

GENETIC DETERMINANTS OF ARTERIAL HYPERTENSION IN PEDIATRIC PRACTICE: FROM MONOGENIC FORMS TO POLYGENIC RISK AND EPIGENETIC REGULATION

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ABSTRACT

Arterial hypertension in children and adolescents is no longer an exclusively adult disease: elevated blood pressure and vascular changes are detectable within the first two decades of life, and a substantial proportion of this inter-individual variability is genetically determined, with heritability estimates of 30-60%. This review synthesizes current evidence on the genetic architecture of pediatric hypertension across three levels of regulation. First, rare monogenic forms with Mendelian inheritance-caused by mutations in the renin-angiotensin-aldosterone system, renal ion transporters, and adrenal steroidogenic enzymes-present with severe, early-onset, treatment-resistant hypertension and respond to pathway-specific pharmacotherapy once diagnosed. Second, the polygenic architecture of essential hypertension is traced from candidate-gene studies to genome-wide association studies, culminating in the Consortium of Childhood Blood Pressure meta-analysis of 28,425 children, which identified eight loci and only moderate genetic correlation ($r_g = 0.4-0.7$) with adult blood pressure, implying age-specific effects. We discuss the translational potential and limitations of polygenic risk scores derived from childhood data for predicting adult cardiovascular outcomes. Third, epigenetic mechanisms-DNA methylation of obesity- and sodium-transport-related genes, and persistent effects of prenatal tobacco exposure-mediate gene-environment interaction and represent the most therapeutically tractable layer of regulation. Finally, we address the emerging role of pharmacogenetics in guiding antihypertensive therapy. We conclude that a tiered approach integrating clinical suspicion of monogenic disease, polygenic risk stratification, and awareness of reversible epigenetic contributors offers the most promising path toward personalized pediatric hypertension care, while noting the predominance of European-ancestry cohorts as a limitation requiring multi-ethnic validation.

KEYWORDS: pediatric hypertension; monogenic hypertension; genome-wide association study; polygenic risk score; DNA methylation; blood pressure genetics

1. INTRODUCTION

Pediatric hypertension is now recognized as a strong predictor of adult cardiovascular morbidity and mortality, with twin and family studies placing the heritability of blood pressure at 30-60% [1-4]. The International Childhood Cardiovascular Cohort (i3C) Consortium, pooling seven long-running pediatric cohorts from the United States, Finland, and Australia, has shown that youth systolic blood pressure predicts adult cardiovascular events and correlates with self-reported hypertension in middle age [5-7]. This heritability, however, is not uniform across the life course: the genetic variants that influence blood pressure in childhood are only partially the same as those operating in adulthood, and environmental modifiers act on this genetic substrate from the earliest stages of development.

The genetic architecture underlying pediatric hypertension, however, is not a simple scaled-down version of the adult picture. Three features distinguish it. First, secondary and monogenic causes make up a disproportionately larger share of pediatric hypertension than of adult hypertension, since severe genetic syndromes tend to manifest early [8-9]. Second, the genetic determinants of blood pressure appear to shift across the life course: the largest genome-wide association study of childhood blood pressure to date found only a moderate genetic correlation ($r_g = 0.4-0.7$) with adult blood pressure traits, indicating that some variants exert age-restricted effects [10]. Third, childhood is the period in which environmental exposures-diet, physical activity, adiposity, prenatal tobacco exposure-interact most intensely with genetic predisposition, and epigenetic mechanisms are the molecular interface at which this interaction is thought to occur [11-12].

This review organizes the genetics of pediatric hypertension along these three levels: monogenic disease, polygenic risk, and epigenetic modulation, closing with a discussion of the clinical translation of this knowledge into genetic testing strategies and pharmacogenetically informed therapy. Figure 1 provides a conceptual framework for how these three levels interact and are integrated across the remainder of this review.

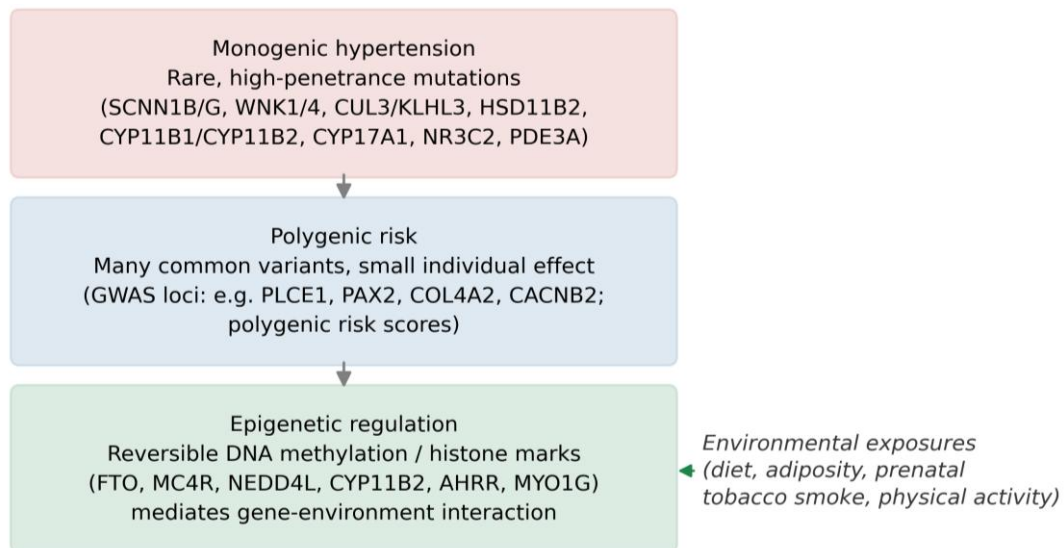


Figure 1. Three interacting levels of genetic and epigenetic regulation of pediatric blood pressure.

