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Genetic Determinants of Arterial Stiffness

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Abstract Stiffness of large arteries (called arteriosclerosis) is an independent predictor of cardiovascular morbidity and mortality. Although previous studies have shown that arterial stiffness is moderately heritable, genetic factors contributing to arterial stiffness are largely unknown. In this paper, we reviewed the available literature on genetic variants that are potentially related to arterial stiffness. Most variants have shown mixed depictions of their association with arterial stiffness across multiple studies. Various methods to measure arterial stiffness at different arterial sites can contribute to these inconsistent results. In addition, studies in patient populations with hypertension or atherosclerosis may overestimate the impact of genetic variants on arterial stiffness. Future studies are recommended to standardize current measures of arterial stiffness in different age groups. Studies conducted in normal healthy subjects may also provide better opportunities to find novel genetic variants of arterial stiffness.

Keywords Arterial stiffness · Arteriosclerosis · Atherosclerosis · Genotype · Hypertension · Intimal calcification · Medial calcification · Pulse wave velocity · Single nucleotide polymorphism

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Introduction

Cardiovascular disease (CVD) is the number one cause of death and accounts for 32.3 % of (or one of every three) deaths in the USA [1]. Large artery stiffness called arteriosclerosis has been identified as an independent predictor of CVD mortality and morbidity [2–4]. Arterial stiffness is characterized by structural remodeling and functional changes in the arterial wall. Major changes, typically seen with "physiologic" arterial aging, include fragmentation and calcification of elastic fibers, and increased collagen deposition and collagen cross-linking in the media [5, 6]. Oxidative stress, decreased bioavailability of endothelial-derived vasodilators (e.g., nitric oxide), and low-grade inflammation process have also been recognized to promote arterial stiffness [7]. Diminished elasticity of arterial walls results in earlier arrival of wave reflection, and reflected waves that arrive during left ventricular ejection increase left ventricle afterload, the amplification of systolic blood pressure, and pulse pressure [8, 9]. The exposure of small arterioles to high pulsatile pressure caused by arterial stiffness also explains the microvascular damage in the brain and the kidneys [10, 11]. Arterial stiffness has been found to be an independent and consistent predictor of left ventricular hypertrophy [12], hypertension [13, 14], myocardial infarction [15] and stroke [16], and cardiovascular mortality in patients with end-stage renal disease [17, 18].

Despite the tremendous emphasis on the role of arterial stiffness in the development of CVD, relatively little is known about the biological mechanisms and pathways underlying the development of arterial stiffness. Studies on heritability of arterial stiffness suggest that genes explain a moderate (range from 23 to 50 %) proportion of the variability in arterial stiffness. This has been reported from populations in a number

of studies including: the Framingham Heart Study [19], the Strong Heart Family Study [20], twin studies [21, 22], and the Erasmus Rucphen Family study [23]. The influence of a genetic component in arterial stiffness has been shown to be independent of well-known cardiovascular risk factors such as age and blood pressure [20, 23]. Identification of genetic variations related to arterial stiffness may provide novel insights into its pathophysiology. Moreover, potential preventive measures may be developed to benefit those with a high genetic risk of arterial stiffness.

Arterial stiffness can be noninvasively assessed by determining the speed of energy conduction through the arterial wall, analyzing pulse waveforms, or relating diameter change to pressure change [24]. These methods produce parameters including pulse wave velocity (PWV), augmentation index (AIx), arterial compliance, arterial distensibility, elastic modulus, Young's elastic modulus, and stiffness index [24]. Pulse pressure measured using a standard sphygmomanometer is also recognized as a surrogate marker of arterial stiffness in persons aged more than 50 years [25].

In this paper, we reviewed genetic variants that have been reported for their association with arterial stiffness (Table 1). We next discussed several potential factors that contribute to the inconsistent results of the reviewed studies. Lastly, we proposed the model (Fig. 1) explaining arterial stiffness pathophysiology with the genes reviewed in this study.tgroup

Method

We performed a PubMed literature search for relevant articles with no date restriction. The keywords used included single nucleotide polymorphism (SNP), gene, genetics, association, arterial stiffness, pulse wave velocity, augmentation index, distensibility, elastic modulus, and arterial stiffness β. In order to make the findings comparable, studies that examined the associations between combined variables and arterial stiffness (e.g., haploblock) were excluded. We focused on cross-sectional association between SNP and commonly used measures of arterial stiffness. A total of fifty articles that met our criteria were selected for the review.

Genetic Variants Related to Arterial Stiffness

Renin-Angiotensin-Aldosterone System-Related Genes

Renin-angiotensin-aldosterone system (RAAS) is involved in blood pressure regulation by sodium-fluid balance and is known to play an important role in arterial tone [81]. Studies that have investigated the angiotensinogen gene (*AGT*) have frequently examined the Met235Thr (T704C) polymorphism in exon 2. Although one study with hypertensive subjects reported that those homozygous for the threonine allele in the Met235Thr polymorphism had significantly higher arterial stiffness [29], this relationship was not found in the Rotterdam Study [28] or in two other studies with hypertensive subjects [26, 27].

For the angiotensin-converting enzyme gene (*ACE*) which converts angiotensin I to vasoactive angiotensin II, the insertion/deletion polymorphism of intron 16 has been extensively investigated. Previous studies have shown that the number of D allele was positively related to the level of ACE expression in T-lymphocytes [82] and serum levels of ACE [83]. The 287-bp deletion in intron 16 has been shown to influence arterial stiffness in both the general population and diabetic and hypertensive patients [28, 30–33, 35]. However, the allele related to increased arterial stiffness varied between general population and patient groups. While those with the D allele had significantly greater arterial stiffness in general populations [28, 30, 31], type 2 diabetes [33] and untreated hypertensive [36] patients with the D allele had less arterial stiffness. Possibly, the activity of the D allele on arterial stiffness may be modified in hypertension or diabetes through its interaction with mechanisms involved in their pathophysiology.

As for the A1166C polymorphism of angiotensin II type 1 receptor gene (*AGTR1*) in the 3′ untranslated region, the C allele is related to increased arterial stiffness in hypertensive patients [27, 35, 37], in contrast to the A allele which is related to higher arterial stiffness in more severe hypertensive patients (50 % in grade 3 hypertension) [38]. In two studies with normotensive White subjects [35] and the random general population [40], arterial stiffness measured by carotid-femoral PWV was not different across the genotypes. However, arterial stiffness measured by femoral–dorsalis pedis or tibialis posterior PWV was significantly associated with the C allele of the A1166C polymorphism [40], suggesting that the A1166C polymorphism may have different effects on central elastic arteries and peripheral muscular arteries. There is also a potential combined effect of this genotype with age. For example, a recent longitudinal study showed that the C allele carrier in the A1166C polymorphism had a 35 % more pronounced increase in carotid-femoral PWV over a 16-year period than the AA alleles subjects, and this difference in PWV was only observed after the age of 55 years [84].

In another study examining polymorphisms in the aldosterone synthase gene (*CYP11B2*), the C allele of the T-344C polymorphism in the promoter region was associated with higher peripheral and central augmentation index than T allele homozygotes in a healthy random population [34]. Inconsistent results in both arterial stiffness and age-related changes of arterial stiffness were found with this T-344C polymorphism in studies with hypertensive patients [27, 41].

