MOLECULAR GENETIC MARKERS IN THE DEVELOPMENT OF ARTERIAL HYPERTENSION

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Abstract. Arterial hypertension (AH) has a pronounced genetic determination. A brief historical review of molecular genetic markers of AH is presented: from candidate genes (ACE, AGT, AGTR1, NOS3, etc.) to genome-wide association studies (GWAS) that have identified dozens of replicated small-effect loci (ATP2B1, CACNB2, CYP17A1, NPR3, UMOD, etc.), and to multi-omic approaches (epigenetics, microRNA). Polygenic risk scores are shown to improve prognosis accuracy beyond traditional factors, while pharmacogenetic signals outline personalized therapy choices. Limitations (ethnic tolerance, phenotyping) and prospects for integrating genetics with digital phenotyping to create clinically applicable, ethically verified tools for personalized cardiology are noted.

Keywords: candidate genes; GWAS; polygenic risk score; renin-angiotensin-aldosterone system; microRNA; pharmacogenetics; personalized medicine;

Arterial hypertension remains the leading cause of cardiovascular mortality and premature disability, with interindividual variability in risk and treatment response suggesting a significant genetic component. The relevance of a historical review of molecular genetic markers of hypertension lies in its twofold objective: first, to trace the evolution of scientific concepts—from the era of " candidate genes" to genome-wide association studies and multi-omic models; second, to critically evaluate the clinical transferability of these results for personalized prevention and treatment. A historical perspective allows us to understand how methodological standards (sample size, replication, phenotyping) have evolved, how the emphasis has shifted from the search for a "single master gene" to a polygenic architecture, and why the integration of genetics with epigenetics, transcriptomics , and 24-hour blood pressure monitoring data creates more realistic risk stratification tools.

Early research focused on candidate genes selected for their physiological relevance. The renin-angiotensin- aldosterone system was central: the I/D polymorphism of the ACE gene, M235T of angiotensinogen (AGT), and A1166C of the angiotensin II receptor (AGTR1) were repeatedly studied in cohorts of varying size and composition. These markers promised to link molecular variability with vasoconstriction , sodium retention, and myocardial remodeling . Genes encoding nitric oxide synthesis (NOS3 Glu298Asp), steroidogenesis (CYP11B2 -344C/T), intracellular signaling proteins (GNB3 C825T), and renal sodium transport

mechanisms (ADD1 Gly460Trp, WNK kinase) were also studied . Taken together, a physiologically compelling picture emerged: genetic predisposition modifies vascular tone, salt sensitivity , and circulating blood volume. However, limitations quickly emerged: suboptimal sample sizes, ethnic heterogeneity, risk of publication bias, and poor phenotyping (lack of 24-hour monitoring, mixing of office-based and "masked" hypertension). Many associations proved unstable when the cohort was expanded or the population was changed; individual SNPs explained a small proportion of the variance in blood pressure, which conflicted with the high heritability found in twin studies. These methodological lessons paved the way for the transition to the next paradigm.

The second stage is associated with genome-wide association studies (GWAS), in which hypotheses regarding specific "candidates" gave way to agnostic screening of hundreds of thousands of variants in large consortia and biobanks. It was here that a robust catalog of replicable loci of small effect sizes emerged, distributed across regulatory pathways of smooth muscle tone, calcium homeostasis, the natriuretic system, and channel transport. Signals near ATP2B1 (calcium currents), CACNB2 (calcium channels), CYP17A1 (steroidogenesis), NPR3 (natriuretic peptide receptors), and UMOD (Tall protein , associated with tubular function and salt sensitivity) are frequently reproduced. The strength of GWAS is statistical power, rigorous procedures for controlling false-positive results, and forced replication on independent samples; Weak—the small magnitude of individual effects and limited transferability of polygenic models across ethnic groups. Nevertheless, GWAS convincingly solidified the concept of the polygenic nature of hypertension and paved the way for polygenic risk scores (PRS), which summarize the contribution of hundreds and thousands of SNPs to the cumulative probability of developing hypertension.

The third, modern stage has added layers of regulatory biology—epigenetics and transcriptomics— to DNA sequence variability . Methylation patterns in promoter regions of RAAS genes, sodium transport channels, and inflammatory mediators, as well as microRNA expression profiles (e.g., miR-21, miR-155) link genetic background to environmental factors such as salt intake, obesity, stress, and physical activity. Unlike sequence variability, epigenetic marks are more flexible and therefore potentially modifiable through lifestyle measures and pharmacotherapy. Translationally, these layers enhance the biological plausibility of statistical associations, identifying specific mechanisms of vascular reactivity, renal tissue remodeling , and inflammatory cascades that can serve as targets for intervention.

