A Review of Vascular Traits and Assessment Techniques, and Their Heritability

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Abstract

Various tools are available to assess atherosclerosis, arterial stiffening, and endothelial function. They offer utility in the assessment of hypertensive phenotypes, in cardiovascular risk prediction, and as surrogate endpoints in clinical trials. We explore the relative influence of participant genetics, with reference to large-scale genomic studies, population-based cohorts, and candidate gene studies. We find heritability estimates highest for carotid intima-media thickness (CIMT 35–65%), followed by pulse wave velocity as a measure of arterial stiffness (26–43%), and flow mediated dilatation as a surrogate for endothelial function (14–39%); data were lacking for peripheral artery tonometry. We furthermore examine genes and polymorphisms relevant to each technique. We conclude that CIMT and pulse wave velocity dominate the existing evidence base, with fewer published genomic linkages for measures of endothelial function. We finally make recommendations regarding planning and reporting of data relating to vascular assessment techniques, particularly when genomic data are also available, to facilitate integration of these tools into cardiovascular disease research.

Keywords: Heritability, Genetic, Vascular, Arterial stiffening, Endothelial, CIMT

1 Introduction

Hypertension is a major risk factor for Cardiovascular Disease (CVD); in turn CVD is the underlying cause of more than a quarter of deaths in the UK [1]. There are no validated tests that can identify early in the disease process which individuals will develop hypertension-mediated organ damage. Dysfunctional vascular traits represent key pathophysiological processes in the development of hypertension and cardiovascular disease, with both inherited and reversible elements. These traits include stiffness of the large arteries, microvascular abnormalities, endothelial dysfunction, and atherosclerosis, phenotypes often apparent prior to established hypertension or organ damage. Hence the interest in measuring vascular function, and in understanding the relationship between measurement techniques and hypertensive phenotypes, including the relative influence of participant sex and genetics. We explore this topic with reference to large scale genomic studies, population-based cohorts, and candidate gene studies.

1.1 Definitions for the Non-expert

Genome: complete set of genes in an organism including introns (non-coding sequences) and exons (coding sequences).

Genome-wide association study: entire genome surveyed for genetic variants occurring more frequently in cases than in controls.

Candidate gene study: specify fewer variants of interest a priori, and aim to establish if a disease association can be confirmed.
Epigenetics: genetic modification without mutations of the DNA sequence; occur in normal development or induced by environmental factors.

Exome: complete set of exons present in an organism which accounts for all the coding regions of genes present.

SNP: single nucleotide polymorphism—DNA sequence variations with a single nucleotide (adenine, thymine, cytosine, or guanine) in the genome sequence altered.

Common variants: SNPs with minor allele frequency (MAF) of greater than 1%, accounting for over 90% of genetic variation between individuals.

Mendelian Randomization: method of using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease.

2 Assessment of Vascular Function and Disease
Cardiovascular outcome measures in clinical trials generally relate to coded events such as myocardial infarction or death; alternatively, research trials may employ surrogate markers such as vascular stiffness and endothelial dysfunction—early functional traits known to be predictors of more advanced structural changes and development of cardiovascular disease. Assessment techniques quantifying such traits reflect different aspects of vascular health, assessed in the European Society of Cardiology Working group position paper [2]. First, carotid ultrasound to measure intima-media thickness (CIMT) has clinical utility in diagnosing carotid atherosclerotic vascular disease [3]–[5], but is also linearly associated with blood pressure (BP) [6] and adds prognostic value in the prediction of cardiovascular events and mortality, see Sect. 3.1 [7, 8]. Second, pulse wave analysis (PWA), PWA-derived augmentation index (AIX), and carotid-femoral pulse wave velocity (cfPWV) assess for arterial stiffness, a process characterised by functional changes and structural remodelling within the arterial wall, with associated fibrosis and calcification. These measures of arterial stiffening are independent and reliable predictors of hypertension, myocardial infarction and stroke [9]–[11], with meta-analyses of individual patient data showing the alternative brachial-ankle PWV method also associated with cardiovascular complications [12], and stiffening of the carotid artery with incident stroke [13]. The predictive strength of arterial stiffness is, however, greater in subjects with an established cardiovascular risk [14]. Finally, endothelial function refers to its’ ability to detect physical (shear stress) and biochemical signals, and respond through expression of surface molecules and production of vasoactive and inflammatory mediators. Endothelial dysfunction precedes structural micro-circulatory changes. Hypertension can be both cause and consequence of microcirculatory dysfunction, closely tied to peripheral vascular resistance, with vascular tone in turn regulated by many systems (sympathetic nervous system, endocrine, and local autoregulation), each with polygenic influences [15]. Endothelial function can be assessed using ultrasound of the brachial artery with ‘flow-mediated dilation’ (FMD), dilation predominantly mediated by nitric oxide release from endothelial cells. Alternatively, peripheral arterial tonometry (PAT), commonly quantified by the Endo-PAT2000 device (Itamar Medical) also assesses microcirculatory and endothelial function by measuring arterial tone or ‘hyperaemic response’ in the fingertips in response to proximal occlusion. EndoPAT-2000 device also generates an augmentation index adjusted to a heart rate of 75 bpm (AI@75), similar to PWA but derived from peripheral vessels. Hence, these techniques not only reflect different aspects of the pathophysiology of hypertension and cardiovascular disease but may aid identification of different hypertensive phenotypes [16]–[18]. They are also well accepted as being influenced by age, BP, and sex; factors that should be accounted for when comparing techniques. Less well defined are the effects of underlying genetic differences, i.e. the inherited component, or ‘heritability’ of data pertaining to techniques measuring vascular health. Genotypic effects on these vascular assessment tools are myriad, but key checkpoints where influence may be hypothesised include vascular endothelial cell sensitivity to extracellular stimuli, intra-cellular signalling cascades, and effects on transcription, ultimately influencing production of vasoactive substances, vascular tone, and remodelling.

3 Genetics of Hypertension
Familial and twin studies estimate that the heritable component of BP lies between 22 and 65% [19]–[22]. BP is a complex trait with no single gene playing a dominant role; instead multiple genes demonstrate minor additive effects. These genes encode for a variety of proteins, ion channels, receptors, and enzymes involved in endocrine, cardiac, renal, vascular and neural systems that influence BP regulation. This complexity is illustrated by the heterogeneity of underlying pathology in the (rare) monogenic cases of secondary hypertension, examples of which are discussed in Sect. 2.1.1. Other genes are identified only by genome wide association studies (GWAS); an illustrative example follows in Sect. 2.1.2.

