GENERAL

GENETIC DETERMINANTS IN ISCHEMIC HEART DISEASE

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Abstract: The present paper is a review of current knowledge about the relations between gene polymorphism and predisposition for ischemic heart disease. Many studies investigate polymorphic variants of genes whose protein products contribute to the genesis and development of atherosclerosis of coronary arteries, thrombogenesis and fibrinolysis and other processes significant for the progression of ischemic heart disease. In ischemic heart disease the most often analyzed genes are those connected with metabolism of lipids, the coagulation and fibrinolytic system and the renin-angiotensin-aldosterone system. Factors of inflammation (cytokines, TNF), proliferation of smooth muscles cells and vasoactivation are also important. Manifestation of the illness is connected with accumulation of several genetic determinants, while the clinical picture is additionally modified by environmental factors. Studies of genetic etiopathogenesis of ischemic heart disease may result in effective prevention and treatment in particular patients.

Keywords: genetic polymorphism, ischemic heart disease

Ischemic heart disease (IHD) is a complex of clinical symptoms of various pathogenesis caused by insufficient oxygen and nutritional compounds supply in relation to the actual requirements of the myocardium. In Poland we can observe high death rate caused by IHD, which results from common exposure to risk factors.

The most significant risk factors for ischemic heart disease include: atherogenic diet, smoking, lack of physical activity, obesity, excessive consumption of alcohol, disturbed lipids profile, high blood pressure, hyperglycemia, elevated concentration of homocysteine and fibrinogen, as well as factors which cannot be modified, such as male sex and age (above 55 years for men and above 65 years for women). An important role is also played by genetic factors which interacting with environmental factors, determine the clinical picture and course of ischemic heart disease. In the majority of cases accumulation of several genetic factors (polygeneity) is necessary for the manifestation of the illness. Besides, inheriting IHD is of heterogeneous character, which means that different patients with the same type of the illness may show different genetic factors.

Association studies by means of genetic markers are a commonly used method of investigating the genetic origin of ischemic heart disease. Genetic markers are polymorphic variants of genes whose protein products take part in the etiopathogenesis of processes important for the development, course and complications of IHD. Polymorphism is a monogenic feature resulting in situation when in a population at least two persons of 2 different genotypes with corresponding phenotypes can be found. The prevalence of each must be > 1%. Gene polymorphism is caused by genetically transmitted mutations in DNA. Point mutations related to single nucleotide polymorphism (SNP) due to substitution of a base pair are among the most common mutations of genes encoding such proteins. Other types of mutations such as deletion or insertion of a base pair are less frequent than single base pair substitution, with whole gene deletion or amplification being an extremely rare case.

In the investigations, the frequency of appearance of the genetic marker in sick persons is compared with that in general population or control group. The existence of an association between a given marker and the illness may be suspected when the marker is found significantly more often in sick persons than in the control group.

Genes whose polymorphisms seem to be potentially connected with a given illness are called

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candidate genes. Common genetic variations of polymorphic candidate genes contributing to ischemic heart disease are presented in Table 1 (1).

**Genes regulating lipid metabolism**

The most important genes connected with lipid metabolism are apolipoprotein B (ApoB) and E (ApoE) genes, cholesterol esters transporting protein (cholesterol ester transfer protein – CETP ) genes and genes of lipoprotein lipase (lipoprotein lipase – LPL ).

Apolipoprotein B (ApoB) is a protein component of membrane of low density lipoprotein (LDL). ApoB is responsible for the junction of LDL with a specific receptor and for proper uptake of LDL from blood stream. Several variants of polymorphic genes of ApoB have been found. The C516T variant was connected with elevated level of LDL, while studies of other variants did not bring any unequivocal results (2).

General polymorphism of ApoE gene significantly affects the lipid level in serum. The E4 variant of ApoE gene in many studies was found to be connected with an increase of the ischemic heart disease and myocardial infarction risk in young age patients. The E4 variant was also responsible for an increase of death risk in IHD and in myocardial infarction (3).

The cholesterol esters transporting protein (CETP) is an important regulator of the high density lipoprotein (HDL). In the case of the CEPT gene polymorphism B1 is responsible for the intensity of atherosclerosis in coronary arteries and for increasing the effectiveness of therapy by means of pravastatin – a drug of statins’ group lowering cholesterol concentration (4). The Ile405Val polymorphism seems to influence the result of the measurement of the intima-media thickening (IMT) of the carotid artery which is the atherosclerosis marker and which shows good correlation with the intensity of atherosclerotic lesions in coronary vessels (5).

Some polymorphic variants of the lipoprotein lipase (LPL) gene influence the enzyme activity, which is connected with the ischemic heart disease revelation. The LPL is responsible for the hydrolysis of triglycerides in chylomicrons and very low density lipoproteins (VLDL) leading to the formation of HDL molecules. It has been reported that polymorphism Ser474Ter of LPL gene significantly decreases the ischemic heart disease risk (high protective HDL concentration and low triglycerides level). No similar dependence has been observed for other variants of this gene (6).