The purpose of this review is to systematize the most reliable markers and their clinical implications based on historical data, determine the limits of applicability, and outline directions for further integration of genetic information into practice. Comparison of these stages reveals consistent results. First, a core of replicable loci associated with systolic and diastolic pressure in general population cohorts has been established. Their individual effects are small, but their combined effect is measurable and can improve prognostic accuracy. Second, PRS complement traditional risk factors and improve early stratification, especially in young and middle-aged patients, when clinical predictors are still moderately pronounced. Third, individual genetic variations demonstrate pharmacogenetic links with therapy response: variants in RAAS and ion transporter pathways are associated with differential efficacy of ACE inhibitors/ARBs, thiazide diuretics, and calcium channel blockers. While these results are still heterogeneous and not universally incorporated into guidelines, historical trends clearly point toward personalized therapy. Fourth, evidence of pleiotropy is accumulating: the same signals are associated with blood pressure and target organ damage—left ventricular hypertrophy, microalbuminuria , decreased eGFR , and subclinical atherosclerosis. This encourages network, causal analysis (including Mendelian randomization) to distinguish between cause- and effect-related markers.

The key methodological conclusions arising from this historical trajectory are the following. Rigorous phenotyping is becoming mandatory: repeated office measurements, 24-hour monitoring, distinguishing between "masked" and resistant hypertension, and taking into account body mass index, kidney function, and glycemic status reduce noise and improve the reproducibility of associations. Ethnic specificity requires local calibration of the PRS and independent replication: models trained on European data, without adjustment, lose accuracy in Asian, African, and mixed populations. Gene-environment interactions are another essential component of interpretation: the effect of UMOD, ADD1, and several channel variants is enhanced by a high-salt diet; obesity and low physical activity modify the strength of genetic predictors. Finally, functional annotation remains critical: many statistically robust signals require experimental confirmation of the mechanism.

The results of the historical analysis translate into practical implications at two levels. At the individual level, it is advisable to consider genetically informed risk stratification as an additional layer to clinical scales, especially with access to expanded phenotyping (ABPM, biomarkers) and lifestyle factor management.

This allows for flexible policy choices: in carriers of "risk" combinations associated with salt sensitivity , it is rational to restrict sodium more strictly and introduce diuretics earlier; in the presence of certain RAAS-blocking variants, ACE inhibitors/ARBs are preferable as a starting option. At the population level, polygenic indices and epigenetic signatures can be used for early screening in groups with low clinical "visibility," thereby shifting interventions to the preclinical stage. However, before large-scale implementation, an assessment of the added value relative to standard models, a cost-effectiveness analysis, and the development of an ethical and legal framework (protection of genetic data, informed consent, non-discrimination) are necessary.

An important part of the conclusion is the recognition of the limitations of current capabilities. Even the best PRSs explain only a fraction of the heritability of hypertension; the remainder is distributed among rare variants with large effects, structural rearrangements, complex interactions, and epigenetic dynamics. The transferability of models across populations is still limited; this is especially important for multi-ethnic countries, where the introduction of universal "Western" indices without local validation is fraught with systematic errors. Functional validation is a bottleneck: the speed of computational discovery exceeds the capabilities of experimental biology, and therefore priority should be given to signals with consensus replication, biological annotation, and clinical plausibility.

Conclusions . In summary, the historical development of molecular genetic markers of arterial hypertension is a progressive advancement from physiologically motivated single hypotheses to polygenic and multiomic risk models, reinforced by rigorous phenotyping and analytical standards. At each stage, expectations were adjusted: instead of "diagnostic SNPs," integrated panels were used; instead of universalism, population adaptation; instead of correlation, a striving for causal interpretation. As a result, a strategy in which genetic information is used as a modifier of clinical assessment, rather than its replacement, appears justified today: PRS and validated variations add accuracy in predicting the onset of hypertension and its complications; epigenetic and transcriptional markers outline potentially modifiable mechanisms; pharmacogenetic signals suggest individualized therapy choices. The scientific and practical significance of this approach lies in its opening a window for early, targeted interventions and the reallocation of healthcare resources toward the greatest expected impact, while maintaining caution and rigorous quality of evidence. The history of hypertension markers is not only a chronicle of ideas and

technologies, but also a set of scientific hygiene rules that help avoid past mistakes, correctly interpret new data, and gradually bring personalized cardiology closer to sustainable clinical practice.

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