3.1 Single Gene Disorders
Monogenic causes of hypertension are rare and mechanisms varied. For example, children with homocystinuria and familial hypercholesterolaemia develop premature atherosclerosis and early endothelial dysfunction [23]; in AD glucocorticoid-remediable aldosteronism, chimeric genes encoding steroid 11ß-hydroxylase (CYP11B1) and
aldosterone synthase (CYP11B2) lead to aldosterone regulation by ACTH rather than angiotensin II [24, 25], salt and water retention, and elevation in BP [26]. Finally, AD hypertension with brachydactyly syndrome results from a gain of function mutation in PDE3A, encoding phosphodiesterase 3A and resulting in cerebral vascular anomalies and baroreceptors hypersensitivity [27]. For an in-depth review of monogenic hypertensive syndromes, we would highlight Burrello et al. [28].

3.2 GWAS
GWAS have identified multitudes of genetic loci associated with BP, covered in-depth elsewhere [29]. For example, ATP2B1 encoding PMCA1, a plasma membrane ATPase expressed in vascular endothelium and involved in calcium pumping from the cytosol to the extracellular compartment. GWAS can, however, be susceptible to false positive associations if statistical analysis lacks rigour, if the panel fails to reflect genomic variation, or the study lacks statistical power; points to remain cognizant of.

3.3 Epigenetics
Processes of epigenetic modification include methylation, post-translational histone modification, and small non-coding RNAs. HSD11B2 gene promoter methylation for example has been associated with hypertension onset [30, 31]; acetylation meanwhile promotes gene transcription in NOS3 (eNOS) and other genes affecting vascular tone and salt and water homeostasis [32, 33]. Finally, small non-coding RNAs (miRNA) may conversely downregulate genes by binding the corresponding mRNA resulting in repression of translation [33]. Population-based studies further support the role of epigenetics in hypertension [34].

3.4 Sex and BP Genetics
The male–female difference in BP, vascular traits, and CVD is complex. Mediating factors include X and Y chromosome differences, sex-hormone influences, renin–angiotensin–aldosterone system divergence [35], societal and behavioral impacts, and even epigenetic differences, with females receiving genetic imprints from each parent’s X chromosome, random X inactivation leading to further genetic heterogeneity. Gene-by-sex interactions, and age (menopause)-dependent effects further complicate interpretation.

3.5 Summary
Bringing together the evidence of different phenotypes of hypertension [16–18, 36, 37], determined by pathophysiology but characterised by the aforementioned vascular traits; and considering the exponentially increasing data regarding hypertension risk alleles; it becomes important to explore the genotypic and sex associations with vascular techniques used to measure these hypertensive phenotypes.

4 Carotid Intima-Media Thickness
4.1 Heritability
A number of studies have reported heritability estimates for CIMT, though with disparate estimates (21 to 65%) despite similar adjustment for covariates, see Fig. 1 and Table 1 [38, 39]. Sacco et al. for example report 65% heritability in 100 Dominican families (1390 individuals, 61% female, mean age 46 years) after adjustment for age, sex, smoking, and BMI [39]; Cecelja et al. estimate age-adjusted heritability at 49% (95% CI 17–63%) in 762 females of the Twins UK cohort with mean age 58 ± 9 years [40]; whilst only 35% heritability is reported by Sayed-Tabatabaei et al. [41] in their assessment of 930 individuals connected in a single pedigree from an isolated population (participants of the Erasmus Rucphen Family study).

4.2 Genes
GWAS identifies numerous genetic loci as having possible significance, and studies of candidate genes approximating to these loci have also been widely reported (Table 2); 16 of the 32 identified (50%) also have evidence of association with BP traits. Figure 2 demonstrates that many genes have a role vascular remodelling, such as MMP9 encoding a gelatinase targeting type IV collagen and gelatin; CXCL12 involved in endothelial and epithelial cell proliferation and migration [43]; and VCAN which encodes chondroitin sulfate proteoglycans (extracellular matrix components), thus regulates cell proliferation, differentiation, and survival [45].

4.3 Interactions
Other genes demonstrate the importance of gene-by-environment interactions in determining CIMT, for example MCPH1 encodes a damage response protein regulating cell cycle [44]. Similarly, gene–gene interactions are apparent, for example genes involved in cholesterol biology and inflammation where high-density lipoprotein composition is altered in an inflammatory state, with apolipoprotein-A-I and –A-II displaced by Serum amyloid A (SAA). SAA SNPs rs2468844 and rs12218 alter binding affinity of SAA proteins [46, 47], with implications for reverse cholesterol transport, CIMT, plaque formation [48], and plaque stability [49].

5 Vascular Stiffness: Pulse Wave Analysis and Pulse Wave Velocity
5.1 Heritability
Genes are estimated to account from 26 to 43% of the variability in vascular stiffness as measured by PWV (see Table 1, Fig. 1), with data derived from both population
and twin studies [40, 41, 52, 53]. For example, the Georgia Cardiovascular Twin Study of 388 twins (41% black; 49% male) aged 12–30 years; report 53% (42–62%) heritability for dorsalis pedis (foot) PWV [53], with no sex or race differences; additionally, the aforementioned Twins UK cohort of 762 females, mean age 58±9 report heritability estimate of 38% (95% CI 16–63%) after adjustment, with annual progression interestingly demonstrating higher adjusted heritability estimates of 55% (31–64%) over 5 years follow-up [40].

5.2 Genes

Many studies of the genetics of arterial stiffness focus on parameters other than PWV, such as pulse pressure and forward and reflected wave amplitude, covered in detail elsewhere [142, 143]. Looking specifically at PWV as the most commonly used technique, GWAS of 644 individuals involved in the Framingham Heart Study did not find any variants achieving genome wide significance in the primary analysis [91], despite the Mitchell et al., study of 2127 participants (mean age of 60 years, 57% female) also derived from the Framingham cohort reporting moderate heritability for PWV ($h^2=0.40$), with suggestive linkage regions in chromosomes 2, 7, 13, and 15 [52]. Informed by GWAS, and based on UK Biobank data, Zekavat et al. [85] generated a six variant polygenic arterial stiffness score, showing a relationship with SBP and DBP, and Mendelian randomization data supporting causality, with genetic predisposition of arterial stiffness preceding hypertension [85].

