In the general population, blood pressure (BP) distribution is close to normal, which indicates a multifactorial etiology of essential hypertension, including both polygenetic and environmental factors. Tracing the natural history of hypertension is difficult because of the progress in the medical management of this condition and favorable changes to health care systems. As a result, a substantial number of hypertensive patients receive antihypertensive drugs that may affect changes in BP and hinder the analysis of genetic factors underlying hypertension. To perform genomic studies, first the extent of the genetic effect on the final phenotype of BP has to be elucidated.

Data from family studies and twin studies have provided evidence for moderate heritability of BP values. The heritability of office BP was estimated at 15% to 40% for systolic BP and 15% to 30% for diastolic BP, while for ambulatory BP monitoring, the proportion of the share of the genetic effect was reported to be 69% and 51% for systolic and diastolic BP, respectively. The importance of genetic factors is best documented by the observation from everyday clinical practice that the presence of parental hypertension in a family history is associated with a 4-fold higher risk of developing hypertension.

The use of modern genomics has enabled a more detailed search for genetic factors associated with BP. A polymorphism within each gene whose protein product is involved in the regulation of BP may have potential importance in the pathogenesis of hypertension. Genetic determinants of essential hypertension involve the participation of a large number of genes whose expression often depends on specific environmental factors, which is an additional challenge and difficulty for the study of genetics of hypertension as a complex phenotype. A significant portion of the variability of the human genome is constituted by single nucleotide polymorphisms (SNPs); variation here is defined as the substitution of nucleotides, leading to the formation of 2 (or more) variants of a gene (alleles), with the prevalence within the general population of more than 1%.

During the past 20 years, most researchers focused on the analysis of SNPs within the various genes encoding proteins involved in the regulation of BP (ie, candidate genes), as components of the renin–angiotensin–aldosterone system, natriuretic peptides, adrenergic receptors, or ion channels involved in renal reabsorption of sodium. Association analyses, the most commonly used in the population studies, are designed to compare the distribution of alleles of the same gene in unrelated patients with hypertension and in normotensive individuals.

It is anticipated that an allele of a particular gene is associated with the disease trait if it is observed with a much higher frequency in patients than in healthy subjects. The main disadvantage of this method is a high risk of false-positive results (if the trait under investigation is relatively frequent in the studied population, the association might be detected for each allele common in this particular population). Thus, the important prespecified conditions for genetic studies include a proper selection of cases and controls, adequate number of participants, ethnically homogeneous groups, and, above all, rigorous phenotyping.

G proteins represent the integral membrane cytoplasmic molecules acting as transmembrane biological signal amplifiers. They couple the receptors of hormones, biogenic amines, neurotransmitters with effectors acting inside cells, with the adenylate cyclase system, a metabolic pathway of inositol triphosphate or diacylglycerol or with ion channels. G proteins are built as heterotrimeric and consist of 3 subunits: α, β, and γ. The main functional domains (associated with hydrolysis of guanine triphosphate) are in the α subunit. The β and γ subunits of G proteins anchor the membrane and are involved in the interaction with
the receptor. Until now, the most investigated G-protein subunit with regard to the association with essential hypertension was the β3 subunit (GNB3).

The presence of the T allele of the C825T polymorphism is associated with the occurrence of alternative splicing, resulting in the creation of the β3 subunit that lacks 41 amino acids. It results in increased activity of the sodium-hydrogen exchanger (natrium-hydrogen exchanger). Consequently, the 825T allele is associated with an increase in intracellular signal transduction. In 3 large population studies originating from the German part of the MONICA project and the Belgian FLEMENGHO observational population study, the C825T polymorphism in the GNB3 gene has been associated with the prevalence of hypertension. In the long-term follow-up (mean, 4.7 years) of the HARVEST study participants, 825T allele of the C825T polymorphism in the GNB3 gene was associated with increased risk of hypertension and the necessity to start a pharmacological treatment.