2. EPIDEMIOLOGICAL CONTEXT

Reported pediatric hypertension prevalence varies considerably by reference standard, population, and period of ascertainment, so absolute figures should be compared with caution. Depending on which normative standard is applied-2017 AAP criteria versus the older Fourth Report-estimated prevalence in the same population can shift by several percentage points, because the newer pediatric norms exclude overweight and obese children from the reference population, mechanically raising the proportion of children classified as hypertensive when compared with a leaner reference group [13-14]. Longitudinal US survey data spanning 1999-2023 illustrate this sensitivity: measured adolescent hypertension prevalence was lower in recent cycles than earlier ones, a pattern the authors attribute partly to secular changes in screening, reference norms, and methodology rather than a genuine decline in risk-and one that should not be read as evidence against the obesity-hypertension link [15]. Indeed, within every survey cycle and every reference standard examined, adiposity remained the dominant modifiable correlate of both elevated blood pressure and hypertension [15]. In children and adolescents with obesity, hypertension prevalence rises steeply, ranging from roughly 5% to over 30% depending on the degree of adiposity, with a reported four-fold increase in blood pressure abnormality among those with severe obesity compared with a two-fold increase in those with milder obesity [16]. This obesity-hypertension gradient is itself a clue to the underlying genetics, since several of the loci and epigenetic marks discussed below are shared between adiposity and blood pressure regulation, rather than being independent risk pathways that happen to co-occur [17-18].

3. MONOGENIC FORMS OF HYPERTENSION IN CHILDHOOD

Although polygenic essential hypertension accounts for the majority of pediatric cases, monogenic forms deserve disproportionate clinical attention. They typically present early, follow a severe and often treatment-resistant course, and-critically-are amenable to pathway-specific pharmacotherapy once the underlying mutation is identified [8-9]. Physiologically, nearly all monogenic hypertensive syndromes converge on a single final pathway: enhanced sodium reabsorption in the distal nephron, producing volume expansion, renin suppression, and variable aldosterone levels [8]. Table 1 summarizes the biochemical phenotype and targeted therapy of the principal syndromes discussed below, and the diagnostic algorithm in Figure 2 (section 3.5) outlines how they can be distinguished at the bedside using renin, aldosterone, and potassium.

Table 1. Major monogenic forms of pediatric hypertension, biochemical phenotype, and targeted therapy

Syndrome	Gene(s)	Inheritance	Renin	Aldosterone	Serum K+	Targeted therapy
Liddle syndrome	SCNN1B, SCNN1G (rarely SCNN1A)	AD	Low	Low	Low	Amiloride, triamterene [24,25]
Gordon syndrome (PHA II)	WNK1, WNK4 (most common); CUL3, KLHL3 (rare, more severe)	AD (KLHL3 also AR)	Low	Normal/low	High	Thiazide diuretics [19,20]

Apparent mineralocorticoid excess	HSD11B2	AR	Low	Low	Low	Spirolactone/eplerone +/- low-dose dexamethasone [29,33]
Glucocorticoid-remediable aldosteronism	CYP11B1/CYP11B2 chimera	AD	Low	High	Low	Dexamethasone [34,35]
11beta-hydroxylase deficiency (CAH)	CYP11B1	AR	Low	Variable	Low	Glucocorticoid replacement +/- MR antagonist [40,41]
17alpha-hydroxylase deficiency (CAH)	CYP17A1	AR	Low	Variable	Low	Glucocorticoid + sex-steroid replacement [42,44]
Geller syndrome	NR3C2	AD	Low	Low	Low	Amiloride; worsens in pregnancy [46,47]
Hypertension with brachydactyly	PDE3A	AD	Normal	Normal	Normal	Standard antihypertensives; vascular mechanism [48,50]

3.1 Low-renin, hyperkalemic syndromes

Gordon syndrome (pseudohypoaldosteronism type II) is an autosomal dominant condition most commonly caused by mutations in WNK1 or WNK4, with rarer, typically more severe forms arising from their regulators CUL3 and KLHL3 (the latter also recessive) [19-21]. These kinases and their regulatory partners normally restrain activity of the thiazide-sensitive sodium-chloride cotransporter (NCC) in the distal convoluted tubule; loss of that restraint drives excessive sodium and chloride reabsorption, producing the syndrome's hallmark triad of hypertension, hyperkalemia, and hyperchloremic metabolic acidosis despite preserved renal function [19-20]. Genotype predicts phenotype severity: patients with heterozygous CUL3 variants tend to present earlier, with more pronounced hyperkalemia, more severe acidosis, and greater growth impairment, than those with the more common WNK1 or WNK4 variants [21-22]. Because the pathophysiology converges on NCC, thiazide diuretics are effective and often diagnostic in their own right, normalizing blood pressure and electrolytes within days [19,23].

