Research Article

Genetic Determinants Of Arterial Hypertension And Atherosclerosis Development In Adolescence: A Review Of The Current State

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Abstract

Arterial hypertension (HTN) and atherosclerosis (AS) are no longer regarded as exclusively adult-onset disorders. Pathological precursors of both diseases—including elevated blood pressure trajectories, endothelial dysfunction, and early arterial wall changes—are detectable as early as the first two decades of life, and longitudinal cohort data confirm that adolescent risk factor burden predicts adult cardiovascular disease with high fidelity. A substantial proportion of inter-individual variability in blood pressure and atherogenic lipid traits during adolescence is attributable to heritable genetic variation. This review summarizes current knowledge on the genetic determinants of HTN and AS relevant to the adolescent period, covering monogenic forms of hypertension, polygenic contributions identified through genome-wide association studies of blood pressure and coronary artery disease, key lipid-metabolism genes (APOE, LDLR, PCSK9, LPA, APOB) driving early dyslipidemia and subclinical atherosclerosis, and the expanding role of polygenic risk scores in pediatric and adolescent risk stratification. We further discuss gene-environment interactions—diet, physical activity, obesity, and smoking initiation—that modulate genetic susceptibility during this developmental window, along with emerging epigenetic and mitochondrial mechanisms. We conclude by outlining the translational potential and current limitations of incorporating genetic and polygenic information into adolescent cardiovascular risk assessment and prevention strategies.

Keywords: Arterial hypertension; Atherosclerosis; Adolescence; Genetic determinants; Genome-wide association studies; Polygenic risk score; Lipid metabolism genes; Cardiovascular prevention.

Introduction

Arterial hypertension and atherosclerosis remain the principal drivers of cardiovascular morbidity and mortality worldwide, and although their clinical complications typically manifest in mid-to-late adulthood, the biological processes underlying both conditions begin much earlier in life. Autopsy studies of young accident victims and large prospective pediatric cohorts have repeatedly demonstrated that fatty streaks, early intimal thickening, and elevated blood pressure trajectories are already present in adolescence, and that the burden of these early lesions correlates strongly with the cardiovascular risk factor profile measured during the same period [1].

The recognition that cardiovascular disease has its origins in childhood and adolescence has reframed prevention as a developmental, rather than purely adult, public health priority [2]. Within this framework, genetic susceptibility has emerged as a central determinant of who develops early elevated blood pressure, dyslipidemia, and subclinical vascular changes, and who does not, even under broadly similar environmental exposures. Twin and family studies have consistently estimated the heritability of blood pressure at 30-50% and of major lipid traits at 40-60% [3,4], indicating a substantial genetic component that is, in principle, detectable from birth and that interacts with diet, adiposity, and physical activity across adolescent development.

The objective of this review is to synthesize the current understanding of genetic determinants of arterial hypertension and atherosclerosis as they pertain specifically to the adolescent period. We address four main areas: (1) monogenic and oligogenic forms of hypertension with pediatric/adolescent onset [5], (2) polygenic architecture of blood pressure and coronary artery disease identified through large-scale genome-wide association studies (GWAS) and its relevance to youth [6,7], (3) genes governing lipid metabolism and early atherogenesis [8,9], and (4) the translational application of polygenic risk scores and gene-environment interactions for adolescent cardiovascular risk stratification and prevention [10].

Developmental Origins of Hypertension and Atherosclerosis

Longitudinal cohorts such as the Bogalusa Heart Study, the Cardiovascular Risk in Young Finns Study, and the Muscatine Study have established that blood pressure, lipid levels, and adiposity track substantially from childhood and adolescence into adulthood, and that adolescent risk factor clustering is associated with measurable increases in adult carotid intima-media thickness and arterial stiffness [11,12]. These findings support the concept that the same biological pathways responsible for adult HTN and AS are already active, and partly genetically determined, during the second decade of life.

Because environmental exposure time is comparatively limited in adolescents relative to adults, the relative contribution of inherited genetic variation to inter-individual differences in blood pressure and lipid traits is, if anything, more apparent earlier in life, before cumulative environmental damage and age-related comorbidities obscure the genetic signal [13]. This makes adolescence a particularly informative window both for genetic research and for early identification of individuals who would benefit most from intensified preventive counseling [14].

Genetic Determinants of Arterial Hypertension

Monogenic Forms of Hypertension Presenting in Youth

A small but clinically important subset of adolescent hypertension is attributable to single-gene (Mendelian) disorders affecting renal sodium handling [5]. These include Liddle syndrome (gain-of-function variants in SCNN1B/SCNN1G encoding the epithelial sodium channel), glucocorticoid-remediable aldosteronism (a chimeric CYP11B1/CYP11B2 gene), apparent mineralocorticoid excess (loss-of-function variants in HSD11B2), and Gordon syndrome (pseudohypoaldosteronism type II, caused by variants in WNK1/WNK4) [15]. Although individually rare, these disorders typically present with early-onset, often severe hypertension, frequently with characteristic biochemical signatures (e.g., suppressed renin and aldosterone), and their recognition in adolescents with resistant or unusually early hypertension carries direct therapeutic implications, since management differs substantially from standard antihypertensive therapy.