In the current issue of the Polish Archives of Internal Medicine (Pol Arch Med Wewn), Hejduk et al reported the results of their study on the association of 5 different SNPs with another G protein subunit gene, namely, the G protein γ5 subunit (GNG5) and the risk of essential hypertension. The authors recruited 536 patients with essential hypertension and 302 controls. All hypertensive patients received antihypertensive medications, whereas BP value in controls was confirmed by at least 2 separate BP measurements on 2 different days. Three polymorphisms in the coding region and two polymorphisms in the promoter region of the GNG5 gene were analyzed. For the first time, a significant association between rs13093 (−195 C/A) polymorphism in the GNG5 gene and the prevalence of hypertension was observed. The odds ratio for essential hypertension associated with the presence of the −195A allele in the promoter region of the GNG5 gene was 2.9. Moreover, the other polymorphism within the promoter region of the GNG5 gene, rs41284589, showed an association with elevated levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, as well as with reduced levels of high-density lipoprotein cholesterol. Of note, both polymorphisms are located within the recognition sequence for transcription factors, which suggests the importance of the regulatory, and not only coding, parts of the human genome for the development of essential hypertension and metabolic disturbances. As the authors admit, their findings require validation in studies on a larger population of patients.

So far, studies on the association of SNPs in candidate genes with BP value, the presence of hypertension, or response to antihypertensive drugs (pharmacogenetic research) have shown a considerable inconsistency between research groups, which might have been caused by the small size of the populations studied, carelessly defined phenotype (based on a patient history or a single BP measurement), or the modulation of the genotype–phenotype relationship by environmental factors (eg, dietary sodium intake).

A specific type of the analysis of genetic factors in the pathogenesis of hypertension is the genome-wide association study (GWAS). These studies have become possible only with the development of molecular biology and genotyping possibilities on a large scale, resulting in a significant reduction in cost and time, as well as with the development of advanced genetic statistics. The largest GWAS conducted to date concerning the genetic determinants of BP was published by the International Consortium for Blood Pressure Genome-Wide Association Studies, based on the data of 200 000 people of European descent. The study identified 29 independent SNPs that were significantly associated with systolic or diastolic BP, 16 of which have not been described so far as an SNP associated with hypertension, including the NPPA and NPPB genes, encoding natriuretic peptides A and B, respectively. Surprisingly, the majority of SNPs identified in GWASs as being associated with BP are located in noncoding areas of the genome, thus it is still challenging to find their mechanisms of action. In addition, most GWASs analyzed BP as a quantitative trait, and only 2 studies analyzed hypertension as a dichotomous trait.

Despite detecting numerous SNPs for BP in GWASs, it is surprising that all of them have little impact and the cumulative percentage of inheritance explained so far is astonishingly low. The size of the effect of each individual SNP identified in the GWAS is small, usually 1 mmHg for systolic BP and 0.5 mmHg for diastolic BP. Even when 29 genetic variants were analyzed together, only 1% to 2% of the population’s BP variance could be attributed to them, which is a far lower proportion than BP heritability estimated in family or twin studies.

This led to the introduction of the term “missing heritability.” Currently, it is postulated that the “missing heritability” of hypertension may be caused by the existence of genetic variants in the population less widespread than the SNPs, while exerting a greater effect on the final phenotype (ie, BP). Unfortunately, a reliable research strategy that would allow to detect variants of this type has not been developed yet.

The new field of research is also epigenetics, a genetic variation which can be passed on during cell division without changing the DNA sequence. Epigenetics includes DNA methylation, histone posttranslational modifications, and others. The linking of SNPs detected in a GWAS with pathophysiological pathways leading to the development of hypertension will be the main challenge of genetic studies in primary hypertension in the near future. However, what is most important, in all studies on the genetic background of hypertension, the most limiting factor is the lack of a reliable assessment of the phenotype.
REFERENCES