Box 1. Clinical Vignette

A 7-year-old boy presents with resistant hypertension (150/95 mmHg), hypokalemia (K^+ 2.9 mmol/L), metabolic alkalosis, and suppressed plasma renin activity with low aldosterone. Targeted sequencing identifies a heterozygous pathogenic variant in SCNN1B. Amiloride is started, with normalization of blood pressure and potassium within 72 hours-illustrating how a single genetic result redirected therapy away from empirical polypharmacy and toward a mechanism-specific, curative regimen.

3.2 Low-renin, hypokalemic syndromes

Liddle syndrome is caused by gain-of-function mutations in SCNN1B or SCNN1G (and, more rarely, SCNN1A), the genes encoding the beta- and gamma-subunits of the epithelial sodium channel (ENaC) [24-25]. The mutations typically truncate or otherwise disrupt a PY motif required for channel internalization and degradation, leaving constitutively active ENaC at the apical membrane of the distal nephron. The clinical consequence is early, severe, salt-sensitive hypertension accompanied by hypokalemia, metabolic alkalosis, and suppressed renin and aldosterone. A systematic review of 54 published pediatric cases found hypertension in the great majority, with hypokalemia and suppressed renin present in over 80% and nearly 100% of cases respectively [26-27]. As with Gordon syndrome, the response to targeted therapy—here, ENaC blockers such as amiloride or triamterene—is essentially pathognomonic, and several case series describe blood pressure and potassium normalizing within a narrow treatment window once the correct diagnosis is made [24,28]. Box 1 illustrates this principle with a representative pediatric case in which genetic confirmation of Liddle syndrome redirected therapy from empirical polypharmacy to a mechanism-specific regimen.

Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder caused by loss-of-function mutations in HSD11B2, encoding 11beta-hydroxysteroid dehydrogenase type 2, the enzyme that normally inactivates cortisol to cortisone within mineralocorticoid-receptor-expressing tissues [29-30]. When this enzymatic shield fails, cortisol—present at concentrations several orders of magnitude higher than aldosterone—floods the unprotected mineralocorticoid receptor, producing a clinical picture that mimics primary hyperaldosteronism: early-onset hypertension, hypokalemia, metabolic alkalosis, and suppressed renin, but with aldosterone itself low or undetectable [29,31]. A systematic review of over 100 genetically confirmed AME cases found homozygous HSD11B2 mutations associated with lower birth weight, and identified nephrocalcinosis in nearly 80% of patients, underscoring that this syndrome carries lasting renal consequences if unrecognized [32].

The diagnostic biochemical signature is an elevated urinary free cortisol-to-cortisone ratio, and treatment relies on mineralocorticoid receptor antagonists such as spironolactone or eplerenone, sometimes supplemented with low-dose dexamethasone to suppress endogenous cortisol production [29,33].

Glucocorticoid-remediable aldosteronism (GRA, familial hyperaldosteronism type I) arises from unequal meiotic crossing-over between the closely homologous CYP11B1 (11 β -hydroxylase) and CYP11B2 (aldosterone synthase) genes, producing a chimeric gene whose product retains aldosterone-synthesizing capacity but falls under the transcriptional control of adrenocorticotrophic hormone rather than the renin-angiotensin system [34-35]. The result is ACTH-driven, rather than renin-driven, aldosterone overproduction, producing early hypertension with hypokalemia, low renin, and elevated aldosterone that responds specifically to dexamethasone suppression. GRA carries a distinctive and clinically consequential risk beyond blood pressure itself: intracranial aneurysms and hemorrhagic stroke occur in a substantially elevated proportion of patients, historically estimated near 14% at a mean age of only 32 years, which justifies a lower threshold for screening MR angiography once the diagnosis is confirmed [36-37].

3.3 Congenital adrenal hyperplasia variants associated with hypertension

Two enzymatic defects in adrenal steroidogenesis produce hypertension by allowing mineralocorticoid precursors to accumulate upstream of the enzymatic block, distinguishing them sharply from the far more common 21-hydroxylase deficiency, which does not cause hypertension.

11 β -hydroxylase deficiency (CYP11B1) accounts for roughly 5-8% of congenital adrenal hyperplasia in populations of European ancestry, rising considerably where consanguinity is common [38-39]. Loss of enzyme activity blocks conversion of 11-deoxycortisol to cortisol and of 11-deoxycorticosterone (DOC) to corticosterone; DOC accumulates and exerts potent mineralocorticoid activity, while diversion of precursors into the androgen pathway virilizes affected females. Hypertension develops in roughly two-thirds of pediatric patients, usually of moderate severity, though severe courses have been documented [40-41].