Table 1 Single nucleotide polymorphisms (SNP) related to arterial stiffness

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
AGT	Met235Thr (rs699)		Pulse pressure	No	Hypertensive patients	1425, median age 50.9	[26]
			Carotid-femoral PWV	No	Untreated hypertensive subjects of European origin	441, aged 18–74	[27]
			Carotid-femoral PWV	No	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28]
			Carotid distensibility	No	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28]
			Pulse pressure	No	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28]
		Met/Met<Met/Thr<Thr/Thr	Carotid distensibility	Yes	Untreated hypertensive White patients	98, aged 24–80	[29][b,c]
		Met/Met<Met/Thr<Thr/Thr	Young's elastic modulus	Yes	Untreated hypertensive White patients	98, aged 24–80	[29][b,c]
	C-532T	TT+CT<CC	Pulse pressure	Yes	Hypertensive patients	1425, median age 50.9	[26][b]
	Thr174Met (rs4762)		Carotid-femoral PWV	No	Untreated hypertensive subjects of European origin	441, aged 18–74	[27]
ACE	I/D (rs4340)	II<ID<DD	Carotid compliance	Yes	White participants from the Flemish Study living in Belgium	756, mean age 44.5	[30][b,c]
			Carotid-femoral PWV	No	Untreated hypertensive subjects of European origin	441, aged 18–74	[27]
		II<ID+DD	Carotid distensibility	Yes	Population based from the Rotterdam study	3001, aged more than 55	[31][b,c]
			Carotid-femoral PWV	No	Population based from the Rotterdam study	3001, aged more than 55	[31]
		II<ID+DD	Pulse pressure	Yes	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28][b]
		DD<ID+II	Carotid-femoral PWV	Yes	Healthy adults (in Greece)	282, aged 39.7±8.9	[32][b,c]
		DD+ID<II	Carotid-femoral PWV	Yes	Japanese patients with type 2 diabetes	137, aged 53.0±13.7	[33][b,c]
		DD+ID<II	Carotid stiffness B	Yes	Japanese patients with type 2 diabetes	137, aged 53.0±13.7	[33][b,c]
			Carotid-femoral PWV	No	Healthy adults	260, 50.6±11.6	[33]
			Carotid stiffness B	No	Healthy adults	260, 50.6±11.6	[33]
			Central and peripheral AI	No	Random European population	622, mean age 40.2	[34]
		DD<ID<II	Carotid-femoral PWV	Yes	Untreated White hypertensive	311, aged 18–74	[35][c]
			Carotid-femoral PWV	No	Normotensive White subjects	128, aged 19–72	[36]
AGTRI	A1166C (rs5186)	AA<AC<CC	Carotid-femoral PWV	Yes	Untreated White hypertensive patients	311, aged 18–74	[35][b,c]
			Carotid-femoral PWV	No	Normotensive White subjects	128, aged 19–72	[35]
		AA<AC<CC	Carotid-femoral PWV	Yes	Untreated White hypertensive patients	134, aged 21–72	[37][b,c]
		CC<AC<AA	Carotid-femoral PWV	Yes	Hypertensive patients (in France)	185, aged 52.5±13.3	[38][b,c]
		AA+AC<CC	Carotid-femoral PWV	Yes	Untreated hypertensive subjects of European origin	441, aged 18–74	[39][b,c]
			Carotid-femoral PWV	No	Random general population (in Pilsen)	250, aged 48.03±0.7	[40]
		AA<AC<CC	Femoral-tibial PWV	Yes	Random general population (in Pilsen)	250, aged 48.03±0.7	[40][b]
	A-153G (rs275653)		Carotid-femoral PWV	No		441, aged 18–74	[39]

Table 1 (continued)

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
					Untreated hypertensive subjects of European origin		
	Leu220Leu (rs5182)		Carotid-femoral PWV	No	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28]
			Carotid distensibility	No	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28]
			Pulse pressure	No	Population based from the Rotterdam study	3706, aged 72.4±7.1	[28]
CYPIIB2	T-344C (rs1799998)		Carotid-femoral PWV	No	Untreated hypertensive subjects of European origin	441, aged 18–74	[2]
		TT<CC<TC	Carotid-femoral PWV	Yes	European origin hypertensive patients	216, middle aged	[41][b,c]
	Val386Ala		Carotid-femoral PWV	No	European origin hypertensive patients	216, middle aged	[41]
	T-344C (rs1799998)		Carotid-femoral PWV	No	Untreated hypertensive Caucasian patients	425, aged 54.28±12.11	[9]
		TT<TC+CC	Central and peripheral AI	Yes	Random European population	622, mean age 40.2	[34][b,c]
ADRB1	Arg389Gly (rs1801253)	Arg/Arg<Arg/Gly<Gly/Gly	aorta-femoral PWV	Yes	White adults from the Bogalusa heart Study	455, aged 19–44	[42][b,c]
			aorta-femoral PWV	No	Black adults from the Bogalusa heart Study	159, aged 19–44	[42]
			Carotid-femoral PWV	No	Hypertensive patients in Japan	300, aged 62.0±0.7	[43]
	Ser49Gly (rs1801252)	Ser/Ser+Ser/Gly<Gly/Gly	Carotid-femoral PWV	Yes	Hypertensive patients in Japan	300, aged 62.0±0.7	[43]
ADRB2	Arg16Gly (rs1042713)		aorta-femoral PWV	No	White adults from the Bogalusa heart Study	455, aged 19–44	[42]
		Arg/Gly<Gly/Gly<Arg/Arg	aorta-femoral PWV	Yes	Black adults from the Bogalusa heart Study	159, aged 19–44	[42][b,c]
		Arg/Arg<Arg/Gly+Gly/Gly	Pulse pressure	Yes	European Americans	395, aged 14.7±3.0	[44][b]
			Pulse pressure	No	African Americans	275, aged 14.3±3.0	[44]
			Carotid-femoral PWV	No	Hypertensive patients in Japan	300, aged 62.0±0.7	[43]
	Glu27Gln (rs1042714)		Carotid-femoral PWV	No	Hypertensive patients in Japan	300, aged 62.0±0.7	[43]
			Pulse pressure	No	European Americans	395, aged 14.7±3.0	[44]
			Pulse pressure	No	African Americans	275, aged 14.3±3.0	[44]
ADRB3	Trp64Arg (rs4994)		aorta-femoral PWV	No	White adults from the Bogalusa heart Study	455, aged 19–44	[42]
		Trp/Trp<Trp/Arg+Arg/Arg	aorta-femoral PWV	Yes	Black adults from the Bogalusa heart Study	159, aged 19–44	[42][b,c]
			Carotid-femoral PWV	No	Hypertensive patients in Japan	300, aged 62.0±0.7	[43]
ECE1	A2013(+289)G (rs212528)		Brachial-ankle PWV	No	Japanese subjects	191, aged 65±1	[45]
ECE2	T669(+17)C (rs2272471)		Brachial-ankle PWV	No	Japanese subjects	191, aged 65±1	[45]
ETAR	His98His (A958G, rs5333)		Brachial-ankle PWV	No	Japanese subjects	191, aged 65±1	[45]
ETBR	Leu277Leu (A831G, rs5351)		Brachial-ankle PWV	No	Japanese subjects	191, aged 65±1	[45]
ETAR	A-231G (rs1801708)	AA<AG+GG	Carotid-femoral PWV	Yes	Never-treated hypertensive females of European origin	214, aged 48±0.5	[27][b,c]
			Carotid-femoral PWV	No	Never-treated hypertensive males of European origin	314, aged 48±0.5	[27]

Table 1 (continued)

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
	C1363T		Carotid-femoral PWV	No	Never-treated hypertensive subjects of European origin	528, aged 48±0.5	[27]
ETBR	Leu277Leu (G30A, rs5351)	AA+AG<GG	Carotid-femoral PWV	Yes	Never-treated hypertensive females of European origin	214, aged 48±0.5	[27][b,c]
			Carotid-femoral PWV	No	Never-treated hypertensive males of European origin	314, aged 48±0.5	[27]
ET-1	A I138D		Carotid-femoral PWV	No	Never-treated hypertensive subjects of European origin	528, aged 48±0.5	[27]
	Lys198Asn (G5665T, rs5370)		Carotid-femoral PWV	No	Never-treated hypertensive subjects of European origin	528, aged 48±0.5	[27]
eNOS	Glu298Asp (G894T, rs1799983)	TT+TG<GG	Peterson's and Young's elastic modulus	Yes	African Americans	118, aged 25–37	[46][b,c]
				No	White Americans	285, aged 25–37	[46]
		TT<GT+GG	Central pulse pressure	Yes	Female, Framingham Heart Study participants	604, aged 62±9	[47][b]
			Carotid-femoral PWV	No	Female, Framingham Heart Study participants	604, aged 62±9	[47]
			Central pulse pressure	No	Male, Framingham Heart Study Participants	553, aged 62±10	[47]
			Carotid-femoral PWV	No	Male, Framingham Heart Study Participants	553, aged 62±10	[47]
			AI at hear rate75	No	Children with Type 1 Diabetes	36, aged 10–21	[48]
			Carotid-femoral PWV	No	Untreated hypertensive of European ancestry	311, aged 18–74	[49]
	T-786C (rs2070744)		Carotid-femoral PWV	No	Random general population in Pilsen	250, aged 48.03±0.7	[40]
		TT+TC<CC	Femoral-tibial PWV	Yes	Random general population in Pilsen	250, aged 48.03±0.7	[40][b]
		TT<TC+CC	AI at hear rate75	Yes	Children with Type 1 Diabetes	36, aged 10–21	[48][b]
	G10T (rs1808593)		Carotid-femoral PWV	No	Normotensive of European ancestry	128, aged 19–72	[49]
p22phox	Tyr72His (C242T, rs4673)	CC+CT<TT	Carotid-femoral PWV	Yes	Brazilian general population	1178, aged 45.1±10.6	[50][b,c]
		TT+CT<CC	Carotid-femoral PWV	Yes	Caucasian Male amateur runners	73, aged 37.2±6.0	[51][c]
		TT+CT<CC	AI	Yes	Caucasian Male amateur runners	73, aged 37.2±6.0	[51][c]
TXNIP	rs7212 (G>C)		Carotid-femoral PWV	No	General population in Brazil	1251, aged 25–64	[50]
		CC<CG+GG	Carotid-femoral PWV	Yes	Diabetic patients in Brazil	267, aged 25–64	[50][b,c]
TGF-β1	G-800A (rs1800468)		PWV, distensibility coefficient, pulse pressure	No	Population based from the Rotterdam study	3863, aged 72.4±7.0	[52]
	C-509 T (rs1800469)			No	Population based from the Rotterdam study	3863, aged 72.4±7.0	[52]
	Leu10Pro (rs1982073)			No	Population based from the Rotterdam study	3863, aged 72.4±7.0	[52]
	Arg25Pro (rs1800471)			No	Population based from the Rotterdam study	3863, aged 72.4±7.0	[52]
CRP	Leu184Leu (rs1800947)		Carotid-femoral PWV	No	Healthy males from the Caerphilly study	790, aged 45–59	[53]
	rs1205 (C>T)		Carotid-femoral PWV	No	Healthy males from the Caerphilly study	790, aged 45–59	[53]
	C1444T (rs1130864)		Carotid-femoral PWV	No		790, aged 45–59	[53]