Identification of these monogenic causes in adolescent patients is important not only for individualized treatment but also because it illustrates, in an extreme and tractable form, the broader principle that variation in renal sodium-handling pathways is a fundamental determinant of blood pressure across the population [16].

Polygenic Architecture of Blood Pressure

The overwhelming majority of essential hypertension, including hypertension first detected in adolescence, is polygenic, reflecting the combined small effects of hundreds to thousands of common genetic variants. Large-scale GWAS meta-analyses, comprising over one million participants, have identified several hundred independent loci associated with systolic and diastolic blood pressure, implicating genes involved in the renin-angiotensin-aldosterone system (AGT, ACE, AGTR1), renal sodium transport (NPPA/NPPB, SLC4A7, ATP2B1), vascular smooth muscle tone (NOS3, ADRB1), and natriuretic peptide signaling [6,17,18].

Classical candidate-gene studies preceding the GWAS era—most notably investigating the angiotensinogen M235T variant, the ACE insertion/deletion polymorphism, and the NOS3 G894T (Glu298Asp) variant—reported associations with blood pressure level and hypertension risk [19], although replication across populations has been inconsistent [20,21], underscoring the modest individual effect sizes typical of common blood-pressure-associated variants and the importance of adequately powered, multi-ethnic GWAS for robust locus discovery [22,23].

Individually, each blood-pressure-associated common variant exerts a very small effect, on the order of a fraction of a millimeter of mercury, but their aggregate effect, captured through polygenic risk scores, can meaningfully stratify individuals—including adolescents—into higher- and lower-risk categories for elevated blood pressure trajectories and subsequent hypertension [24].

Gene-Environment Interaction in Adolescent Blood Pressure Regulation

Genetic susceptibility to hypertension does not act in isolation. Adolescence is a period of substantial physiological and behavioral change—pubertal hormonal shifts, rapid growth, increasing autonomy over diet and physical activity, and, in some individuals, initiation of smoking or alcohol use—all of which can modulate the expression of underlying genetic risk [25,26]. Sodium-sensitivity variants, for example, appear to confer measurably greater blood pressure

elevation in the context of high dietary sodium intake, while physical activity and favorable body composition appear to attenuate the blood-pressure-raising effect of several risk alleles [27,28]. This gene-by-environment interaction provides a strong rationale for combining genetic risk information with lifestyle counseling during adolescence, when behavioral patterns are still being established and are more amenable to modification than later in life [29].

Genetic Determinants of Atherosclerosis and Early Dyslipidemia

Familial Hypercholesterolemia and Monogenic Dyslipidemia

Familial hypercholesterolemia (FH), most commonly caused by loss-of-function variants in the LDL receptor gene (LDLR), and less frequently by variants in APOB or gain-of-function variants in PCSK9 [9,30], represents the most clinically significant monogenic contributor to adolescent atherosclerosis risk. Heterozygous FH, present in approximately 1 in 250-300 individuals in most populations, is associated with markedly elevated LDL-cholesterol from birth and measurably accelerated subclinical atherosclerosis—detectable as increased carotid intima-media thickness—already evident in childhood and adolescence if untreated [31]. Because FH is substantially underdiagnosed, cascade genetic testing initiated through an affected adult relative, or universal/targeted lipid screening in early adolescence, is increasingly recommended as a strategy to identify affected youth before irreversible vascular damage accrues [14].

Apolipoprotein E and Lipoprotein Metabolism

The APOE gene, with its three common isoforms (epsilon-2, epsilon-3, epsilon-4), is among the most extensively studied determinants of lipid metabolism and atherosclerosis risk [8]. The epsilon-4 allele is consistently associated with higher LDL-cholesterol concentrations and increased coronary risk across the life course, with effects already measurable in pediatric and adolescent cohorts, while the epsilon-2 allele is generally associated with lower LDL-cholesterol but, in rare homozygous states, with type III hyperlipoproteinemia [32]. APOE genotype therefore represents an early, stable, and easily genotyped marker of inherited lipid risk that is relevant from adolescence onward.

Lipoprotein(a) and the LPA Locus

Plasma lipoprotein(a) [Lp(a)] concentration is one of the most strongly genetically determined cardiovascular risk traits, with the LPA locus accounting for the large majority of inter-individual variability [33]. Because Lp(a) levels are established early in life and remain relatively stable thereafter, elevated Lp(a)—present in approximately one in five individuals—identifiable from adolescence constitutes a lifelong, largely environmentally non-modifiable contributor to atherosclerotic risk. Current pediatric and adolescent lipid guidelines increasingly recommend at least one Lp(a) measurement, particularly in the context of a family history of premature atherosclerotic cardiovascular disease, given the locus's strong genetic determinism and the trait's clinical actionability as novel Lp(a)-lowering therapies progress through clinical development [34].