17 α -hydroxylase/17,20-lyase deficiency (CYP17A1) is considerably rarer, accounting for roughly 1% of congenital adrenal hyperplasia, but is instructive because it combines mineralocorticoid excess with impaired sex-steroid synthesis [42-43]. The enzymatic block prevents synthesis of both cortisol and sex steroids, again allowing DOC and corticosterone to accumulate; the clinical picture in a large pooled cohort of 465 patients from a global meta-analysis included hypertension in 57%, hypokalemia in 45%, and primary amenorrhea in 38%, with disorders of sexual development frequently the presenting feature that ultimately prompts the correct diagnosis [42]. Management combines glucocorticoid replacement, which suppresses the ACTH drive behind mineralocorticoid overproduction, with sex-steroid replacement timed to physiological puberty [44-45].

3.4 Other monogenic syndromes

Geller syndrome results from a gain-of-function mutation in NR3C2, the gene encoding the mineralocorticoid receptor itself, most classically the S810L substitution first described in 2000 [46]. The mutation broadens receptor ligand specificity so that progesterone, normally a mineralocorticoid-receptor antagonist, instead becomes an agonist. Because progesterone concentrations rise sharply during pregnancy, the syndrome characteristically presents or dramatically worsens in pregnant carriers, producing severe hypertension and hypokalemia that resolve promptly after delivery, when progesterone levels fall [46-47].

Hypertension with brachydactyly (Bilginturan syndrome) is caused by mutations clustered in a small regulatory region of PDE3A, encoding a cyclic-AMP phosphodiesterase expressed in vascular smooth muscle [48-49]. The mutations increase protein kinase A-mediated phosphorylation of PDE3A, producing a gain-of-function enzyme with heightened cAMP-hydrolytic activity that drives vascular smooth muscle proliferation and increased peripheral resistance. The resulting hypertension is unusual among monogenic forms in being salt-independent yet age-dependent, rising progressively through childhood and adolescence, and it carries a severe natural history: untreated patients have historically died of stroke before age 50 [48,50]. Because the mechanism is vascular rather than renal, brachydactyly type E of the hands and feet—a skeletal marker unrelated to the pressor mechanism itself—serves as a valuable clinical flag prompting genetic testing in a child with otherwise unexplained severe hypertension [51-52].

3.5 A pragmatic diagnostic approach

Given the number and rarity of individual monogenic syndromes, indiscriminate genetic testing of every hypertensive child is neither efficient nor recommended [8-9]. Clinical suspicion should instead be raised by early onset, disproportionate severity, a family history of early-onset hypertension, consanguinity, or unexplained hypo- or hyperkalemia [9]. Figure 2 outlines the resulting work-up: plasma renin activity provides the first branch point, separating low-renin monogenic states from renin-normal or renin-high presentations that instead warrant evaluation for secondary causes or polygenic hypertension; aldosterone concentration and serum potassium then narrow the differential to a specific syndrome and drug class. Concretely, the algorithm begins with plasma renin activity: a low level directs attention toward the monogenic syndromes discussed above, whereas normal or elevated renin should instead prompt evaluation for renal parenchymal disease, renovascular causes, or polygenic essential hypertension. Within the low-renin subset, aldosterone concentration and serum potassium further stratify patients: low aldosterone with hypokalemia suggests Liddle syndrome or apparent mineralocorticoid excess; low aldosterone with hyperkalemia points toward Gordon syndrome; and high aldosterone with hypokalemia raises suspicion for glucocorticoid-remediable aldosteronism. This stepwise approach narrows the differential to a single syndrome and guides the choice of confirmatory genetic testing. A positive genetic

diagnosis is not merely academic: it spares children from prolonged, ineffective, and potentially harmful empirical polypharmacy [9].