Table 1 (continued)

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
					Healthy males from the Caerphilly study		
		CC<CT+TT	Carotid stiffness index	Yes	Patients with a history of Kawasaki disease (in Asia)	167, aged 8.9±4.1	[54][b,c]
			Carotid stiffness index	No	Healthy control subjects (in Asia)	124, aged 9.7±4.3	[54]
TNF-α	G-308A (rs1800629)	GG<GA+AA	Carotid stiffness index	Yes	Patients with a history of Kawasaki disease (in Asia)	167, aged 8.9±4.1	[54][b,c]
			Carotid stiffness index	No	Healthy control subjects (in Asia)	124, aged 9.7±4.3	[54]
FAS	rs10509561 (A>T)		Central pulse pressure	Yes	White individuals from the Framingham Heart Study	1036	[55][b,c]
IL-6	G-174C (rs1800795)	GG+GC<CC	Carotid-femoral PWV	Yes	Population based the Rotterdam study	3849, mean age 72.16	[52][b,c]
		GG+GC<CC	Pulse pressure	Yes	Population based the Rotterdam study	3849, mean age 72.16	[52][b,c]
			Carotid distensibility	No	Population based the Rotterdam study	3849, mean age 72.16	[52]
SELP	Ser290Asn (rs6131)	Ser/Ser<Ser/Asn+Asn/Asn	Aorto-radial PWV	Yes	Black and White American Youth from the Georgia CV Twin Study	702, aged 17.7±3.3	[56][b]
		Ser/Ser<Ser/Asn+Asn/Asn	Aorto-foot PWV	Yes	Black and White American Youth from the Georgia CV Twin Study	702, aged 17.7±3.3	[56][b]
	rs2244529 (C>T)	CC+CT<TT	Aorto-foot PWV	Yes	Black and White American Youth from the Georgia CV Twin Study	702, aged 17.7±3.3	[56][b]
ICAM1	Gly241Arg (rs1799969)	Arg/Arg+Arg/Gly<Gly/Gly	Aorto-foot PWV	Yes	Black and White American Youth from the Georgia CV Twin Study	702, aged 17.7±3.3	[56][b]
VCAM1	Asp693Asp (rs3176878)	CT+TT<CC	Aorto-foot PWV	Yes	Black and White American Youth from the Georgia CV Twin Study	702, aged 17.7±3.3	[56][b]
GLO1	Ala111Glu (rs2736654)	GG<GT<TT	Pulse pressure	Yes	The Cohort study of Diabetes and Atherosclerosis Maastricht (CoDAM) and the Hoorn Study (Dutch)	1289, aged 64.5±8.58	[57][b,c]
RAGE	T-374A (rs1800624)	AA<AT+TT	Pulse pressure	Yes	Subjects with Normal glucose metabolism from the Hoorn study	210, aged 64.5±8.6	[58][b,c]
		AT+TT<AA	Pulse pressure	Yes	Subjects with impaired glucose metabolism from the Hoorn study	341, aged 64.5±8.6	[58][b,c]
		AA<AT+TT	Compiled score of distensibility and compliance in carotid, femoral, and brachial and carotid Young's elastic modulus	Yes	Subjects with normal glucose metabolism from the Hoorn study	210, aged 64.5±8.6	[58][b,c]
				No	Subjects with impaired glucose metabolism from the Hoorn study	341, aged 64.5±8.6	[58]
	rs1035798 (C/T)	TT<CT+CC		Yes	Subjects with normal glucose metabolism from the Hoorn study	210, aged 64.5±8.6	[58][b,c]

Table 1 (continued)

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
		CT+CC<TT		Yes	Subjects with impaired glucose metabolism from the Hoorn study	341, aged 64.5±8.6	[58][b,c]
ER-α	T-401C (rs2234693)	CC<CT+TT	Brachial-ankle PWV	Yes	Healthy older women (in Japan)	115, aged 63±1	[59][*‡]
			Brachial-ankle PWV	No	Healthy older men (in Japan)	85, aged 66±1	[59]
			Carotid-femoral PWV,	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
		TT+TC<CC	AI	Yes	Framingham offspring cohort of European descent	1261, age 62±10	[60][b]
	T30C (Ser10Ser, rs2077647)	CC<CT<TT	Brachial-ankle PWV	Yes	Healthy older women (in Japan)	115, aged 63±1	[59][b,c]
			Brachial-ankle PWV	No	Healthy older men (in Japan)	85, aged 66±1	[59]
			Carotid-femoral PWV,	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
		TT+TC<CC	AI	Yes	Framingham offspring cohort of European descent	1261, age 62±10	[60][b]
	(TA)n		Carotid-femoral PWV,	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
		SS+LS<LL	AI	Yes	Framingham offspring cohort of European descent	1261, age 62±10	[60][b]
	rs9340799 (A>G)		Carotid-femoral PWV,	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
		AA+AG<GG	AI	Yes	Framingham offspring cohort of European descent	1261, age 62±10	[60][b]
ER-β	rs944460 (C>G)		Carotid-femoral PWV,	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
		CG<CC	AI	Yes	Framingham offspring cohort of European descent	1261, age 62±10	[60][b]
	rs1256034 (C>T)		Carotid-femoral PWV,	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
		GA<GG	AI	Yes	Framingham offspring cohort of European descent	1261, age 62±10	[60][b]
CYP19A1	rs4646 (A>C)		Carotid-femoral PWV	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
			AI	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
	Val80Val (rs700518)		Carotid-femoral PWV	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
			AI	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
	(TTTA)n		Carotid-femoral PWV	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
			AI	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
	rs726547(G>A)		Carotid-femoral PWV	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
			AI	No	Framingham offspring cohort of European descent	1261, age 62±10	[60]
ADIPOQ	G276T (rs1501299)	GG<GT+TT	Brachial-ankle PWV	Yes	Hypertension Japanese patients	353, aged 62.9±0.6	[61]
APOE	Arg176Cys (rs7412)	ε2 (TT), ε3(TC), ε4(CC)	Carotid-femoral PWV	No	Brazilian general population	1493, aged 25–64	[62]

Table 1 (continued)