PCSK9 and Additional Lipid-Pathway Loci

Variants in PCSK9 illustrate the bidirectional nature of genetic risk: gain-of-function mutations cause autosomal dominant hypercholesterolemia and accelerated atherosclerosis [9], whereas loss-of-function variants—first identified in population studies of individuals with lifelong low LDL-cholesterol—are associated with substantially reduced cardiovascular risk, providing the genetic rationale that subsequently underpinned the development of pharmacological PCSK9 inhibitors. Beyond LDLR, APOB, PCSK9, and LPA, GWAS of coronary artery disease have identified several hundred additional loci of generally modest individual effect, spanning pathways of lipid metabolism, vascular inflammation, and smooth muscle cell biology, that collectively contribute to the polygenic burden of atherosclerosis detectable, in aggregate form, from adolescence [7,35,36].

Mitochondrial and Epigenetic Contributions

Beyond nuclear genetic variation, accumulating evidence implicates mitochondrial DNA heteroplasmy and epigenetic modifications—including DNA methylation at loci such as ABCG1 and CPT1A—in the early pathogenesis of atherosclerosis. Mosaic mitochondrial genetic variants have been detected within atherosclerotic lesions of the human aorta, suggesting that somatic mitochondrial mutation accumulation may interact with inherited nuclear

susceptibility to influence the rate of early plaque development [37,38]. While mechanistic understanding of these contributions in the specific context of adolescence remains incomplete, they represent an active area of investigation that may eventually refine genetic risk models beyond common-variant polygenic scores.

Polygenic Risk Scores and Translational Applications in Adolescence

Polygenic risk scores (PRS), which aggregate the effects of hundreds of thousands of common variants into a single quantitative risk estimate, have demonstrated the ability to identify individuals with cardiovascular risk comparable to that conferred by monogenic FH mutations, despite the absence of any single high-impact variant [10,24]. Because PRS can, in principle, be calculated from a single genotyping assay performed at any age, including early adolescence, they offer a theoretically attractive tool for risk stratification well before clinical risk factors such as elevated LDL-cholesterol or blood pressure become apparent.

Several practical and ethical considerations currently limit the routine adolescent application of PRS. Most existing scores were developed and validated predominantly in adult European-ancestry cohorts, raising concerns about transportability across ages, ancestries, and populations such as those of the Russian Federation [36]. The clinical actionability of a high polygenic score in an otherwise healthy adolescent—absent monogenic disease or markedly abnormal lipid/blood pressure values—remains an area of active debate, as does the psychological impact of disclosing lifelong genetic risk information to minors and their families. Nevertheless, in the specific context of a family history of premature atherosclerotic cardiovascular disease or borderline lipid/blood pressure values, integration of polygenic and monogenic genetic information with conventional risk factors may refine adolescent risk stratification and help prioritize more intensive lifestyle counseling or, where appropriate, pharmacological intervention [2].

Implications for Prevention and Future Directions

The convergence of developmental, genetic, and epidemiological evidence supports a shift toward earlier, genetically informed cardiovascular risk assessment beginning in adolescence [11]. Practical implications include: targeted lipid and family-history-based screening to identify FH and severely elevated Lp(a) [31,33]; consideration of monogenic hypertension syndromes in adolescents with early-onset or treatment-resistant hypertension [15]; incorporation of family history and, where available, polygenic risk information to identify adolescents who would benefit from more intensive dietary, physical activity, and smoking-prevention counseling [28,39]; and continued investment in large, ancestrally diverse pediatric and adolescent genetic cohorts to improve the accuracy and generalizability of polygenic risk tools.

Future research priorities include longitudinal validation of polygenic risk scores specifically within adolescent populations, clarification of optimal communication strategies for genetic risk information in minors, integration of epigenetic and mitochondrial markers with established nuclear genetic determinants [38], and pragmatic trials testing whether genetically informed risk stratification in adolescence translates into improved long-term cardiovascular outcomes relative to conventional risk-factor-based screening alone [40].

Conclusion

Arterial hypertension and atherosclerosis have substantial genetic determinants that are already biologically active during adolescence, ranging from rare monogenic syndromes with direct therapeutic implications to highly polygenic architectures shared with adult disease. Recognition of this genetic substrate, together with its interaction with diet, physical activity, and other modifiable exposures during a developmentally critical period, offers a rational basis for earlier identification of at-risk adolescents and for more individualized, mechanistically grounded prevention strategies. Continued research into population-specific genetic architecture, polygenic risk score validation, and the ethical framework for genetic risk disclosure in minors will be essential to translate these advances into adolescent clinical practice.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

All authors contributed to the conception, literature analysis, drafting, and critical revision of this review and approved the final version for submission.

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