrates components of the renin–angiotensin–aldosterone system (AGTR1, ACE, AGT, CYP11B2, ADD1), elastic fibre structural components (ELN, FBNI), metalloproteases (MMP3, MMP9), and the NO pathway (NOS3). Aldosterone synthase and endothelial nitric oxide synthase genes are associated with arterial stiffness both in linkage and common polymorphism association studies, suggesting relevant mechanisms whereby genes may influence collagen and fibronectin accumulation in the arterial wall and endothelium-dependent vascular tone. One potentially interesting finding of the recent GWA study was to point to LOXL2, the most predominant LOX family member expressed in primary endothelial cells and recently shown to be the main actor of elastogenesis in the absence of VE statin/egfl7. However, again, it is surprising that genes encoding certain proteins considered to be strongly implicated in stiffness (e.g. collagens, integrins, and cytoskeletal proteins) and differentially expressed in microarray studies did not come up as candidate genes in this study.

The genes likely to be involved in arterial stiffness include the β-adrenergic receptors and the G-protein β3 subunit (ADRB, GBN3), endothelin receptors (EDNRA, EDNRB), and inflammatory molecules (CRP, TNF, SELE, SELP, ICAM1, VCAM1, TGFBI). All were only identified by polymorphism association studies with regard to their possible causal role in arterial stiffness. The importance of β1-adrenoceptor and β3-adrenoceptors located on both endothelial cells and vascular smooth muscle cells (in relation with caveola) in mediating arterial relaxation has been recently documented. Supporting this role, the reduction in arterial stiffness in response to the vasodilating β-blocker nebivolol may result from both inhibition of α1-adrenoceptors and activation of β3-adrenoceptors. Endothelin receptors also represent attractive genes since we already know that ETA receptor blockade suppresses endothelin-1-mediated increased arterial stiffness. Inflammatory genes also appear as possible contributors to arterial stiffness. Although, such genetic associations were not replicated in recent GWA studies, they are in agreement with clinical observations of increased arterial stiffness in inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus. It appears logical that inflammation should have repercussions on arterial stiffness as it induces structural modifications of the vascular wall, but studies formally linking inflammatory molecules to increased stiffness phenotype are currently lacking.

The last set of genes has no a priori causal role in arterial stiffness. These genes (ESR1, FAS, and ENPP1) encode for the estrogen receptor α, the TNF receptor super-family member 6, and the ectonucleotide pyrophosphatase phosphodiesterase 1. Endothelial function is a key target for these three genes. The estrogen receptor α is involved in 17β-estradiol-induced dilation in response to flow. TNF receptor superfamily, member 6 induces either Akt-dependent upregulation of eNOS expression or Akt-independent
apoptosis of endothelial cells. Finally, ectonucleotide pyrophosphatase/phosphodiesterase 1 down-regulates insulin signalling associated with endothelial dysfunction and also generates inorganic pyrophosphate, a physiological inhibitor of calcification.

In the quest for new biological pathways contributing to arterial stiffness, genes identified by GWA using powerful SNP technology should bring new impetus to hypothesis generating. Myocyte enhancer factor 2C, implicated in nuclear factor of activated T cells (NFAT) signalling, points to transcriptional pathways controlling gene expression. Spectrin repeats containing nuclear envelope 1 (SYNE1) co-localized with nesprins to regulate differentiation and contractility of vascular smooth muscle cells. TFN ligand superfamily, member 11 (TNFSF11) may play a role in the development of calcifications as a ligand for osteoprotegerin but also in the T cell-dependent immune response. It is currently becoming clear that immune regulation is crucial with regard to hypertension/vascular remodelling. In the context of atherogenesis, collagen type VIII α1 interferes in many cell functions such as adhesion, proliferation, differentiation, and migration. Finally, transforming growth factor, β receptor II (TGFBR2) is involved in mechanotransduction in vascular smooth muscle cells and mutations in this receptor have been shown to cause the Loeys-Dietz syndrome characterized by arterial aneurysms. Thus, some genes not obviously related to arterial stiffness may nevertheless have implications in arterial wall function via their role as receptors or via their implication in indirect or general functions, such as differentiation or apoptosis.

4. Conclusion

Progress has been made in identifying genetic determinants using GWA strategy and measurement of PWV as the most reliable quantitative trait of arterial stiffness in large populations. With the exception of the renin–angiotensin system and structural components of the arterial wall, many candidate genes extend well beyond the basic concepts of arterial stiffness. For example, the TNF ligand superfamily, member 11 and the TNF receptor superfamily member 6 likely modulate the T cell-dependent immune response and apoptosis of endothelial cells, respectively.

In recent years, genetic studies have revealed several significant associations but have failed to identify any new specific molecular determinants of arterial stiffness, probably mainly because of its multifactorial aetiology and weak associations with each individual allele. The limitation of therapeutic strategies based on functional genomics lies at present in the fact that we do not know which molecules to target within newly identified pathways. In this respect, the selection of the most pertinent genes will depend on the correlation between their tissue expression or circulating levels and arterial stiffness. Cytokines and their receptors, transcription factors and network-forming collagen (type VIII) represent potential candidates, but the question of their specificity remains open. Genetic analysis should be followed by a post-genomic approach, which has never been performed in terms of pathophysiology of arterial stiffness. The post-genomic approach is dedicated to linking polymorphism data identified in GWA studies to specific biological systems in the vascular wall.

From the standpoint of drug development in arterial stiffness, several questions should be borne in mind. Are there specific determinants of arterial stiffness? Does PWV represent a robust phenotype of elasticity related to a specific trait? What is the distribution of PWV in various diseases? Is it necessary to consider absolute values or adjusted values of PWV for such a causative relation between genetic determinants and phenotype? The response to these questions will ultimately come from more complete knowledge of the mechanisms involved. Results from future GWA studies using the latest SNP technology should hopefully uncover new genes and thus promote the development of new experimental transgenic models to further test the implication of these genes.

Finally, it is tempting to determine whether there is a specific factor contributing to arterial stiffness which outweighs all other known cardiovascular risk factors. GWA studies offer the potential to identify a global effect of individual SNPs on PWV that integrates both the main effect and various interactions, including those linked to underlying diseases.

Conflict of interest: none declared.

References