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
	Cys130Arg (rs429358)		Carotid-femoral PWV	No	Brazilian general population	1493, aged 25–64	[62]
ELN	Ser422Gly (A>G)	GG<GA+AA	Carotid distensibility and elastic modulus	Yes	Subjects form a cohort study in France	320, aged 49±12	[63][b,c]
			Radial distensibility & elastic modulus	No	Subjects form a cohort study in France	320, aged 49±12	[63]
	-/A	−/−<−/A+A/A	Brachial-ankle PWV	Yes	Japanese population I from the Suita Study	3654, aged 30–79	[64][b,c]
		−/−<−/A+A/A	Brachial-ankle PWV	Yes	Japanese population II from the Suita Study	289, aged 30–79	[64][*]
	Ala73Val (C<T)		Brachial-ankle PWV	No	Japanese population I from the Suita Study	3654, aged 30–79	[64]
COL4A1	A4002C (Gln1334His, rs3742207)	AA<AC+CC	Carotid-femoral PWV	Yes	Population from the SardiNIA study, the Sardinian Cohort, and the Old-order Amish	4221,1828,813 aged 14–102	[65][b]
COL1A1	G+2046 T	GG<GT+TT	PWV at aortoiliac, aorto-radial, and aorto-dorsalis-pedis	Yes	Healthy young individuals	489, aged 22.6±1.6	[66][b,c]
			Aortic distensibility	No	Healthy men in Sweden	79, aged 28–81	[67]
MMP3	5A/6A (rs3025058)		Carotid femoral PWV	No	Tetralogy of Fallot repair patients	79, aged 19.9±9.5	[54]
			Aortic stiffness index	No	Tetralogy of Fallot repair patients	79, aged 19.9±9.5	[54]
			Ascending aortic input impedance	No	Individuals in Australia	126, aged 30–60	[68]
		5A/6A<6A6A+5A5A		Yes	Individuals in Australia	77, aged greater than 60	[68][b,c]
MMP9	C-1562 T (rs3918242)	CC<CT+TT	Arterial stiffness β, Elasticity Modulus, One-point PWV	Yes	Stroke and MI menopausal females (in Taiwan)	704, aged 54.7±9.9	[69][b]
				No	Stroke and MI males (in Taiwan)	514, aged 54.7±11.6	[69]
		CC<CT<TT	Carotid-femoral PWV	Yes	Healthy individuals	865, aged 18–81	[70][b,c]
			AI	No	Healthy individuals	865, aged 18–81	[70]
		CC<CT<TT	Carotid-femoral PWV	Yes	Untreated hypertensive patients	215, aged 46±13	[71][b,c]
		CC<CT+TT	Aortic impedance	Yes	Patients with coronary artery disease	84,, aged 61±8	[72][b,c]
		TC+TT<CC	Carotid femoral PWV	Yes	Tetralogy of Fallot repair patients	79, aged 19.9±9.5	[54][b,c]
		TC+TT<CC	Aortic stiffness index	Yes	Tetralogy of Fallot repair patients	79, aged 19.9±9.5	[54][b,c]
	Arg279Gln (rs 17576)	Arg/Arg<Gln/Arg<Gln/Gln	Carotid-femoral PWV	Yes	Healthy individuals	865, aged 18–81	[70][b,c]
			AI	No	Healthy individuals	865, aged 18–81	[70]
FBN1	$(TAAAA)_n$ repeat in intron 28		Carotid-femoral PWV	No	Individuals free from cardiovascular disease or risk factors	646, aged 49±1	[70]
			Carotid and radial PWV	No	Individuals free from cardiovascular disease or risk factors	646, aged 49±1	[70]
			AI	No	Individuals free from cardiovascular disease or risk factors	646, aged 49±1	[70]
		2–4+2–2<2–3	Aortic impedance, central pulse pressure	Yes	Patients with coronary artery disease	145, aged 62±9	[73][b,c]
		2–4<2–2<2–3	Pulse pressure	Yes	Healthy men	245, aged 50–61	[74]
		2–4+2–2<2–3	Aortic stiffness β and elastic modulus, Pulse pressure	Yes	Healthy men	79, aged 28–81	[67][b,c]
LMNA	C-1030 T	TT+CT<CC	Brachial-ankle PWV	Yes	Men in Japan	261, aged 64.4±0.7	[75][b,c]

Table 1 (continued)

Gene	SNP	Alleles[a]	Phenotype	Results	Subjects	Sample size, age in years	Reference
	His566His (C1908T, rs4641)		Brachial-ankle PWV	No	Men in Japan	261, aged 64.4±0.7	[75]
ATP2B1	rs17249754 (G>A)	AA<GA+GG	Carotid-femoral PWV	Yes	Untreated hypertensive patients in China	164, aged 51.3±8.2	[76][b,c]
	rs1401982 (G>A)	GG<AG+AA	Carotid-femoral PWV	Yes	Untreated hypertensive patients in China	164, aged 51.3±8.2	[76][b,c]
Fetuin-A	Thr256Ser (C766G)	Thr/Thr+Thr/Ser<Ser/Ser	Carotid-femoral PWV	Yes	Randomly selected men from the FLEMish study in Belgium	61, aged 26–72	[77][b,c]
			Carotid-femoral PWV	No	Randomly selected women from the FLEMish study in Belgium	46, aged 26–72	[77]
ENPP1	Lys173Gln (A>C, rs1044498)	Lys/Lys<Lys/Gln	Carotid-femoral PWV	Yes	Austrian patients with end-stage renal failure and controls	30, mean age 65.5	[78]
GNB3	C825T (Ser275Ser, rs5443)	CC<CT+TT	Carotid-femoral PWV	Yes	Young and healthy males (in Germany)	99, mean age 27.34	[79][b]
		CC<CT+TT	Radial AI	Yes	Young and healthy males (in Germany)	72, mean age 27.34	[79][b]
3′BCL11B desert	rs7152623 (G>A)		Carotid-femoral PWV	Yes	Nine community-based European ancestry cohorts	20,634, mean age 43–75	[80][b,c]
			Carotid-femoral PWV	Yes	Two community-based European ancestry cohorts	5306, mean age 34–46	[80][b,c]

AGT angiotensinogen, *ACE* angiotensin-converting enzyme, *AGTR1* angiotensin II type 1 receptor, *CYP11B2* aldosterone synthase gene, *ADRB1*, *B2*, *B3* adrenergic receptors B1, B2, B3, *ECE* endothelin-converting enzyme, *ETAR* endothelin A receptor, *ETBR* endothelin B receptor, *eNOS* endothelial nitric oxide synthase, *TXNIP* thioredoxin interaction protein, *IL-6* interleukin-6, *SELP* P-selectin, *ICAM1* intercellular adhesion molecules-1, *VCAM1* vascular cell adhesion molecules-1, *FAS* tumor necrosis factor (TNF) receptor superfamily member 6, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor alpha, *RAGE* receptor for advanced glycation endproducts, *GLO1* glyoxalase1, *ER α and β* estrogen receptor alpha and beta, *CYP19A1* cytochrome P450 family 19 subfamily a polypeptide 1, *LMNA* lamin A/C*ATP2B1* calcium transporting ATPase 1, *ENPP1* ectonucleotide pyrophosphatase/phosphodiesterase-1, *ADIPOQ* adiponectin, *ELN* elastin, *COL4A1* collagen type 4 alpha 1, *FBN1* fibrillin-1 glycoprotein, *MMP* matrix metalloproteinase, *GNB3* G protein B3 subunit, *BCL11B* B-cell lymphoma/leukemia 11B, *PWV* pulse wave velocity, *AI* augmentation index

[a] Being greater always means more stiffness of arteries regardless of their measures