Paraoxonase (PON1) is a glycoprotein connected with antioxidant properties of HDL. Three polymorphisms: T107C, Q192R and L55M modulate the enzyme activity, whereas results of studies of their influence on atherogenesis are ambiguous and they require further research (7).

The hepatic lipase (HL) gene is another interesting candidate gene. HL causes lipolysis of VLDL and conversion of HDL2 molecules into smaller HDL3 molecules. High level of the enzyme activity leads to an increase of LDL and thus increases the atherosclerotic risk. The -480C variant of the gene is connected with low enzyme activity and high HDL concentration. The HL promoter activity is higher in patients with -480C allele than in patients with -480T allele (8).

**Genes regulating inflammation**

Other important genes in the ischemic heart disease pathogenesis are genes regulating inflammation and influencing adhesion molecules. Polymorphisms of the following genes have been investigated — genes of: the tumor necrosis factor (TNF alpha and beta) transforming growth factor beta (TGF-beta 1), interleukin, CD14, selectine P and E, and platelet endothelial cell adhesion molecule (PECAM-1).

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**Table 1 Pathophysiological processes involving the appearance of protein products of ischemic heart disease candidate genes (1)**

| Lipid metabolism (apolipoproteins, lipolytic enzymes, receptors for lipoproteins) |
| Coagulation system and fibrinolysis (fibrinogen, thrombosis factors, plasminogen activator inhibitor type 1) |
| Platelet glycoproteins (GPIIb/IIIa, GP1a/IIa) |
| Renin-angiotensin-aldosterone system (angiotensinogen, angiotensin converting enzyme, AT1 receptor, aldosterone synthetase) |
| Vasoactive factors (ANP, BNP, CNP) |
| Factors of adhesion and migration for monocytes and macrophages |
| Inflammation factors (cytokines, tumor necrosis factor) |
| Proliferation factors of smooth muscle cells of vessels |
Genes of the renin – angiotensin – aldosterone system

Other investigated genes concern the renin – angiotensin – aldosterone system (RAA) which is considered an important factor in the etiopathogenesis of circulatory system diseases. Several studies focus on the polymorphism of genes coding particular elements of the RAA system and their connection with the predisposition for cardiovascular diseases. Particular attention is devoted to the angiotensin converting enzyme (ACE) connected with regulating blood pressure and keeping water-electrolyte balance in human organism. Insertia/deletia (I/D) type of polymorphism of the ACE gene is connected with the presence (I) or absence (D) of 287 base pairs in the 16th intron. It has been observed that the DD genotype increases the cardiac infarction risk while its effect upon the development of coronary heart disease has not been proved (21, 22).

Genetic researches embrace also the gene of angiotensin receptor type 1 (AT1R), the polymorphism A1166C being in the centre of interest. The CC genotype is most often detected in patients with past myocardial infarction. Interesting results can be also found in investigations concerning the coexistence of polymorphism I/D of gene ACE and polymorphism A1166C of gene AT1R. Such genetic profile significantly influences the restructuring, function and mass of the left ventricle of the heart in ischemic heart disease (23-25).

Genes of the coagulation system and fibrinolysis

The thrombotic process is a very important factor in ischemic heart disease, particularly in acute coronary events. Polymorphism G455A of fibrinogen gene has effect on concentration of fibrinogen. Although the increased level of fibrinogen is an independent factor favoring the development of IHD, no results point thus far to an unquestionable connection between G455A polymorphism and clinical manifestation of ischemic heart disease. Only a correlation between polymorphism G455A and the degree of the advancement of coronary arteries atherosclerosis has been noted (26, 27).

Another candidate gene is the plasminogen activator inhibitor type 1 (PAI-1) gene. Polymorphism 4G/5G determines the level of PAI-1 activity, that is, the presence of allele 4G increases the activity of PAI-1. Studies conducted on small groups of patients show a dependence between the presence of allele 4G and past cardiac infarction; studies on large population did not, however, confirm these results (28-30).

Genes connected with thrombocytes

Genes regulating the function of thrombocytes constitute another group of genes significant for the development of ischemic heart disease. In the centre of interest are glycoproteins (GP) of platelet cell membrane responsible for their aggregation. It has been reported that polymorphism P1A of glycoprotein GPIIIa is connected with aggregation activity of thrombocytes and the extensiveness of atherosclerotic lesions, while the problem of the dependence between allele P1A2 and acute coronary syndromes seems still an open question for the researches (31, 32). Polymorphisms of GPIIb and GPIb seem to be essential for this problem. In clinical trial with control group Moshfegh et al. showed increased risk of myocardial infarction in patients with genotype 807T/873A (33).

Conclusion

Research concerning the impact of particular genes variants upon ischemic heart disease is difficult and complex because of the multifactorial character of this disease as well as of the interaction of genetic and environmental factors. The paper presents polymorphisms frequently discussed in the literature and also draws attention to factors less known and investigated, for example: proliferation factors of smooth muscle cells of vessels or vasoactive factors.

Studies of genetic etiopathogenesis of ischemic heart disease will certainly result in more effective prevention and therapy of particular patients.
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