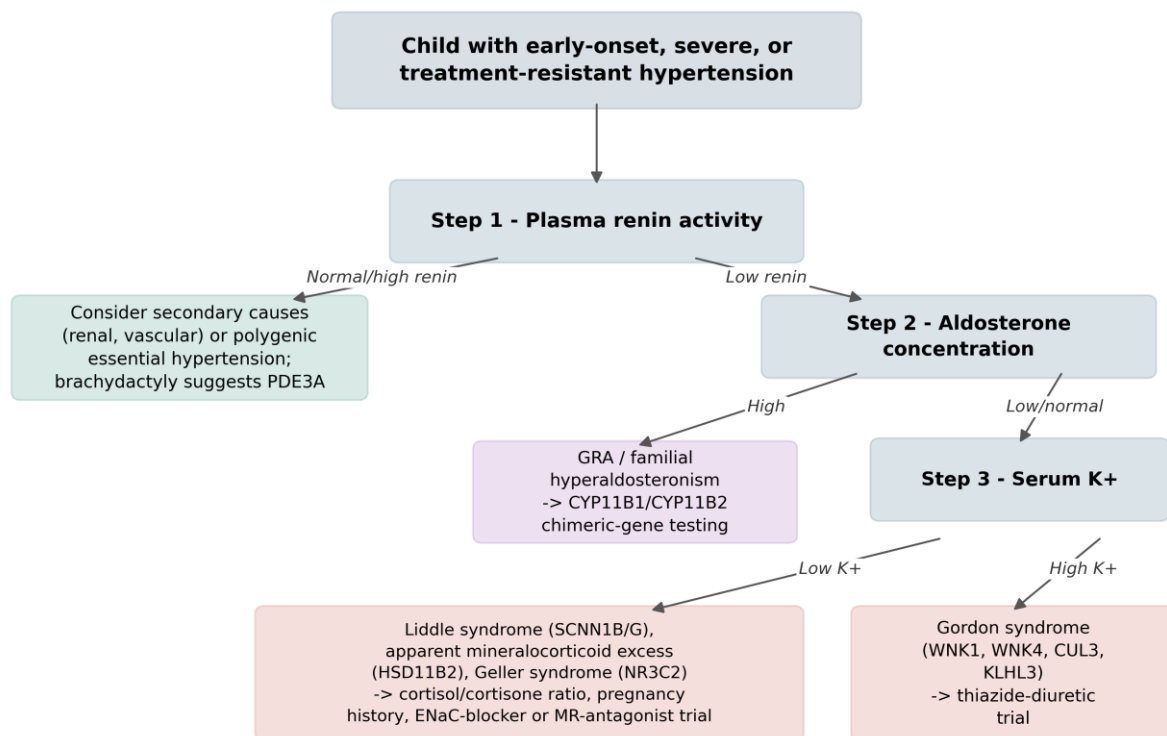


Figure 2. Diagnostic algorithm for suspected monogenic hypertension in a child, based on plasma renin activity, aldosterone concentration, and serum potassium.

4. POLYGENIC ARCHITECTURE OF PEDIATRIC HYPERTENSION

4.1 Candidate-gene era

Before genome-wide approaches became feasible, blood pressure genetics was pursued through hypothesis-driven candidate-gene studies, focused overwhelmingly on the renin-angiotensin-aldosterone system. The insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) gene remains the most extensively studied of these variants; the D allele has been repeatedly, though not universally, associated with higher blood pressure and, in pediatric chronic kidney disease cohorts, with a substantially elevated risk of hypertension and progression of renal damage, with one pediatric hemodialysis series reporting hypertension in roughly 89% of DD-genotype patients compared with 61% of non-DD patients [53-54]. Larger analyses in other populations have been more equivocal: a retrospective analysis of the Strong Heart Study, a large American Indian cohort, failed to replicate an association between ACE I/D and hypertension outright, illustrating the broader reproducibility problems that have affected the candidate-gene era across ancestries [54-55].

The M235T polymorphism of the angiotensinogen gene (AGT) has shown a similarly inconsistent pattern: several studies report a significant association between the T allele and essential hypertension, including modestly improved blood pressure response to ACE inhibitor therapy in TT homozygotes, while other analyses find none [55-58]. Table 2 summarizes these and other candidate-gene and genome-wide findings alongside their pediatric relevance. The Gly460Trp polymorphism of the alpha-adducin gene (ADD1), once proposed as a marker of salt-sensitive hypertension, illustrates the problem still more starkly: a meta-analysis pooling over 14,000 hypertensive cases and nearly 16,000 controls found no overall association with hypertension risk, even as smaller studies in specific populations continued to report positive associations [59-62]. Taken together, the candidate-gene literature demonstrates both the biological plausibility of renin-angiotensin pathway genes and the practical limits of underpowered, ethnically heterogeneous case-control designs for detecting genuinely small effect sizes.

4.2 The genome-wide association era in adults

Genome-wide association studies (GWAS) removed the requirement for a prior biological hypothesis, scanning the genome for statistically robust associations. Early efforts, including the 2007 Wellcome Trust Case Control Consortium scan, were underpowered and yielded no genome-wide significant hits for hypertension; this period and its methodological limitations are reviewed in detail elsewhere [63]. The field's first breakthrough came with the 2009 CHARGE consortium analysis, which identified the first replicated common variants for systolic and diastolic blood pressure [64]. This was superseded in 2011 by the International Consortium for Blood Pressure Genome-Wide Association Studies, which combined roughly 69,000 individuals for discovery and 133,000 for replication and identified 29 genome-wide significant loci implicating previously unsuspected biological pathways [65]. A composite genetic risk score built from these 29 variants was subsequently shown to associate not only with hypertension but with left ventricular wall thickness, stroke, and coronary artery disease [65].

Subsequent, larger efforts—including meta-analyses exceeding 300,000 participants—have continued to expand the catalogue of blood-pressure-associated loci into the hundreds, collectively explaining approximately 20-30% of the estimated heritability of blood pressure and leaving a substantial "missing heritability" gap [66-68]. Figure 3 places these adult milestones on the same timeline as the pediatric and epigenetic studies discussed below.