[b] Age adjusted in significant association

[c] BP adjusted in significant association

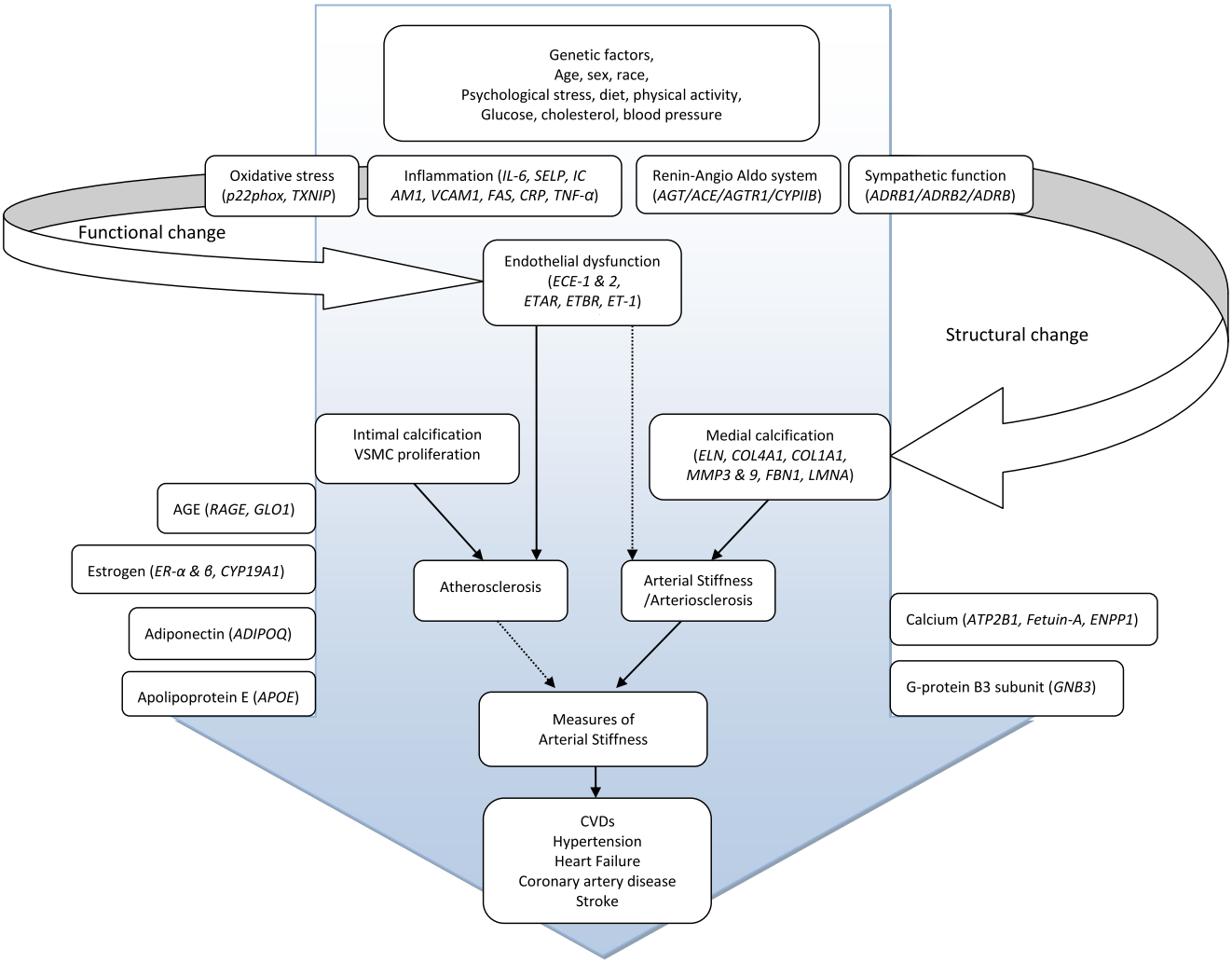

Fig. 1 *AGT* angiotensinogen, *ACE* angiotensin-converting enzyme, *AGTR1* angiotensin II type 1 receptor, *CYP11B2* aldosterone synthase gene, *ADRB1*, *B2*, *B3* adrenergic receptors B1, B2, B3, *ECE* endothelin-converting enzyme, *ETAR* endothelin A receptor, *ETBR* endothelin B receptor, *VSMC* vascular smooth muscle cell, *eNOS* endothelial nitric oxide synthase, *TXNIP* thioredoxin interaction protein, *IL-6* interleukin-6, *SELP* P-selectin, *ICAM1* intercellular adhesion molecules-1, *VCAM1* vascular cell adhesion molecules-1, *FAS* tumor necrosis factor (TNF) receptor superfamily member 6, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor alpha, *RAGE* receptor for advanced glycation endproducts, *GLO1* glyoxalase1, *ER α and β* estrogen receptor alpha and beta, *CYP19A1* cytochrome P450 family 19 subfamily a polypeptide 1, *ATP2B1* calcium transporting ATPase 1, *ENPP1* ectonucleotide pyrophosphatase/phosphodiesterase-1, *ADIPOQ* adiponectin, *ELN* elastin, *COL4A1* collagen type 4 alpha 1, *FBN1* fibrillin-1 glycoprotein, *LMNA* lamin A/C, *MMP* matrix metalloproteinase, *GNB3* G protein B3 subunit

β-Adrenergic Receptor Genes

β-adrenergic receptors, which are a class of G-protein-coupled receptors, play an important role in cardiovascular function. Chronic stimulation of β-adrenergic receptors by the sympathetic nervous system may contribute to physiological and pathological remodeling of vascular function and structure. There are three β-adrenergic receptors: β1 (ADRB1), β2(ADRB2), and β3(ADRB3) [85]. Compared with the studies on RAAS-related genes, studies that investigated the effect of genetic variants of β-adrenergic receptor genes on arterial stiffness have been conducted in racially more diverse groups, including Asians, White, and Black adults. In one study with White and Black young adults aged 19–44 years, the glycine allele of the Arg389Gly polymorphisms in *ADRB1* was associated with arterial stiffness in White young adults, but not in Blacks. In contrast, the arginine allele of the Arg16Gly polymorphism in *ADRB2* and the arginine allele of the Trp64Arg polymorphism in *ADRB3* were associated with arterial stiffness in Black young adults, but not in Whites. These three polymorphisms were not associated with blood pressure and heart rate [42], suggesting the independent role of β-adrenergic receptor genes on arterial elasticity in young adults. Interestingly, the alleles of the Arg16Gly polymorphism in *ADRB2* may have an opposite influence on arterial stiffness in different racial groups. The glycine allele was associated with a higher pulse pressure in European American youth [44]. In Japanese hypertensive patients, arterial stiffness and these

three polymorphisms (Arg389Gly, Arg16Gly, and Trp64Arg) were not associated; instead, homozygotes of the glycine allele of the Ser49Gly polymorphism in *ADRB1* had higher arterial stiffness [43].

Endothelin-Related Genes

Endothelin-1 (ET-1) is a potent vasoconstrictor produced in endothelial cells. It binds to two G-protein-coupled receptors, endothelin A receptor (ETAR) and endothelin B receptor (ETBR), which are expressed mainly on vascular smooth-muscle cells and endothelial cells, respectively [86]. Whereas ETAR plays a role in vasoconstriction of smooth muscle cells, ETBR facilitates endothelial synthesis of nitric oxide (NO) and prostacyclin [87]. In a study with untreated hypertensive subjects, women with the G allele of the A-231G polymorphism in *ETAR* and with the GG alleles of the Leu277Leu polymorphism (without amino acid change) in *ETBR* had significantly higher carotid-femoral PWV than other groups, but these results were not found in men [39]. In another study, the A958G polymorphism in *ETAR*, and the Leu277Leu polymorphism in *ETBR* did not contribute to the levels of arterial stiffness measured by brachial-ankle PWV in a general Japanese population [45]. Endothelin-converting enzyme (ECE) converts a 39-amino-acid precursor to a 21-amino-acid endothelin-1 protein, thus it may be important in regulating vascular tone. However, the polymorphisms, A2013(+289)G in *ECE-1* and T669(+17)C in *ECE-2*, were not significantly related to arterial stiffness in Japanese subjects [45].

Endothelial Nitric Oxide Synthase Gene

Endothelial NOS (eNOS), also known as nitric oxide synthase 3 (NOS3), plays an important role in modulating vascular smooth muscle tone. In the presence of oxygen, reduced nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), and calmodulin, eNOS released from endothelium catalyzes L-arginine to nitric oxide (NO) which is a short-lived vasodilatory gas [88]. The results on the relationship between *eNOS* polymorphisms and arterial stiffness have shown inconsistencies in different races, sex, and various arterial sites for measuring arterial stiffness. The T allele of G894T (Asp298Glu) polymorphism was related to more arterial elasticity in African Americans, but not in White Americans [46]. This common missense mutation of G298T was associated with changes in central pulse pressure in females but not in males [47]. Furthermore, the C allele of the T-786C polymorphism in *eNOS* was significantly associated with increased PWV measured in peripheral arteries, but not in central elastic arteries [40]. In these studies, none of polymorphisms in *eNOS* were significantly associated with arterial stiffness measured by carotid-femoral PWV which is a direct measure of central elastic arteries. It was also reported that both *eNOS* polymorphisms, G10T and G298T (Glu298Asp), were not associated with aortic PWV in hypertensive or non-hypertensive Europeans [49]. Despite promising evidence of eNOS in endothelial function and vascular function, the effect of *eNOS* polymorphisms on arterial stiffness remains unclear.

Oxidative Stress-Related Genes

The crucial role of NADPH oxidase system in vascular oxidative stress and atherosclerosis has been well described in previous studies. NADPH oxidase has been identified to be a major source of reactive oxygen species (ROS), such as superoxide anion, which causes oxidation of low density lipoprotein (LDL) [89]. Studies have shown that the C242T (Tyr72His) polymorphism of gene encoding NADPH oxidase p22phox subunit is significantly related to arterial stiffness in Caucasian male runners [51] and in the general population of Brazil [90]. However, the allele related to arterial stiffness was different in each study. While runners with the CC alleles had higher carotid-femoral PWV (measured with the PulsePen device) than runners with the CT and TT alleles, individuals with the TT alleles had higher carotid-femoral PWV (measured by the Complior device) than those with the CC or CT alleles in the Brazilian population.