5.3 Interactions

Fifteen of the 24 genes (62.5%) implicated in arterial stiffness have evidence of BP associations, see Table 2. Many candidate gene polymorphisms studied in greater detail relate to the renin angiotensin aldosterone system; in particular angiotensin-converting enzyme (ACE) gene polymorphisms are known to influence vascular tone, fibrosis, and ultimately arterial stiffness, though with discordant results between healthy, diabetic, and hypertensive populations, despite adjustments for demographic and lifestyle factors [104, 106, 142], suggesting either an additional interaction or confounding factor is involved. Similarly, the A1166C polymorphism of angiotensin II type 1 receptor gene (AGTR1) was associated with arterial stiffness in hypertensive participants [103, 108], but not among normotensive participants of the same study, nor the Rotterdam Study population [103, 110]. Study participant age needs to be considered in such publications as combined effects may be apparent, e.g. C allele carriers showing increased PWV, but only beyond 55 years of age [103], though the Rotterdam study population was over 55 years of age but still did not support the association. Additionally, heterogeneous methods of estimating arterial stiffness

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**Fig. 1**

Evidence regarding heritability of techniques assessing vascular function

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Percent heritability

CIMT estimates in orange, PWV/PWA blue, PAT no data, FMD green
Table 1  Evidence regarding heritability of techniques assessing vascular function

| Technique | Heritability | BP considerations of study |
|-----------|--------------|---------------------------|
| CIMT | 35–65% | 40% had hypertension, which met inclusion criteria as a covariate for CIMT. A chromosome 14q-hypertension interaction suggested for CIMT. Sacco 2009 [39] |
| | 65% (95% CI 60–70%): 100 Dominican families after adjustment for age, sex, smoking, and BMI. | |
| | 49% (95% CI 17–63%) adjusted for age: 762 females (Twins UK cohort), mean age 58 ± 9 years; average follow up 4.9 years; heritability of annual progression of CIMT only 8% (95% CI 0–36%). Cecelja 2018 [40] |
| | 35% ± 8 (after adjustment; P < 0.001): 930 individuals connected in a single pedigree from an isolated population (Erasmus Rucphen Family cohort); mean age females 51, males 54 yrs. Sayed-Tabatabaei 2005 [41] |
| | 38% ± 6 heritability, adjusted for multiple covariates; n = 906 men, 980 women (mean age 57 years) from 586 extended families of the Framingham Offspring cohort. Fox 2003 [50] |
| | 21% ± 6 after adjustment for multiple covariates; n = 950 American Indians of the Strong Heart Study (SHS); ≈30% with diabetes and hypertension; mean ages of different communities 41 to 44 years. North 2002 [38] |
| | 36%: 74 male twin pairs, 20 MZ, aged 42 to 69, one twin migrating to Sweden; IMT values also correlated between twin pairs (rMZ = 0.64, P = 0.002; rDZ = 0.46, P = 0.0006). Jartti 2002 [51] |
| PWV and PWA Heritability: 26–43% | Heritability 36% unadjusted, 26% adjusted for BP (and other factors), suggesting pleiotropic genes. Sayed-Tabatabaei 2005 [41] |
| | 26% ± 8 (after adjustment, P < 0.001) for PWV: n = 930, from an isolated population (Erasmus Rucphen Family); mean age females 51, males 54 yrs. Sayed-Tabatabaei 2005 [41] |
| | 40% ± 9 among 1480 participants representing 817 pedigrees in the Framingham Study offspring cohort. Mean age 60 ± 10 years. Variance components linkage analysis identified chromosomes 2, 7, 13, and 15 for PWV. Mitchell 2005 [52] |
| | 38% (95% CI 16–63%) adjusted. 762 females (Twins UK cohort), mean age 58 ± 9 years; average follow up 4.9 years; heritability of annual progression of PWV 55% (31–64%). Cecelja 2018 [40] |
| | 43% (95% CI 30–54%)/ 53% (95% CI 42–62%) for radial / foot PWV respectively. No ethnicity or gender differences in estimates. 41% black; 49% male; aged 12–30 (mean 17.7 ± 3.3) years; n = 388, twins: 89 pairs MZ, 105 pairs DZ. Ge 2007 Georgia Cardiovascular Twin Study [53] |
| PAT heritability: unknown | Overlap with genes influencing DBP. Ge 2007 [53] |
| | No published heritability estimates identified; though race, sex, and age influence EndoPAT results. Mulukutla 2010, Schnabel, 2011 [34, 55] |
| FMD heritability: 14–39% | Concluded SBP is an important correlate of FMD, but not directionality or whether associated through a third factor. Benjamin 2004 [56] |
| | 14%: n = 883, 53% women; mean age 61; adjusting for stepwise model covariates, estimated heritability of brachial artery baseline diameter was 33 ± 7%, and FMD% was 14 ± 6%, with age-gender interaction (P = 0.01). Benjamin 2004 [56] |
| | 24%: 74 male twin pairs, 20 MZ, aged 42–69, one twin migrating to Sweden. FMD did not correlate between twins, (rMZ = 0.23, P = 0.34, rDZ = 0.11, P = 0.43), suggesting modest genetic component; h2 = 2 x (0.23 – 0.11) = 0.24. Jartti 2002 [51] |
| | 39% (95% CI 18–56%): 94 male twin pairs, mean age 55 ± 28 years; adjusted for age, cholesterol, DBP, and body mass index. Zhao 2007 [57] |
| | 14% (95% CI 60–70%): 100 Dominican families after adjustment for age, sex, smoking, and BMI. Sacco 2009 [39] |
| | 40% of males and 36% of females had hypertension. Estimated age- and sex-adjusted heritability (c.f. the multivariable-adjusted) was 44% Fox 2003 [50] |
| | Hypertension did not reach significance as a covariate for CIMT. Proportion of variance due to covariates: 46%. North 2002 [38] |
| | IMT correlated with SBP (r = 0.24, P = 0.004). Jartti 2002 [51] |