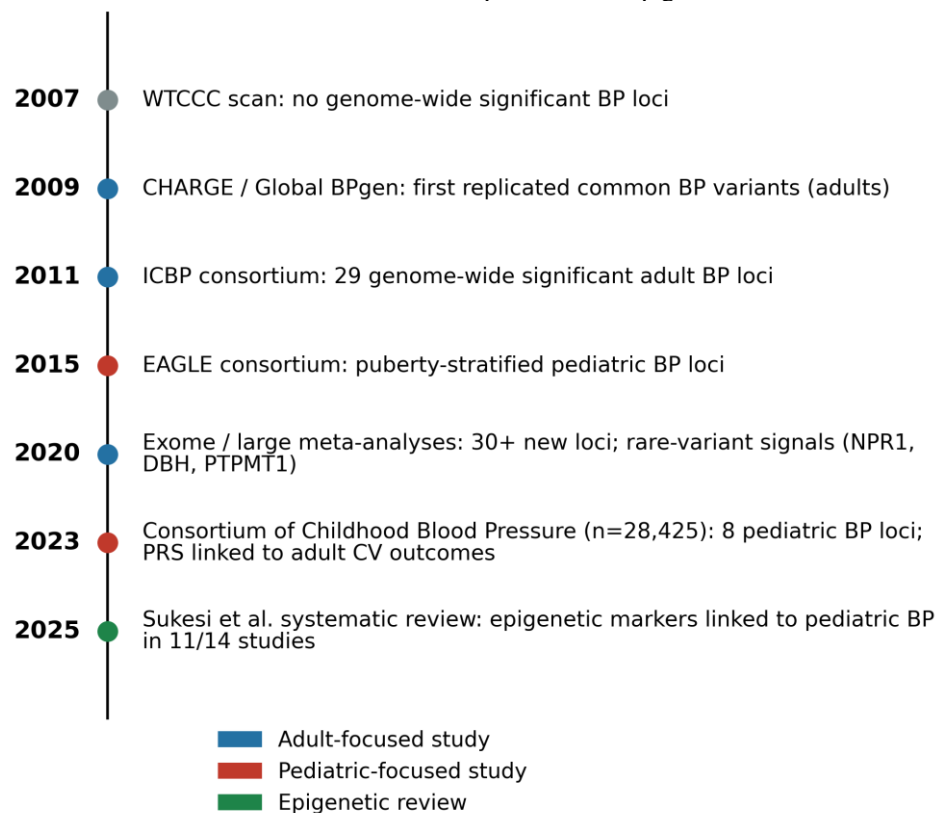


Figure 3. Timeline of major genome-wide and epigenome-wide milestones in blood pressure genetics (adult vs. pediatric).

4.3 Pediatric genome-wide association studies

Translating this adult GWAS architecture to children required dedicated pediatric cohorts, since childhood blood pressure is measured differently, varies with pubertal stage, and—as later became clear—is not governed by an identical set of genetic variants. An early effort by the international EAGLE (Early Genetics and Lifecourse Epidemiology) consortium, stratifying by pubertal stage, identified several loci reaching genome-wide significance within specific developmental windows—prepubertal, pubertal, and postpubertal—with limited overlap between them, an early hint that genetic effects on blood pressure are not constant across childhood [69]. Parental and offspring contributions of adult blood pressure genetic markers in early life have also been explored in family-based designs [70].

The definitive pediatric effort to date is the Consortium of Childhood Blood Pressure meta-analysis, combining 28,425 children of European ancestry aged 4 to 17 years across 22 studies for blood pressure traits, and a further 22,565 children across 16 studies for resting heart rate [10]. This analysis identified eight independent genome-wide significant loci for childhood blood pressure traits—three for systolic pressure, two for diastolic, and three for pulse pressure, with no overlap among categories—mapping to genes including KIAA2013, CACNB2, PLCE1, PAX2, COL4A2, CFDP1, and TPX2 [10]. Every one of these loci had previously been implicated in adult blood pressure GWAS, indicating substantial mechanistic continuity across the life course. Yet the genetic correlation between childhood and adult signals was only moderate, 0.4 to 0.7, meaning that a meaningful share of the genetic influence on childhood blood pressure reflects age-restricted biology rather than simply an early echo of adult genetic risk [10]. This argues against simply importing adult polygenic scores wholesale into pediatric risk stratification, and instead motivates continued dedicated pediatric genetic research.

4.4 Polygenic risk scores and their translational potential

Polygenic risk scores (PRS) aggregate the individually modest effects of many genetic variants into a single quantitative index of genetic liability. In the Consortium of Childhood Blood Pressure analysis, PRS derived from the childhood GWAS explained up to approximately 1.6% of blood pressure variance and up to 5.2% of heart rate variance in an independent pediatric replication sample—modest figures that are nonetheless consistent with the small per-variant effect sizes expected under a polygenic model, and which can still meaningfully stratify population-level risk [10]. Notably, the predictive utility of a blood-pressure PRS may be higher in childhood than in adulthood, as the genetic signal is less confounded by decades of accumulated environmental and lifestyle exposures, thereby making the pediatric period a uniquely informative window for early risk stratification.