Thioredoxin-interacting protein (TXNIP) is a protein known to increase the production of ROS and oxidative stress [91]. The G allele carriers of rs7212 in *TXNIP* showed significantly higher carotid-femoral PWV than CC homozygotes in diabetic patients in Brazil, but not in the non-diabetic group, suggesting a possible interaction of TXNIP and pathophysiology in diabetes [50].

Inflammation-Related Genes

Although inflammation may contribute to arterial stiffness, biomarkers of inflammation are not always related to arterial stiffness, even in patients with coronary artery disease [92]. One population-based study showed that the C allele of the G-174C polymorphism in the interleukin-6 gene (*IL-6*) promoter was significantly associated with increased carotid-femoral PWV and pulse pressure [52]. A study in young Americans also demonstrated that polymorphisms, Ser29Asn and rs2244529 in the P-selectin gene (*SELP*), Gly241Arg in the intercellular adhesion molecules-1 gene (*ICAM1*), and Asp693Asp (C>T) in the vascular cell adhesion molecules-1 gene (*VCAM1*) were significantly related to aorto-foot PWV, suggesting that genetic variations of adhesion molecules may be involved in the process of arterial stiffness [56].

However, another population-based study showed that among the polymorphisms in 12 inflammatory biomarkers genes, only the polymorphism rs10509561 of the TNF receptor superfamily member 6 gene (*FAS*) was significantly related

to central pulse pressure. This polymorphism was not associated with either carotid-femoral PWV or augmentation index [55]. The C1444T polymorphism of C-reactive protein gene (*CRP*) and G-308A of the tumor necrosis factor alpha gene (*TNF*-α) were found to be determinants of carotid stiffness in patients with a history of Kawasaki disease, but not in control subjects [54]. Two studies reported that circulating levels of inteleukin-6 were significantly associated with carotid-femoral PWV and with its genetic variants; nevertheless, the genetic variants were not associated with carotid-femoral PWV [53, 55]. Inflammation does not seem to be a direct causal factor of arterial stiffness, but it may influence arterial stiffness indirectly through different mechanisms such as endothelial dysfunction enhanced by inflammation [93].

A recent meta-analysis of genome-wide association data has reported that the SNP, rs7152623, located in the B-cell lymphoma/leukemia 11B gene (*BCL11B*) desert was significantly associated with carotid-femoral PWV in nine community-based European ancestry cohorts and two other European cohorts [80]. Since *BCL11B* is known to participate in interleukin-2 gene (*IL2*) expression [94] and maybe important in the inflammatory process, further studies are needed to define the association of this genetic variation with inflammation.

Advanced Glycation Endproducts-Related Genes

Advanced glycation endproducts (AGE) is known to contribute to the development of vascular complications in diabetes. Binding AGE to the receptor for AGE (RAGE) may initiate the production of reactive oxygen species (ROS), resulting in pro-inflammatory cellular responses [95]. Data from two Dutch population-based cohort studies demonstrated that the AA genotype of the T-374A and the TT genotype of the C5878T in *RAGE* were associated with less arterial stiffness in individuals with normal glucose metabolism. However, in individuals with impaired glucose metabolism or type 2 diabetes, these genotypes were associated with higher pulse pressure and higher arterial stiffness, respectively [58]. This result suggests that the effect of the polymorphism under the condition of normal glucose metabolism may be different in altered glucose metabolism such as diabetes. An analysis on the part of the data from a Dutch population explored the glyoxalase1 (GLO1) gene which is used to detoxify methylglyoxal, a main precursor of AGEs. In 1289 participants with 33.3 % of DM2, the Ala111Glu of *GLO1* was only weakly associated with pulse pressure, but not with other arterial stiffness measures [57].

Estrogen-Related Genes

Estrogen is considered a cardioprotective hormone which enhances NO production and inhibits inflammation and vascular smooth muscle cell (VSMC) proliferation [96]. Estrogen receptors (ER) are expressed in vascular smooth muscle cells [97, 98]. The associations between polymorphisms and arterial stiffness have been examined in ER-α, ER-β, and aromatase (*CYP19A1*) genes. One study conducted in healthy older adults in Japan reported that in the T-401C and the T30C (Ser10Ser) polymorphisms of *ER*-α, women with the T allele had higher brachial-ankle PWV as compared with women with the C allele. This relationship was not found in men [59], showing a sex-specific effect of the *ER*-α polymorphism on arterial stiffness. Another population-based study demonstrated that these polymorphisms, T-401C and Ser10Ser, were related to augmentation index (AI), but with the CC alleles relating to higher AI. In this study, the polymorphisms, T-401, Ser10Ser, (TA)n, and rs9340799 in ER-α, and rs944460 and rs1256034 in *ER*-β, were significantly related to AI but not to carotid-femoral PWV in the sex-pooled analysis [60]. Further, the polymorphisms, rs4646, Var80Val, (TTTA)n, and rs726547 in *CYP19A1* were neither associated with augmentation index nor carotid-femoral PWV.

Adiponectin Gene

Adiponectin (ADIPOQ), produced by adipose tissue, is identified as an important adipocytokine that improves insulin resistance through its anti-inflammatory and anti-atherogenic properties [99, 100]. Adiponectin is implicated in the metabolic syndrome by regulating glucose levels and reducing fatty acids [101]. In a Japanese cohort study, hypertensive patients with the T allele of the G276T had significantly lower HDL cholesterol, higher HbA1c, and higher brachial-ankle PWV [61]. Further studies are required to replicate these results and to elucidate the direct relationship between the G276T of *ADIPOQ* and arterial stiffness in healthy individuals.

Apolipoprotein E Gene

Apolipoprotein E (APOE) is known to facilitate plasma cholesterol homeostasis by the hepatic uptake of lipoproteins and stimulation of cholesterol effluxes from macrophages [102]. *APOE* has four alleles (ε1, ε2, ε3, and ε4) according to the combination of C in rs429358 and T in rs7412 (ε1 is very rare) [102]. Many studies have shown the association between the ε4 allele (CC) and coronary disease [103]. However, in a study in the general population in urban Brazil, carotid-femoral PWV was not different among subjects with the ε2, ε3, and ε4 alleles. These *APOE* polymorphisms did not seem to have a direct effect on arterial stiffness, although, the ε4 allele was significantly associated with an unfavorable lipid profile [62].

Elastin Gene

Medial degeneration is a key feature of arterial stiffness and is characterized by a decrease in elastin fibers and an increase of

collagen [5]. Elastin is one of the major components of the extracellular matrix. In a study on the A/G polymorphism of exon 16 (Ser422Gly) in the elastin gene (*ELN*), the A allele carriers had significantly lower distensibility of carotid arteries than the GG homozygous subjects. But this association was not found in radial arteries from the same cohort, which suggests that this polymorphism is associated with distensibility of elastic arteries only, but not with muscular arteries [63]. Another polymorphism, deletion/A in the *ELN* 3′ untranslated region, was associated with higher brachial-ankle PWV in A allele carriers from a Japanese population [64], showing the variant's effect on muscular arteries. Given the important role of central arteries in the development of CVD, further studies are recommended to examine the influence of these *ELN* polymorphisms on carotid-femoral PWV.

Fibrillin-1 Glycoprotein Gene

Fibrillin-1 glycoprotein (FBN1) is an essential connective protein for the formation of microfibrils which constitute arterial elastic fibers [104]. Previous studies have examined the relationship between arterial stiffness and the variable nucleotide tandem repeat (VNTR) polymorphism in intron 28 of *FBN1*, but their results have not been consistent. While one study reported that the *FBN-1* VNTR polymorphism was not associated with either carotid-femoral PWV nor other measures of stiffness in a healthy general population [70], other studies have shown that participants with the 2-3 genotype of the VNTR polymorphism had greater pulse pressure [74] and arterial stiffness (measured by aortic stiffness β and elastic modulus) [67] in healthy men. Another study in participants with coronary artery disease also reported that those with the 2-3 genotype of the VNTR polymorphism had greater arterial stiffness (measured by aortic impedance) and higher central pulse pressure than those with the 2-2 and 2-4 genotypes [73].