CIMT carotid intima-media thickness, FMD flow-mediated dilatation, PWA pulse-wave analysis, PWV pulse-wave velocity, PAT peripheral arterial tone, BP blood pressure, MZ monozygous, DZ dizygous, N/A not applicable (no evidence of BP association)
| CIMT Candidate Genes with implicated role | Design | Evidence of BP association |
|------------------------------------------|--------|---------------------------|
| ATG10—E2-like enzyme involved in 2 ubiquitin-like modifications essential for autophagosome formation Strawbridge 2020 [44] | GWAS (UK Biobank) | N/A |
| RPS23—encodes a ribosomal protein Strawbridge 2020 [44] | GWAS (UK Biobank) | N/A |
| ATP6AP1L—ATPase H+-Transporting Accessory Protein 1 Like, a protein coding gene; Strawbridge 2020 [44] | GWAS (UK Biobank) | N/A |
| MIR8055 and MIR4693—RNA Genes affiliated with the miRNA class; Strawbridge 2020 [44] | GWAS (UK Biobank) | N/A |
| CBFA2T3—encodes a myeloid translocation gene family member which interact to repress transcription; Strawbridge 2020 [44] | GWAS (UK Biobank) | Larsson 2013 [58] |
| CYP2A6 and CYP2A7—encodes a member of the cytochrome P450 superfamily of enzymes; Strawbridge 2020 [44] | GWAS (UK Biobank) | Liu 2013 [59] |
| APOE E2 allele encodes a major apoprotein of the chylomicron Nataraajan 2016; Bis 2011; Strawbridge 2020 [44, 60, 61] | Meta-analysis of exome-WAS & GWAS (CHARGE) | N/A |
| BCAM—basal cell adhesion molecule; encodes Lutheran blood group glycoprotein, a member of the immunoglobulin superfamily and a receptor for laminin Strawbridge 2020, Bis 2011 [44, 61] | Meta-analysis of GWAS (CHARGE) | N/A |
| ZHX2—acts as a transcriptional repressor, rs11781551 associated with lower CIMT; Bis 2011 [61] | Meta-analysis of GWAS (CHARGE) | N/A |
| APOCI—expressed primarily in the liver, activated when monocytes differentiate into macrophages Bis 2011 [61] | Meta-analysis of GWAS (CHARGE) | N/A |
| PINX1—Microtubule-binding protein essential for chromosome segregation, Trs6601530 copy number associated with higher CIMT; Bis 2011 [61] | Meta-analysis of GWAS (CHARGE) | Feitosa 2018 [62] |
| PIK3CG—phosphorylates inositol lipids involved in immune response, rs17398575 associated with 18% increased odds of plaque Bis 2011 [61], not supported by López-Mejías 2014 [63] | Meta-analysis of GWAS (CHARGE) | Carnevale 2012 [64] |
| EDNRA—encodes the receptor for endothelin-1; role in vasoconstriction, rs11878406 associated with 22% increased odds of plaque; Bis 2011 [61], not supported by López-Mejías 2014 [63] | Meta-analysis of GWAS (CHARGE) | Hoffman 2017 [65] |
| ADAMTS7—a member of the ADAMTS family, a disintegrin and metalloproteinase with thrombospondin motifs; van Setten et al., 2013 [67], not supported by López-Mejías 2014 [63] | GWAS (Dutch and Belgian Lung Cancer Screening population) | Warren 2017 [66], Wirtwein 2017 [68] |
| THBS2—thrombospondin 2, a disulfide-linked homotrimeric glycoprotein that mediates cell-to-cell and cell-to-matrix interactions; McCarthy 2004 [69] | GWAS (GeneQuest, USA) | Oguri 2009 [66] |
| CFDPI—protein coding gene, may play a role during embryogenesis; Gertow, 2012 [70] | GWAS (IMPROVE population, European) | The UK Biobank Cardio-metabolic Traits Consortium Blood Pressure Working Group [66] |
| SLC17A2—involved in phosphate transport into cells; rs17526722 associated with lower CIMT in Mexican-Americans; Arya 2018 [71] | GWAS (RA patients) | N/A |
| PPDCD—necessary for biosynthesis of coenzyme A; rs1867148 associated with lower CIMT in European-Americans; Arya 2018 [71] | GWAS (RA patients) | Nandakumar 2019 [72] |
| CIMT Candidate Genes with implicated role | Design | Evidence of BP association |
|----------------------------------------|--------|----------------------------|
| PNPT1—RNA-binding protein involved in multiple processes e.g. importing RNA into mitochondria. Vojinovic 2018 [73] | GWAS (Erasmus Rucphen Family) | Ali 2019 [74] |
| NOS3—nitric oxide has a role in vascular tone; Asp/Asp genotype demonstrated greater CIMT (P = 0.0002) Paradossi 2004 [75] | Candidate gene study | Hoffman 2016 [65], Nassereddine 2018 [76], Giri [77] and others |
| SAA1 (rs12218) and SAA2 (rs2468844)—acute phase protein, associated with CIMT in healthy Chinese population Xe 2010[48] | Candidate gene study | N/A |
| MMP9—involved in the breakdown of extracellular matrix; associated with internal carotid but not common carotid artery IMT Armstrong 2007[42], | Candidate gene study | Dhingra 2016 [78] |
| MMP3—involved in the breakdown of extracellular matrix; relationship between increasing copy number and CIMT Armstrong 2007[42] | Candidate gene study | Armstrong 2007 [42], Beilby 2005 [79] |
| TIMP3—inactivates metalloproteinases; shows relationship between increasing copy number and CIMT. Armstrong 2007[42] | Candidate gene study | Armstrong 2007 [42] |
| CA112—arterial remodeling and thickening, rs1746048 associated with IMT. Zabalza 2015[43] | Candidate gene study | Liu 2018 [80] |
| WDR12—involved in cell cycle/proliferation, signal transduction and gene regulation; inverse association with CIMT; Zabalza 2015 [43] | Candidate gene study | Wirtwein 2017 [68] |
| CYBA encodes p22phox, a component of NADPH oxidase. C242T polymorphism was a predictor of internal CIMT following multivariable adjustment (b-coefficient = 0.119, p = 0.011). Lambrinoudaki [81] | Candidate gene study | N/A |
| GCKR—product is a regulatory protein that inhibits glucokinase in liver and pancreatic islet cells; rs780094 associated with carotid plaque in the American Indian but not European-, African-, or Mexican–American populations Zhang 2013 [82] | Candidate gene study | N/A |
| ADAM33—transmembrane protein, role in inflammation and regeneration; rs14174 associated with CIMT, Zhang 2019 [83] | Candidate gene study | N/A |
| TRAF1—adapter molecule that regulates the activation of NF-kappa-B and JNK, Heßler 2016 [84] | Linkage analysis | N/A |
| SMOC-1—glycoprotein mediating cell–matrix interactions Sacco 2009 [39] | Linkage analysis | N/A |
| FBLN5—secreted protein involved in cell adhesion Sacco 2009 [39] | Linkage analysis | N/A |
| CIMT Studies reporting sex-specific findings | Design | Evidence of BP association |
| VCAN—female-specific locus; encodes a chondroitin sulfate proteoglycan of the adventitia and intima. Strawbridge 2020 [44] | GWAS (UK Biobank) | N/A |
| MCPH1—DNA damage response protein Strawbridge 2020 [44] | GWAS (UK Biobank) | N/A |
| PWV and PWA Candidate Genes with implicated role | Design | Evidence of BP association |
| TEX41 (rs1006923), testis expressed 41 RNA gene. Zekavat 2019, Fung 2019 [85, 86] | GWAS (UK BioBank) | Zekavat 2019 included causal inference analyses with BP [85]. Also Warren 2017 [66] |
### Table 2 (continued)