The more clinically striking finding came from applying these childhood-derived PRS to UK Biobank adults: individuals with higher childhood blood pressure PRS showed significantly elevated risk across adult cardiometabolic outcomes, including hypertension, angina, myocardial infarction, and cardiovascular mortality [7,10]. This provides direct genetic evidence, independent of any measured childhood phenotype, that early-life genetic predisposition to elevated blood pressure carries forward into measurable adult disease risk. A further layer of complexity emerges when comparing hypertensive children with and without obesity: a study assessing 48 metabolically relevant SNPs in 436 hypertensive pediatric patients and young adults found significant allele-frequency differences at five loci (rs6232, rs6235, rs12145833, rs59744560, rs9568856) between obese and non-obese hypertensive participants, suggesting at least partially distinct genetic architectures underlie adiposity-driven and non-adiposity-driven pediatric hypertension [18,71]. This reinforces the case for phenotypically stratified genetic research, rather than treating pediatric hypertension as a single genetically homogeneous entity.

Table 2. Selected candidate-gene and genome-wide association findings relevant to pediatric blood pressure

Gene/locus	Variant/study	Population	Key finding
ACE	I/D polymorphism	Pediatric CKD cohorts	DD genotype linked to hypertension (~89% vs ~61% for non-DD) and renal progression [53,54]
AGT	M235T	Multiple studies/meta-analyses	Inconsistent association with essential hypertension across studies [55-58]
ADD1	Gly460Trp	22-study meta-analysis (n>30,000)	No overall association with hypertension risk [59]
ICBP loci	29 genome-wide significant SNPs	~202,000 adults (discovery+replication)	First large adult BP GWAS catalogue; risk score linked to LV mass, stroke, CAD [65]
Consortium of Childhood BP	8 genome-wide significant loci	28,425 children, European ancestry	Loci include PLCE1, PAX2, COL4A2, CACNB2; rg=0.4-0.7 with adult BP [10]
FTO (rs9939609)	Obesity x BP interaction	3,494 Chinese children	AA genotype amplifies obesity-associated hypertension risk (OR up to ~10) [17]

5. EPIGENETIC MECHANISMS: WHERE GENOME MEETS ENVIRONMENT

Epigenetics refers to stable, and at least partially reversible, modifications of the genome—including DNA methylation and histone modification—that regulate gene expression in response to environmental cues without altering the underlying DNA sequence. This layer of regulation has become central to understanding how genetic predisposition and environmental exposure jointly shape pediatric blood pressure. A 2025 systematic review by Sukesı and colleagues, synthesizing 14 observational studies, found that 11 of the 14 (nearly 79%) reported a significant association between epigenetic markers and blood pressure outcomes in children and adolescents [11]. Three mechanistic threads recur across this literature.

First, DNA methylation at obesity-associated loci—including FTO, MC4R, PAX5, and LSS—has repeatedly been linked to childhood blood pressure, offering a plausible molecular bridge between early adiposity gain and subsequent hypertension [11,17]. The FTO rs9939609 variant illustrates this interaction concretely: in a large cohort of over 3,400 Chinese children, the effect of obesity on blood pressure was substantially amplified in carriers of the AA genotype compared with TT carriers, with odds ratios for high blood pressure among obese children ranging from roughly 4.3 in TT carriers to over 10 in AA carriers, demonstrating a genuine gene-by-adiposity interaction rather than two independent risk factors [17]. Not every study finds a direct methylation-blood pressure relationship at this locus, however—one investigation of FTO methylation and expression in obese children found significant correlations with adiposity measures but not with blood pressure itself, underscoring that the epigenetic signal is present but not yet fully consistent across cohorts and methodologies [72-73].

Second, epigenetic regulation of genes governing renal sodium transport—including ADD1, CYP11B2, NEDD4L, and HSD3B1—may modulate an individual's sensitivity to dietary salt loading independent of any coding-sequence variant [11]. NEDD4L is a particularly well-characterized example: it encodes an E3 ubiquitin ligase that tags the epithelial sodium channel for degradation, and functional variants have been associated with salt sensitivity, altered plasma renin, and differential blood-pressure response to diuretic and beta-blocker therapy, positioning it as a plausible node for epigenetic modulation layered atop the coding-sequence variation described in the monogenic syndromes above.

Third, prenatal environmental exposures leave a durable epigenetic signature that persists into childhood and correlates with later cardiometabolic risk. Maternal smoking during pregnancy is the best-studied example: large epigenome-wide meta-analyses have identified dozens of differentially methylated CpG sites in offspring cord blood, concentrated in genes including AHRR, MYO1G, CYP1A1, CNTNAP2, and FRMD4A [74-76]. Several of these changes are not transient neonatal artifacts: longitudinal follow-up through adolescence shows that methylation at AHRR, MYO1G, CYP1A1, and CNTNAP2 remains persistently perturbed years after birth, independent of the child's own subsequent smoke exposure, while a smaller set of sites (GFI1, KLF13, ATP9A) shows partial reversibility over time [76-78]. One adolescent cohort found that methylation at an FTO-associated CpG site linked to maternal smoking was significantly associated with diastolic blood pressure in female offspring, directly linking a defined prenatal exposure to a measurable adolescent cardiovascular phenotype [77].

