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THE ROLE OF GENETICS IN THE DEVELOPMENT OF ARTERIAL HYPERTENSION

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Annotation: Hypertension is one of the causes of mortality and morbidity worldwide. Various studies of blood pressure have shown the influence of many factors on its pathogenesis, one of which is genetic mutations. The study of these genetic factors is essential for a better understanding of their role in the development of this disease, prevention and improved treatment.

Key words: hypertension, genetic factors, cardiovascular diseases, genetic mutations, locus.

Hypertension is one of the common diseases of the cardiovascular system. Moreover, 95% of patients have an unknown genesis of hypertension. Various family examinations have shown the presence of heredity in 30-50% of cases of hypertension. Genetic factors play an important role, along with environmental factors, age, patient sex, lipid levels, and obesity. To date, the main data in the study of arterial hypertension are genome-wide association studies (GWAS). GWAS provides detailed analysis of multiple single nucleotide polymorphisms (SNPs) in large study populations. These

studies have helped identify more than 100 SNPs that are associated with changes in blood pressure levels. [1] Susceptibility to end organ damage and blood pressure levels are often associated with hypertension and may be separately inherited. Studies of data on changes in blood pressure in a population over three generations have shown an important relationship between the development of the disease and heredity. Thus, in 30-50% of cases, the relationship between the development of hypertension and the presence of genetic factors has been proven. Research and data analysis have also identified about 280 different genetic variants for high blood pressure. Such genetic variants are also associated with the development of other cardiovascular diseases such as coronary heart disease. Although a significant effect of individual nucleotide polymorphisms (SNPs) on changes in systolic and diastolic pressure values was not observed, their cumulative effect is obvious. A huge risk factor for the development of arterial hypertension in patients is the presence of first- and second-degree relatives with arterial hypertension under the age of 55 years. [2] Data from GWAS studies were assessed to identify expression quantitative trait loci (eQTLs). Loci (eQTL) were divided into 2 categories: cis-eQTL and trans-eQTL. Cis-eQTLs are located within ≤1 Mb of the gene encoding the transcript. Trans-eQTLs influence distal gene expression levels and are involved in the regulation of disease susceptibility. According to the data obtained, up to 30% of mammalian genes are controlled by eQT loci, which contribute to the development of susceptibility to severe diseases.A statistical analysis of the weighted gene co-expression network (WGCNA) was also carried out, which helps to identify clusters of highly correlated genes. There is information about the influence of the FBN1 gene in the development of vascular damage. Interleukin-6 (IL-6) is a proinflammatory cytokine produced by macrophages and T cells that stimulates the immune response. It is responsible for the production of C-reactive protein in hepatocytes and is involved in the response to endothelial damage. Nitric oxide (NO) is a strong vasodilator and, of course, plays a critical role in the regulation of blood pressure. In a study conducted by Vecchione et al., 416 subjects had their haplotypes examined. They found that carriers of the rare haplotype exhibited a significant increase in diastolic blood pressure (DBP, $p = 0.013$), while systolic blood pressure

also increased, though to a lesser degree (SBP, $p = 0.067$). The authors also demonstrated that overexpression of the BPIFB4 gene in mice resulted in elevated blood pressure, offering new avenues for potential therapeutic interventions. Protein convertase subtilisin/pexin type 9 (PCSK9) is an enzyme that binds to subunits of the renal epithelial sodium channel (ENaC), promoting ENaC degradation and regulating sodium reabsorption. In a study involving 31 single nucleotide polymorphisms (SNPs), none of the combinations reached statistical significance ($p > 0.05$). However, the influence of rare genes, primarily nonsynonymous single nucleotide variations (SNVs) found in PCSK9, showed a significant association with DBP in the HyperGEN cohort ($p = 0.04$) and with SBP in the REGARDS study ($p = 0.04$). The variation in phenotypes was likely influenced by differences in the age of the study groups. [1] Genetic studies examining hypertension in the context of lipid spectrum disorders have produced promising results. A locus on chromosome 7q has been identified, linking blood pressure, fasting insulin, and leptin. Another locus associating familial combined hyperlipidemia, diabetes, and blood pressure has been found on chromosomes 1q21-q23. A similar locus may also exist on chromosome 4p. Additionally, the Lys198Asn variant in the endothelin-1 gene (located on 6p24-p23) appears to interact with BMI, potentially increasing the risk of hypertension in carriers of the 198Asn variant with a high BMI. The 460Trp variant of the adducin gene may also be related to BMI and triglycerides. The SA (SAH) gene variant is associated with increased BMI, waist/hip circumference ratio, triglycerides, and blood pressure. The Trp64Arg β-adrenergic receptor gene (ADRB3) is linked to some features of metabolic syndrome. Notably, changes in lipid levels are closely connected to hypertension, and a pleiotropic influence of lipid-associated loci on the development of hypertension can be hypothesized. Recent studies have identified three novel common variants in the BRAP, ACAD10, and ALDH2 genes at locus 12q24.12, reliably linked to both systolic blood pressure (SBP) and diastolic blood pressure (DBP). Furthermore, this locus exhibited associations with high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, plasma glucose, body mass index, and waist-to-hip circumference ratio. Subsequently, a longitudinal exome-wide association study (EWAS) focusing on