| Candidate Genes with implicated role | Design | Evidence of BP association |
|--------------------------------------|--------|-----------------------------|
| FOXO1 (rs7331212)—role in T lymphocyte function and cell cycle regulation including osteogenesis and angiogenesis. Zekavat 2019, Fung 2019 [85, 86] | GWAS (UK BioBank) | Animal model Qi 2014 [87] |
| MRVI1 (rs10840457), synonym: IRAG. Role as regulator of IP3-induced calcium release in platelet activation and NO-dependent smooth muscle relaxation. Fung 2019[86] | GWAS (UK BioBank) | Animal model association with BP: Desch 2010 [88], association not evidenced in human studies |
| COL4A1 and COL4A2 (rs3742207, rs9521719, rs872588)—type 4 collagen and associated with arterial stiffness [by PulseTrace PCA2] Zekavat 2019 and Fung 2019 [85, 86], Tarasov 2009 [89] | GWAS (UK BioBank and SardiNIA) | N/A |
| TCF20 (rs55906806): transcription factor recognises platelet-derived growth factor-responsive element in MMP3 promoter. Zekavat 2019 and Fung 2019[85, 86] | GWAS (UK BioBank) | N/A |
| C1orf21 (rs1930290): chromosome 1 open reading frame. Fung 2019 [86] | GWAS (SardiNIA) | Evangelou 2018 [90], Giri 2018 [77] |
| MAGI1 (rs1495448): membrane associated guanylate kinase i.e. scaffolding protein; associated with PWV. Tarasov 2009 [89] | Meta-analysis of 9 European ancestry GWAS | Levy 2007 [91] |
| BCL11B (rs7152623) role in immune regulation; linked to carotid-femoral PWV and CVD. Mitchell 2012 [92] | IL6 (pro-inflammatory cytokine). Mitchell 2005 [52](Framingham Study offspring cohort, n = 1480) | Association with nocturnal dipping (GENRES (n = 204), DYNAMIC (n = 183) and DILGOM cohorts (n = 180) Rimpelä 2018 [93] |
| PHACTR1 (rs949379) regulates cytoskeleton; G allele linked to decreased arterial stiffness (PulseTrace PCA2) Zekavat 2019[85] | IGF1R (insulin-like growth factor 1 receptor) complex effects on vasculature including cellular proliferation, vasodilation via NO, and other endothelial functions. Mitchell 2005 [52] | Gupta 2017, n = 38,817 (UK BioBank) [94] |
| ME2F2A (myocyte-specific enhancer factor 2A), DNA-binding transcription factor, activates growth factor and stress-induced genes. Mitchell 2005 [52] | PACE4 (PCSK6) and FURIN, encodes a protease with multiple substrates including pro-hormones, growth factors and von Willebrand factor, Mitchell 2005 [52] | Evangelou 2018 [90], Giri 2018 [77] |
| CHSY1 (chondroitin synthase 1), role in biosynthesis of chondroitin sulfate, a glycosaminoglycan required for cell proliferation and morphogenesis. Mitchell 2005[52] | ADD2 (β-adducin), encode subunits of membrane skeletal proteins. Mitchell 2005[52] | N/A |
| TACR1 (tachykinin/neurokinin-1 receptor) encodes receptor for and mediates metabolism of tachykinin substance P. Mitchell 2005[52] | ADRA2B (beta adrenergic receptor) mediate catecholamine-induced inhibition of adenylate cyclase through G proteins. Mitchell 2005[52] | N/A |