An important methodological caution runs through this literature. Several studies use the terms "genetic" and "epigenetic" loosely or interchangeably, particularly when reporting single-nucleotide polymorphisms alongside methylation data without clearly distinguishing the two [12]. A fixed germline polymorphism is not an epigenetic mark, and conflating the two risks overstating the maturity of the epigenetic evidence base specifically, since genuinely reversible, environmentally responsive methylation changes carry different biological and therapeutic implications than a static coding or regulatory variant inherited unchanged from a parent [11-12]. This distinction is not merely semantic: it is precisely the reversibility of true epigenetic marks that makes them the most therapeutically promising layer of the genetic architecture discussed in this review, and blurring the boundary between fixed genotype and malleable epigenotype risks misdirecting both research priorities and clinical expectations. It is worth emphasizing explicitly that the methylation marks listed in Table 3—including those in ADD1 and CYP11B2—are distinct from the germline polymorphisms in the same genes discussed in section 4.1; methylation reflects an environmentally responsive regulatory layer superimposed on the gene, not the fixed coding or regulatory variant itself, and the two should not be read as contradictory findings about the same locus.

Table 3. Epigenetic mechanisms linked to pediatric blood pressure

Exposure/mechanism	Genes/loci involved	Reported outcome
Obesity-related DNA methylation	FTO, MC4R, PAX5, LSS	Higher blood pressure; gene-by-adiposity interaction [11,17]
Renal sodium-transport methylation	ADD1, CYP11B2, NEDD4L, HSD3B1	Altered salt sensitivity of blood pressure [11]
Prenatal tobacco exposure	AHRR, MYO1G, CYP1A1, CNTNAP2, FRMD4A	Persistent methylation into adolescence; associated with diastolic BP [74-78]

6. PHARMACOGENETICS AND TOWARD PERSONALIZED THERAPY

For monogenic hypertension, genotype dictates therapy with unusual precision: ENaC blockers for Liddle syndrome, thiazide diuretics for Gordon syndrome, mineralocorticoid receptor antagonists for apparent mineralocorticoid excess, and dexamethasone for glucocorticoid-remediable aldosteronism and hypertensive congenital adrenal hyperplasia (Table 1, Figure 2) [8-9]. In each case, the causal mutation sits directly upstream of a druggable node in the same pathway, which is why genetic confirmation so reliably translates into an effective prescription.

For polygenic essential hypertension, pharmacogenetic evidence remains less mature but is not absent. ACE genotype has been proposed as a modest predictor of response to ACE inhibitors, and angiotensinogen TT genotype has similarly been linked to a somewhat greater blood-pressure-lowering response to enalapril than MM or MT genotypes [56,79]. Dedicated pediatric pharmacogenetic trials are lacking; most dosing regimens remain extrapolated from adult studies without genotype-based stratification [80-82]. ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers currently have the strongest pediatric evidence base, while data for beta-blockers, vasodilators, and pharmacogenetically guided dosing of any class lag considerably behind [80]. As sequencing costs fall and pediatric pharmacogenetic cohorts mature, incorporating polygenic risk scores and monogenic screening results into initial drug-class selection represents a plausible next step toward personalized pediatric antihypertensive therapy [8-9].

CONCLUSION

The genetics of pediatric hypertension has progressed from the study of rare, single-gene Mendelian syndromes to the mapping of a genuinely polygenic architecture, and now toward an integrated understanding that also accounts for reversible epigenetic modulation. Clinical suspicion and targeted biochemical screening for monogenic hypertension remain the priority in any child presenting with severe, early-onset, or electrolyte-associated hypertension, since an accurate genetic diagnosis directly determines effective, pathway-specific treatment and can prevent years of inappropriate empirical therapy. Polygenic risk scores derived in childhood, though still modest in the variance they explain, meaningfully predict adult cardiovascular outcomes and support earlier preventive intervention. Epigenetic mechanisms, particularly those linked to obesity and prenatal tobacco exposure, offer the most immediately actionable target for non-pharmacological intervention, precisely because they are, by definition, at least partially reversible.

The principal limitation across this body of work is its demographic narrowness: most large-scale genetic and epigenetic studies of pediatric blood pressure have been conducted in populations of European ancestry, and findings require dedicated validation in other ethnic groups before they can be assumed to generalize. Future research should focus on: (i) developing and validating multi-ethnic polygenic risk scores for childhood blood pressure; (ii) incorporating next-generation sequencing panels into routine work-up for suspected monogenic hypertension, and exploring salivary or buccal DNA methylation as a non-invasive epigenetic screening tool; (iii) applying machine-learning approaches to integrate polygenic, clinical, anthropometric, and epigenetic data into a single actionable risk estimate; and (iv) conducting randomized controlled trials of early lifestyle interventions (e.g., dietary sodium reduction, increased physical activity) stratified by genetic risk, to test whether modifying the childhood environment in high-genetic-risk individuals attenuates adult cardiovascular events. Integrating

genetic, epigenetic, and pharmacogenetic information into routine pediatric cardiology practice is the logical next step toward preventing, not merely treating, the adult cardiovascular consequences of pediatric hypertension.

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