East Asian populations identified six hypertension-associated single nucleotide variants (SNVs) at locus 12q24.1. This East Asian-specific haplotype, consisting of five alleles, led to a significantly reduced incidence of hypertension compared to individuals carrying the common haplotype (mean odds ratio = 0.78, $p < 1.0 \times 10\text{-}8$). Moreover, using a recessive model, a SNV located in the COL6A5 gene was significantly associated with SBP (estimate: -2.93; $p = 2.3 \times 10\text{-}8$), highlighting the impact of stop codons on factors related to blood pressure through alterations in protein function. [1] It's also important to bring up the concept of monogenic arterial hypertension. Monogenic hypertension syndromes encompass hypertensive conditions that are inherited in a Mendelian manner due to mutations in a single gene. One example of such a syndrome is glucocorticoid-reducible aldosteronism (GRA), an autosomal dominant disorder that was the first recognized monogenic hypertension syndrome. GRA arises from the fusion of the promoter region of the CYP11B1 gene with the coding region of the CYP11B2 gene, located on chromosome 8q. This chimeric gene activates aldosterone production in response to ACTH, rendering it independent of renin regulation. Consequently, a significant amount of aldosterone is produced, leading to the retention of salt and water in the body, resulting in elevated blood pressure. Another syndrome is apparent mineralocorticoid excess (AME) syndrome, which is an autosomal recessive condition caused by a inactivating mutation in the HSD11B2 gene. This gene encodes the enzyme 11-hydroxysteroid dehydrogenase type II, responsible for converting cortisol into the less active cortisone. In cases of HSD11B2 gene mutations, excess cortisol accumulates and binds to the mineralocorticoid receptor, causing symptoms of mineralocorticoid excess. [4] Liddle syndrome is an autosomal dominant disorder caused by a gain-of-function mutation in the SCNN1B/SCNN1G gene, located on chromosome 16p. This gene encodes the α and β subunits of the epithelial sodium channel ENaC. The mutation leads to ENaC remaining on the cell surface of the cortical collecting tubules, preventing its removal. This results in increased sodium reabsorption and, consequently, hypertension. [5] It's worth noting that AGT (Angiotensinogen) is expressed in glial cells in the brain and individual neurons within the nuclei responsible for regulating the cardiovascular

system. When AGT and renin are overexpressed in neurons, it results in a modest increase in blood pressure. Research has shown that increased expression of renal AGT in the kidney, which also expresses all components of the renin-angiotensin system (RAS), can induce systemic hypertension without simultaneously altering the circulating Ang II levels. This discovery has been replicated by various research teams. Several studies have demonstrated a positive correlation between plasma AGT levels and blood pressure. The administration of antibodies against AGT has been observed to lower blood pressure, while the administration of AGT has led to an increase in blood pressure. One of the most compelling genetic pieces of evidence linking AGT to essential hypertension comes from a study conducted by Jeunemaitre et al. This study identified an association between a marker downstream of AGT and hypertension in siblings of Northern and Western European descent. Subsequently, this association was confirmed in white European and Afro-Caribbean populations but refuted in a separate large European group. Furthermore, a connection between AGT and preeclampsia (hypertension with proteinuria during pregnancy) has been reported in populations in the United States, Japan, and Europe. [6] A substantial body of knowledge has already been accumulated on this matter. Nevertheless, further research is required to enhance the management of hypertension, develop measures for preventing the onset of this condition, and mitigate its complications.

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