Collagen Genes

Collagen is another important determinant of arterial wall mechanics along with elastin [5]. Collagen type 4 is the major structural component of basal lamina. A genome-wide association from the SardiNIA study showed that the minor C allele of A4002C (Gln1334His) in the collagen type 4 alpha 1 gene (*COL4A1*) is associated with higher carotid-femoral PWV. This association was replicated in 1828 Sardinians and 813 Amish individuals in the oldest category [65]. Another study in the UK reported that the G+2046T polymorphism in *COL1A1*, was associated with a higher PWV (measured in three segments; aortoiliac, aortoradial, and aortodorsalis-pedis) in young healthy individuals with the T allele [66]. However, this polymorphism was not associated with aortic distensibility in men from Sweden (mean age 55.3 years) [67]. The role of *COL1A1* polymorphisms in arterial stiffness should be reexamined in further studies due to these inconsistent results.

Matrix Metalloproteinase Genes

Matrix metalloproteinases (MMPs) are a family of proteases that degrade extracellular matrix molecules such as elastin and collagen. It was reported that healthy subjects with the T allele of the C-1562T and the glutamine allele of the Arg279Gln in *MMP-9* had higher serum MMP-9 and aortic PWV [105]. The association with the C-1562T polymorphism was also reported in untreated hypertensive patients [71] and patients with coronary artery disease [72]. The C-1562T polymorphism may have a sex-specific effect on arterial stiffness. In a population-based study conducted in Taiwan, this polymorphism was associated with arterial stiffness (measured by arterial stiffness β, elasticity modulus, and one-point PWV) in menopausal women, but not in men [69].

As for the human stromelysin-1 (MMP-3) gene, a common promoter polymorphism with one allele containing 5 adenosines (5A) and the other allele containing 6 adenosines (6A) was associated with stomelysin-1 gene expression [106]. A study showed that 5A homozygotes and 6A homozygotes have higher ascending aortic input impedance as compared with the heterozygotes in the older group (>60 years of age). However, this relationship was not found in the younger group (30–60 years of age), suggesting an age-related effect of this polymorphism. The gene and protein expression data from this study showed that those with the 5A/6A alleles had intermediate MMP-3 levels which are lower than those with the 5A/5A alleles and higher than those with 6A/6A. These results show that the optimal level of MMP-3 may be an important factor for the homeostasis between degradation and deposition of matrix proteins [68].

Lamins Gene

Lamins are intermediate filament-type proteins which are major components of the nuclear lamina [107]. Studies showed that lamins are involved in cardiac and muscular muscle dystrophy [108, 109]. In the lamin A/C gene encoding for lamin A and C, the C-1030T polymorphism in the promoter region may influence arterial stiffness. In a study of healthy Japanese men, the CC homozygotes of the C-1030T polymorphism had greater brachial-ankle PWV than other genotypes, and the CC alleles were reported to be a significant and independent predictor of brachial-ankle PWV after controlling for other CVD risk factors including age and blood pressure (BP) [75].

Calcium-Related Genes

Calcium phosphate metabolism may influence arterial stiffness both in structure and function. For example, vascular

calcification can be accelerated by calcium accumulation in the extracellular matrix, and calcium is also involved in vascular cell function and smooth muscle contraction [110]. Calcium transporting ATPase 1, which is encoded by the ATP2B1 gene, moves calcium ions from the cells in effort to promote intracellular calcium homeostasis; thus, it may be involved in regulating vascular smooth muscle tone [111]. In untreated hypertensive patients, the A allele homozygotes of rs17249754 and the G allele homozygotes of rs1401982 had lower carotid-femoral PWV than heterozygotes or other homozygotes [76].

Fetuin-A is a systemic inhibitor of calcium-phosphate precipitation [112]. A study conducted in subjects with normal kidney function showed that the plasma fetuin-A level was independently and negatively correlated with aortic PWV. Subjects with the Ser/Ser alleles in the Thur256Ser polymorphism of the fetuin-A gene had significantly lower fetuin-A levels and higher aortic PWV. This relationship was found only in males, suggesting an interaction of this genetic variant with sex [77].

Ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1), which is involved in regulating pyrophosphate levels, is also known to inhibit calcification [113]. In a study in Austrian patients with end-stage renal failure, the patients with the Lys/Gln genotype of the Lys173Gln polymorphism in *ENPP1* had a higher coronary calcium score and a higher carotid-femoral PWV than those with the Lys/Lys genotype after controlling sex, age, diabetes, and duration of dialysis treatment [78]. Further studies are needed to clarify the role of polymorphisms in calcium metabolism related genes in arterial structure and function.

G-Protein B3 Subunit Gene

The family of G-protein-coupled receptors interacts with heterotrimeric G protein complexes (α,β,γ subunits) to transduce extracellular signals to intracellular signals. Upon receptor-ligand binding, the α unit is separated from the receptor and β and γ subunits and then activates other molecules in the cell [114]. It was reported that in the C825T (Ser275Ser) polymorphism of the gene encoding the G-protein β3 subunit (GNB3), carriers of the T allele showed a significantly higher carotid-femoral PWV and augmentation index than those with the CC genotype in 72 young and healthy males [79] Further study is required to replicate this result in a large sample.

Factors Contributing to Inconsistent Results

The studies reviewed here illustrate conflicting results on the association between genetic polymorphisms and arterial stiffness. These inconsistent results can be attributable to several reasons. This review highlights the issues of different methods used to measure arterial stiffness and the selection of the study sample, which have impeded the progress of studies assessing the genetic component of arterial stiffness.

Phenotype of Arterial Stiffness

Various measures of arterial stiffness at different arterial sites can serve as a major source of inconsistent results. Commonly used methods in the studies reviewed include pulse wave velocity (PWV), augmentation index (Alx), arterial stiffness β, arterial compliance, arterial dispensability, and elastic modulus. Noninvasive measures of arterial stiffness can be grouped into three categories: measuring PWV, analyzing pulse waveforms, and measuring diameter change in relation to pressure change in arteries [24].

Determining PWV is generally accepted as the robust and reproducible method to measure arterial stiffness [25, 115]. PWV can be determined by the distance the pulse wave travels between two arterial sites divided by pulse transit time, PWV=D (meters)/Δt(seconds) [116]; thus, PWV provides regional stiffness between two arterial sites. Carotid-femoral PWV is considered the "gold-standard" measure of arterial stiffness because it is measured along the aortic and aorto-iliac pathway which provides the largest BP buffering function [116].

Pulse wave analysis (PWA) is a noninvasive method to generate an ascending aorta pressure wave from arterial pressure waveforms measured either at carotid or radial arterial site by mathematical transformation [117]. A pulse pressure waveform is a composite of forward pressure wave (incident wave) and reversed wave (reflected wave). The augmentation index (AI) is a commonly used measure of arterial stiffness and is obtained from PWA. AI is defined as augmented pressure (AP) by a reflected wave and is expressed as a percentage of pulse pressure (PP) [24]. Although AI is used to measure systemic arterial stiffness, because of differences in elasticity and length of arteries, pulse waveforms are not identical when measured in different arterial sites [118].

The methods to relate diameter change to pressure change (or reverse) include arterial compliance, distensibility, elastic modulus, Young's modulus, and stiffness index β. These methods measure local arterial stiffness of measured sites. The issue regarding the difference between the site to measure diameter change and the site to measure pressure change has been pointed out in several studies [24, 119].

Taken together, methods to measure arterial stiffness represent either regional, systemic, or local arterial stiffness. Most studies have used different arterial sites, such as carotid, femoral, brachial, tibial, and radial arteries for arterial stiffness measurements. However, central arteries and peripheral

arteries differ in their structure and function. While central arteries are more elastic containing smaller amount of smooth muscle, peripheral arteries are less elastic containing more smooth muscle cells and less elastin. Various arterial sites also respond differently to age, sympathetic nervous activity, hormones, and drugs [119, 120]. Thus, arterial stiffness measured even by the same method may not provide the same information when measured in different arterial sites. Due to heterogeneity of arterial system, polymorphisms may exert different effects on various arterial segments. Therefore, caution is required to interpret and compare the results from studies that used different methods to measure arterial stiffness in different arterial sites.

Furthermore, studies are recommended to standardize measures of arterial stiffness that best identify the functional and structural changes of arterial system over different age groups. According to the data from Framingham Heart Study offspring cohort, before age 50 years, carotid-femoral PWV was lower than carotid-brachial PWV, but after age 50 years, carotid-femoral PWV was higher, showing central and peripheral arteries have different progress over aging process [121]. The Anglo-Cardiff Collaborative Trial showed that while PWV was a good measure in older individuals (>50 years), AI is a more sensitive marker for arterial stiffness risk in younger individuals (<50 years). Measures of regional, systemic, or local arterial stiffness can be standardized for different age groups [122].