GWAS: Genome-wide association studies; N/A: Not applicable.
| PWV and PWA Candidate Genes with implicated role | Design | Evidence of BP association |
|------------------------------------------------|--------|---------------------------|
| NOS3 rs179983 related to central pulse pressure and forward wave amplitude parameters of PWA in females only. Mitchell 2007 [98] | Candidate gene study | Hoffman 2016 [65], Nassereddine 2018 [76], Giri 2018 [77] and others |
| TXNIP (rs7212) G allele associated with higher PWV values; functions as sensor for biomechanical and oxidative stress. Alvim 2011 [99] (Brazilian cohort, N = 1518) | Candidate gene study (Brazilian cohort) | N/A |
| COL1A1 polymorphisms—collagen type 1A deposition in arterial compliance. Brull 2001 [100] (Young Hearts Project, UK, N = 489) | Candidate gene study | N/A |
| ETA1 (Endothelin-A and -B receptor, synonym EDNRA); endothelin being a vasoconstrictor; gene variants influenced PWV. Lajemi 2001 [101] (n = 538, untreated hypertensive Europeans) | Candidate gene study | Hoffman et al. 2016 [65] |
| ACE I/D (rs4344)—role in BP regulation and electrolyte balance through hydrolyzing angiotensin I, influence on arterial stiffness. Heterogeneous findings regarding implications of D allele. Mattace-Raso 2004, Benetos 1996, Dima 2008, Tanjiwaki 1999, Lajemi 2001; Benetos 1995; Gardier 2004; Mayer 2008 [102–109] | Candidate gene studies | Hoffman 2016 [65], Sie 2009 [110], and others |
| AGTR1 (AT II type 1 receptor)—AT II acts as a vasoconstrictor and regulates aldosterone; positive association seen with PWV in hypertensive population. Benetos 1996, Lameji 2001; Bozec 2004; Gardier 2004; Mayer 2008. Association not supported by Sie 2009 [103, 105, 107, 108, 110, 111] | Candidate gene studies | Numerous, see www.ensembl.org; e.g. Bonnadeaux 1994 [112] |
| PWV and PWA Studies reporting sex-specific findings | Design | Evidence of BP association |
| FBN1 (Fibrillin-1) 2/3 genotype associated with higher PWA Aix and BP in females only. Malm 2020 [114] (n = 315 hypertensive elderly subjects); Medley 2002 [115] (n = 145) | Candidate gene study | Malm 2020 [114], Medley 2002 [115] |
| PAT Candidate Genes with implicated role | Design | Evidence of BP association |
| CSK—cytoplasmic tyrosine kinase, role in angiotensin II-mediated vascular smooth muscle contraction (Hong 2010) [116] | GWAS (KARE) | Hong 2009 [116] |
| NOS3 (eNOS)—produces nitric oxide which is implicated in vascular smooth muscle relaxation, (Burghardt 2017) [117] | Candidate gene study | Hoffman 2016 [65], Giri 2018 [77] and others |
| APOE/E4—a protein which is a component of lipoprotein (Korsakova 2018) [118] | Candidate gene study | N/A |
| ACE—converts angiotensin I to angiotensin II, resulting in increased vasoconstrictor activity, (Korsakova 2018) [118] | Candidate gene study | Montrezol 2019 [119], Hoffman 2016 [65], Sie 2009 [110], and others |
| SPHK 1—modulates Ang II dependent vascular dysfunction; (Siedlinski et al., 2017) [120] | Animal model/human data | Pietro 2020 [121] (animal and human data) |
| ADORA1—receptor for adenosine, activity of this receptor is mediated by G proteins which inhibit adenyl cyclase (Yoshino 2016) [122] | Linkage analysis | Evangelou 2018 [90] |
### Table 2 (continued)

| PAT Theorised genes, but data lacking | Design | Evidence of BP association |
|---------------------------------------|--------|-----------------------------|
| SH2B3—LNK, lymphocyte-specific adaptor protein, endothelial cell function and vascular regeneration, though not specifically reported in EndoPAT (Newton-Cheh 2009; McMaster 2014 animal model) | GWAS (Global BPgen & CHARGE consortiums) | Dale 2016 [125], Newton-Cheh 2009 [123], Ference 2014 [126] |

| PAT Studies reporting sex-specific findings | Design | Evidence of BP association |
|------------------------------------------|--------|-----------------------------|
| ADORA3 strongest associations in women (member of the adenosine receptor group of G-protein-coupled receptors) (Yoshino 2016) | Linkage analysis | N/A |
| LPA strongest associations in women (protein encoded by this gene is a serine proteinase that inhibits the activity of tissue-type plasminogen activator I) (Yoshino 2016) | Linkage analysis | Smyth 2008 [127], Wirtwein 2017 [68] |
| KIF6 strongest associations in men (encodes a member of a family of molecular motors which are involved in intracellular transport of protein complexes) (Yoshino 2016) | Linkage analysis | N/A |
| NFkB1 strongest associations in men (a rapidly acting primary transcription factor found in all cell types) (Yoshino 2016) | Linkage analysis | N/A |

| FMD Candidate Genes with implicated role | Design | Evidence of BP association |
|-----------------------------------------|--------|-----------------------------|
| PHACTR1 (rs9349379): encoded protein binds actin and regulates reorganization of actin cytoskeleton, also influences vascular endothelin-1 gene expression, G allele associated with decreased FMD. Gupta 2017, n = 16662, aggregated from six cohorts [94] | Candidate gene study | Gu 2020 [128], Zhang 2012 [129] |
| NOS3 (eNOS): Glu298 → Asp polymorphism—Nitric oxide has a role in vascular tone; associated with FMD Paradossi 2004, n = 118; and Ingelsson 2008, n = 959 [75, 130] | Candidate gene study | Hoffman 2016 [65], Nassereddine 2018 [76], Giri 2018 [77] and others |
| CD36 (rs3211938): integral membrane protein expressed by many cell types, imports fatty acids and is a class B scavenger receptor. G allele impairs FMD after adjusting for differences in weight. Shibao 2016; 103 African American females [131] | Candidate gene study | Xueyen 2013 [132] |
| AT1R (synonym AGTR1): AT II acts as a vasoconstrictor and regulates aldosterone, hence blood volume: FMD reduced in C allele carriers Li et al. 2015, and Akpinar et al., 2014, n = 255 [133] | Candidate gene study | Numerous, see www.ensembl.org, e.g. Bonnardaeux 1994 [112] |
| CYBA (C242T polymorphism) encodes p22phox, a component of NADPH oxidase, FMD impaired in CC genotype, and T allele associated with higher FMD in hypertensive individuals. Fan et al. 2007, n = 2058; Raftq 2014, n = 146; Lambrinoudaki 2018 n = 70 [81, 134, 135] | Candidate gene study | N/A |
| APOE FMD associated with E4 allele in stepwise regression analysis. Guangda 2003, n = 255 with diabetes [136] | Candidate gene study | N/A |
| FMD Candidate Genes with implicated role | Design | Evidence of BP association |
|-----------------------------------------|--------|---------------------------|
| NFKB1: encoding NFKB protein, a transcription regulator; reduced reactive forearm blood flow identified in DD genotype; Park 2007, n = 47 | Candidate gene study | N/A |
| PDE3A: Phosphodiesterases regulate endothelial function and smooth muscle contraction through role in the NO/cGMP pathway. Traylor 2020, ALSPAC (Avon Longitudinal Study of Parents and Children; n = 5214, integrated with MEGASTROKE: n = 60,341) [137] | Linkage analysis | Associated with hypertension and brachydactyly syndrome. Maass 2015 [138]; Luft 2019 [139] |
| SH2B3 (LNK—lymphocyte-specific adaptor protein)—endothelial cell function and vascular regeneration, not specifically reported in FMD. Newton-Cheh 2009, also McMaster 2014 [123] | GWAS (Global BPgen and CHARGE consortiums) | Levy 2009 [140]; Ference 2014 [126], Hoffman 2016 [65]; Ehret 2016 [113] and others |
| ACE gene: mostly endothelial-bound, role in BP regulation and electrolyte balance through hydrolyzing angiotensin I; no effect on FMD. Alpinar 2014 and Gelemrjag 1994 [133, 141] | Candidate gene study | Hoffman 2016 [65]; Sie 2009 [110]; and others |
| FMD Theorised genes, but data lacking or no association found | | |
| | | |
| FMD Studies reporting sex-specific findings | Design | Evidence of BP association |
| Sex-specific multivariable models estimated similar effects of age on baseline artery diameter and FMD in mm for both sexes. However, FMD demonstrated age-gender interaction (P = 0.01), age effect being — 0.5 for men and — 0.7 for women. Benjamin 2004 [56] | GWAS (Global BPgen and CHARGE consortiums) | Levy 2009 [140]; Ference 2014 [126], Hoffman 2016 [65]; Ehret 2016 [113] and others |
| ACE gene: mostly endothelial-bound, role in BP regulation and electrolyte balance through hydrolyzing angiotensin I; no effect on FMD. Alpinar 2014 and Gelemrjag 1994 [133, 141] | N/A | |

*CIMT* carotid intima-media thickness, *FMD* flow-mediated dilatation, *PWA* pulse-wave analysis, *PWV* pulse-wave velocity, *PAT* peripheral arterial tone, *BP* blood pressure, *N/A* not applicable (no evidence of BP association)
Fig. 2 Gene polymorphisms relating to techniques measuring vascular health, with genes grouped according to function. Based on data in Table 2.
PWV [145]. Finally, the importance of ancestry when extrapolating data is highlighted by the concordance of results derived from a common population e.g. Zekavat et al. and Fung et al. reporting UK BioBank data [85, 86], and discordant results in candidate genes and heritability estimates across disparate populations [52, 110].

6 Endothelial Function: Flow Mediated Dilatation and Peripheral Arterial Tone

6.1 Heritability
The influence of genetics on endothelial function as measured by FMD is supported by an Italian cohort of 40 healthy young people (age 6–30, 19 male) with a family history of premature myocardial infarction, demonstrating lower FMD (5.7±5.0% vs. 10.2±6.6% in control subjects; \( P = 0.001 \)) [146]; and by a cohort of 50 British young people with a family history of coronary artery disease (31 male, mean age 25 years) also suggesting endothelial dysfunction (FMD 4.9±4.6% vs 8.3±3.5% in control group, \( P < 0.005 \)) [147]. Among 883 participants of the Framingham cohort (53% female; mean age 61), estimated heritability (accounting for covariates) of brachial artery baseline diameter was 0.33±0.07, and FMD% was 0.14±0.06; for FMD%, there was an age-gender interaction (\( P = 0.01 \)), females showing steeper age-related FMD% decline [56]. Twin studies tend to be preferred above family studies for heritability estimation, as they allow a more precise separation of environmental influences from genetic effects [148], including controlling for such age effects. Twin studies reporting FMD heritability estimates include a Finnish cohort reporting FMD heritability of 24%, derived from 74 male twin pairs (20 monzygous), aged 42–69 years, with monozygous twins demonstrating improved FMD after migrating to Sweden (7.2±4.4 vs 3.7±2.9%, \( P = 0.003 \)), a country with lower cardiovascular risk [51]. A higher estimate of 39% was reported from 94 male twin pairs from the USA (58 monzygous pairs), mean age 55±2.8 years, 95% Caucasian [57].

6.2 Genes
Candidate genes linked to FMD are included in Table 2, 5 of the 8 (63%) also linked to hypertension, see Fig. 2. Examples include the Asp/Asp genotype of the endothelial nitric oxide synthase (NOS3) Glu298→Asp polymorphism, which was associated with reduced vascular nitric oxide (NO) generation (a potent vasodilator), decreased brachial artery FMD, and increased CIMT in a group of young healthy individuals free of traditional cardiovascular risk factors [75, 149]. NOS3 regulation involves receptor-mediated mechanisms (e.g. acetylcholine, bradykinin, and substance P) and mechanical stimuli (shear stress). However, NOS3 Asp298 is not unique; more than 100 polymorphisms in NOS3 have been identified [150], with small effect size and significant interaction with other genes and environmental factors [151]. Further elements of the NO system implicated include PDE3A, a phosphodiesterase with a role in the NO/cGMP pathway.

Other genes have more obscure associations, such as PHACTR1 with a role in actin re-organisation but also possibly regulating vasoconstriction via endothelin-1 gene expression [94]; NFKB1 encoding a protein with diverse roles as a transcription regulator [152], and CYBA encoding p22phox, a component of NADPH oxidase involved in vascular ROS generation [134, 135], see Table 2. Yoshino et al. studying the genetics of endothelial dysfunction report coronary vascular responses to Acetylcholine, finding 1563 SNPs connected with cardiovascular physiology and pathology [122]. Variants in adenosine A1 receptor (ADORA 1) were associated with endothelial dysfunction in the entire cohort, while variants in adenosine A3 receptor (ADORA 3) and lipoprotein A (LPA) had the strongest associations with increased risk of endothelial dysfunction in women, again highlighting that sex differences must be considered within this area of research.

We did not find published heritability estimates regarding the EndoPAT assessment tool of peripheral arterial tone, though both race and sex are known to influence results [54, 55]. Numerous candidate genes have been proposed to influence vascular endothelial function, but only six of them reported have specifically been linked to PAT; five of the six (83 percent) had commonality with BP traits. see Fig. 2. The six linked to PAT include NOS3, already discussed in regard to FMD [117]; APO E, ACE [118], and Sphk1 SNPs/alleles [120]. Siedlinski [120] elegantly combine Sphk1 identification through murine transcriptome analysis with in vivo experiments confirming a role in vasoconstriction and endothelial dysfunction, and correlation of human sphingosine-1-phosphate (S1P) serum levels with arterial tonometry.

7 Heritability Study Considerations
BP regulation and vascular function are complex, polygenic traits, additionally influenced by many environmental factors. Molecular genetic analysis is therefore challenging due to the sheer number of relevant genes and their polymorphic effects, as examples in Table 2 illustrate. There are also certain limitations associated with heritability studies, as follows.