Selection of Study Sample

Arterial stiffness is a multifactorial condition which results from the interaction of several genes and environmental factors. Thus, identifying genetic determinants of arterial stiffness can be very challenging unless confounding factors (e.g., race, sex, pathological condition,) are well controlled. Studies reviewed in this paper provide suggestive evidence for racial differences in the associations between arterial stiffness and polymorphisms in *ADRB1*, *ADRB2*, *ADRB3*, and *eNOS*. Studies on the polymorphisms in *ETAR*, *ETBR*, *eNOS*, *ER-α*, *MMP9*, and fetuin A gene showed a sex-specific role for these polymorphisms in arterial stiffness. Furthermore, many studies have been trying to find novel determinants of arterial stiffness in patients with hypertension and atherosclerosis, in which their pathophysiological mechanisms are closely interrelated to ones of arterial stiffness.

Most studies on *AGT*, *AGTR1*, and *CYP11B2* polymorphisms have been conducted in hypertensive patients but their associations have not been replicated by ones conducted in healthy individuals. Population-based longitudinal studies have shown that arterial stiffness may itself predict progression of hypertension in normotensive subjects [13, 14]. However, continuously elevated blood pressure will also contribute to arterial stiffness through structural and functional changes of the vascular wall, showing the "bi-directional" relationship between arterial stiffness and hypertension [123]. In addition, arterial stiffness progressively increases with age, and isolated systolic hypertension affects 50 % of people over age 60 [122]. In order to exclude the influence of hypertension on arterial stiffness, young and non-hypertensive subjects would need to be selected for the study populations. In addition, in all studies that measure arterial stiffness, mean arterial pressure and age which are major determinants of arterial stiffness should be adjusted in data analysis.

The terms of arterial stiffness and atherosclerosis have been used interchangeably, which present challenges in current arterial stiffness research. While atherosclerosis is characterized by a local inflammatory process and accumulation of fatty plaque in the intima, arterial stiffness (called arteriosclerosis) is more likely due to medial degeneration characterized by elastin degradation and collagen deposition [7]. Although several studies have shown the significant relationship between atherosclerosis and arterial stiffness, these studies have been conducted in patients with atherosclerosis [124], or elderly people who may already have progressive subclinical atherosclerosis [125]. Since currently available noninvasive measures of arterial stiffness assess both intimal and medial calcification, data from these subjects would not provide accurate information about the levels of arterial stiffness. Indeed, the significant relationship between atherosclerosis and arterial stiffness was not demonstrated in the studies with middle-aged US populations [126], healthy volunteers [127], middle-aged patients referred for transesophageal echocardiography [128], asymptomatic middle-aged men at cardiovascular risk [129], and women in the general population [130]. In their editorial commentary, Wilkinson and McEniery pointed out that "an important first step is the realization that athGenetic Variants Related to Arterierosclerosis and arteriosclerosis are different conditions." [131] Studies on normotensive population without atherosclerosis may help to answer research questions of whether or not polymorphisms influence arterial stiffness independently of blood pressure and atherosclerosis.

A Proposed Conceptual Model of Arterial Stiffness Pathophysiology

Mechanisms contributing to arterial stiffness were proposed in Fig. 1. Although not many genetic variants have shown definitive causal associations with arterial stiffness, this model includes the genes that were investigated for their potential associations with arterial stiffness in the previous studies. Age, sex, and race, along with genetic makeup, can be important demographic factors that may influence arterial stiffness. There is evidence that psychological stress, diet, and physical

activities are behavioral factors that intervene stiffness of arteries. Uncontrolled cholesterol, glucose, and blood pressure are known as critical factors that may predispose vasculature to be easily insulted by oxidative stress and inflammation [95, 123, 132].

Stiffness of medium and large arteries called arteriosclerosis can be attributable to alterations in function (e.g., endothelial function) and structure (e.g., vascular remodeling). Arterial walls consist of the endothelium, intima, media, and adventitia. The innermost layer of vascular wall, endothelium, releases endothelium-derived relaxing factor (EDRF). One EDRF is NO, which has been identified to play an important role in regulating vascular smooth muscle tone. Endothelial dysfunction from oxidative stress and inflammation process decrease the production of NO and may consequently increase arterial stiffness [133, 134]. Although NO influences smooth muscle tone, its effect on arterial stiffness seems to be relatively less than the stiffness caused by structural change in medial layer of the arterial walls. For example, it was demonstrated that inhibition of NO and cytochrome-related endothelial-hyperpolarizing factor (EDHF) significantly decrease smooth muscle tone and arterial wall stiffness assessed by local measure [134]. However, other studies could not find a significant association between endothelial function and carotid-femoral PWV in young healthy subjects [135], or in adults with type 1 diabetes [136].

Oxidative stress and inflammation are considered key mechanisms in the progression of atherosclerosis [132]. While normal endothelium does not bind leukocytes for a prolonged time, when endothelial cells undergo inflammatory activation, they increase the expression of various leukocyte adhesion molecules (e.g., vascular cell adhesion molecule (VCAM)-1) [137]. Monocytes bound to VCAM-1 penetrate into the intima in the presence of monocyte chemoattractant protein-1 (MCP-1), and become intimal macrophages. Macrophage scavenger receptors bind oxidized LDL, and these lipid-laden macrophages, called foam cells, secrets pro-inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-α, CD-40) and reactive oxygen species (ROS) [138], exacerbating oxidation and inflammation process in endothelium. As continued process of inflammation, vascular smooth muscle cells (VSMC), which are abundant in medial layer of the arterial wall, migrate to the intima, proliferate, and excrete extracellular matrix proteins that contribute to the development of fibrous plaques. This process explains the progress of a simple fatty streak becoming atheromatous plaques and calcificated lesions [139]. This intimal calcification is closely associated with atherosclerosis.

On the other hand, calcification in the medial layer of the arterial wall directly increases arterial stiffness [7]. Medial calcification is characterized by fragmentation of elastin lamellae and collagen accumulation [140]. These structural changes in the medial layer occur both in the presence or absence of atherosclerosis [139] and increase with age and metabolic diseases such as diabetes [141] In vivo studies have demonstrated that catecholamine released by sympathetic function plays an important role in regulating vascular smooth muscle contraction and arterial stiffness [142–144]. Although the studies reviewed in this paper have not clearly demonstrated whether or not polymorphisms in RAAS genes play a dominant or initiating effect on arterial stiffness, several cultured cells and in vivo studies demonstrated that angiotensin II and aldosterone increase collagen synthesis in vascular smooth muscle cells [145], and that ACE inhibitors delay the accumulation of collagen in aorta [146, 147]. It was also reported that aldosterone increases arterial stiffness in absence of oxidative stress and endothelial dysfunction in an in vivo study [148]. Together, these analyses suggest that arterial stiffness may be induced independently of blood pressure and inflammation.

Although atherosclerosis and arterial stiffness (called arteriosclerosis) denote different conditions, current measures of arterial stiffness do not distinguish arteriosclerosis from atherosclerosis [7]. Furthermore, stiffened arteries increase stress within arteries and make the vascular environment more prone to atherosclerosis. In order to identify genetic variants of arteriosclerosis in clinical setting, careful selection of the study sample and proper adjustment of confounding factors should be considered.

Conclusion

In this paper, we reviewed the genetic association studies in arterial stiffness, and most findings showed inconsistent associations. These inconsistent results may have originated for several reasons. Among these existing studies, several methods have been used to measure local, regional, and systemic arterial stiffness at various arterial sites. The arterial system is not identical throughout body and the various arterial sites are different in their structure and characteristics. As such, the effect of genetic variants on arterial stiffness may not be same in different arterial sites. Thus, interpreting and comparing the results from different studies requires caution. Futures studies are also recommended to standardize local, regional, and systemic measures of arterial stiffness for different age groups. Furthermore, in the arterial stiffness studies, selection of participants with confounding underlying conditions such as hypertension and atherosclerosis can induce a biased conclusion. Arterial stiffness is very closely aligned with hypertension and atherosclerosis and they may share some pathophysiological pathways. Research findings would be more convincing when studies are conducted in a normotensive population with normal cholesterol levels. Lastly, the proposed model of arterial stiffness pathophysiology

(Fig. 1) was developed to separate the concept of "measurement of arterial stiffness" and "arteriosclerosis." This is useful to clarify that the current measures of arterial stiffness assess arteriosclerosis (e.g., medial calcification) which is combined with atherosclerosis (e.g., intimal calcification). Considerate adjustment of confounding factors along with careful selection of the study population may progress arterial stiffness studies.

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