7.1 Family Studies
Classical family study design can overlook non-additive genetic effects and shared environmental factors. Additionally, the underlying assumption regarding the genetic relationship is flawed; offspring tend to inherit long segments of DNA resulting in deviations from the expected 50% DNA inheritance from each parent. Furthermore,
family studies often recruit based on participant phenotype, with family members then invited to participate. However, techniques to correct for ascertainment bias should be employed, such as Hopper and Mathews method which adjusts the heritability estimate based on the mean and total variance of the genetic and environmental components for each individual family grouping [153].

7.2 Missing Heritability
Another issue is ‘missing heritability’, i.e., the disparity between heritability estimates derived from genotype data (explaining a low proportion of the variance), and from twin studies (estimating significantly higher heritability). Missing heritability is likely a consequence of restriction of many genetic association studies to SNPs—missing rare mutations. Gene-by-gene interactions, epigenetics, and gene-by-environment interactions also contribute to missing heritability, through assumptions that such interactions are minimal, identifiable, and that variance explained by shared environmental factors is identical in pairs. Such assumptions risk inflating heritability estimates by attributing the contribution of environmental factors to genetics.

7.3 Directionality
Directionality is an inherent challenge when assessing genotypic influences effecting vascular traits: differentiating if an identified gene has a direct impact on e.g., PWV, or alternatively elevates BP which in turn leads to arterial remodeling, stiffness, and results in elevated PWV. The high proportion of identified genetic loci and candidate genes common to both vascular phenotypes and hypertension outlined in Table 2 and Fig. 2 highlights this.

7.4 Design
Most data are cross-sectional in nature, from which change over time in vascular function or BP cannot be inferred. One might also hypothesize that SNPs contributing to vascular ageing for example may influence PWV at 60 years of age, but not at 30. Studies that do report heritability of baseline measures and progression, have found discrepancies [40]; therefore, duration of follow up, or population age of cross-sectional data must be reported in detail. Future studies independently confirming heritability of vascular traits and candidate genes, as well as their independence from each other and from BP are required, and will determine the utility of vascular assessment techniques as surrogate endpoints in trials, separate from their use as predictive risk tools.

8 Vascular phenotype
Various genes in Table 2 appear numerous times suggesting effects on multiple vascular function assessment techniques. For example ACE, which cleaves angiotensin I into angiotensin II with vasoconstrictive effects; ACE also stimulates the production of aldosterone, increasing absorption of salt and water in the kidneys; ACE furthermore causes inactivation of the vasoactive mediator bradykinin. It is therefore not surprising that genetic polymorphisms of ACE impact on many of the vascular assessment techniques described. Similarly, NOS3 (endothelial nitric oxide synthase) has been identified as relevant in multiple assessment tools of vascular function, with local vasodilatory regulation of vascular tone and diameter (see Table 2). Other genes or polymorphisms appear specific to the technique or vascular trait, such as SAA1 in CIMT; COL4A in arterial stiffness (PWV), and CYBA encoding p22phox, a component of NADPH oxidase in FMD. Some furthermore show a gene by sex interaction, such as VCAN locus in females, encoding a chondroitin sulfate proteoglycan of the adventitia and intima in CIMT [44], and NOS3 rs1799983 relating to central pulse pressure and forward wave amplitude parameters again only in females [98]. Others appear to only reach significance in those with hypertension, suggesting gene by gene or gene by environment interactions e.g. CYBA T allele associated with higher FMD only in hypertensive individuals [154]. These highlight the importance of comprehensive demographic reporting and consideration of such factors when comparing data from multiple sources. Finally, fewer studies were identified reporting the genetics of measures of endothelial function (FMD and PAT) compared to those relating to vascular stiffness and remodeling/atherosclerosis; we would propose this as an area for future study. Of note, no single gene or SNP discussed here demonstrates a substantial association with the vascular traits and assessment techniques covered. This is to be expected in polygenic traits, but may also reflect features of study design identified above: necessity for standardised technique with these tools, underpowering and lack of external validation cohorts among many studies, gene–gene or gene–environment interactions. Comparisons between different demographic groups are also complicated if age, sex, race, and BP are not fully adjusted for. Researchers should be cognizant of these in future studies.

9 Sex-Differences
Gene-by-sex interaction may not always be captured by GWAS. Efforts to elucidate sex-specific genomic determinants of BP demonstrated in 120 Canadian families found that one quarter of the 539 hemodynamic, anthropometric, metabolic, and humoral traits studied were
both age and sex dependent, and one eighth were exclusively age or sex dependent [155].

A vascular phenotypic divide related to participant sex may also exist, demonstrating greater discrimination between normotensive and hypertensive PWV and augmentation index for females than males [16] and supported by our own unit’s experience (unpublished). Conversely, a collaboration establishing reference values for PWV describe apparent sex differences being almost fully accounted for by age and BP differences [156]. Two points therefore to consider if undertaking or analysing vascular function data, is whether the groups were well matched or adjustments for age and BP applied, and we suggest that researchers should also report outcome data stratified by sex to facilitate interpretation.

10 Conclusion
In conclusion, CIMT, PWV/PWA, FMD and PAT offer utility as surrogate markers of atherosclerosis, arterial stiffening, endothelial and microcirculatory function i.e. vascular function, and are predictive of cardiovascular risk. They may also have an increasing role as surrogate endpoints in genomic studies and clinical trials [157], however sex differences remain contentious, and dissecting genetic associations independent from hypertension is challenging. The genetics underlying these vascular assessment techniques have been variably studied, CIMT more so than PAT. The genetics of hypertension has a broad literature base; the next step is to integrate characterization of vascular and hypertensive phenotypes with genotypes as a natural symbiosis in studying the pathophysiology of hypertension and cardiovascular disease, and to better personalize cardiovascular medicine.

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Author Contributions
All authors contributed to study design and manuscript writing, and approved the final version. ECM and AC additionally contributed to the literature search, data gathering and analysis.

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Data Availability
All data pertaining to this manuscript are already freely available and full references including DOI have been provided to facilitate access to data.

Declarations
Conflict of interest
The authors have no conflicts of interest to disclose.

Ethics Approval
As a review of published literature, ethics approval was not required.

Consent for Publication
Not applicable.

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