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THE ROLE OF GENE POLYMORPHISM IN THE DEVELOPMENT OF ACUTE PANCREATITIS

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Abstract. The article analyzes scientific works on the role of gene polymorphism in the development of acute pancreatitis. The etiopathogenetic factors of destructive forms of acute pancreatitis are being studied for the purpose of predicting it and early surgical treatment. The authors emphasize the analysis of factors influencing the development of chronic pancreatitis.

Keywords. Pancreatitis, mutation, severe form, pancreatonecrosis, genetic status.

Introduction. In Russia, acute pancreatitis is one of the most common acute surgical diseases [1, 335 p.]. In different regions of the country, the number of patients hospitalized with a similar diagnosis varies from 38 to 95 people per 100,000 population and continues to grow every year [2, 55-59, 4-14]. It should be noted that in 80% of patients, acute pancreatitis occurs easily and spontaneously resolves within a week [3, P. 93–101.]. In other cases, severe forms of the disease develop (destructive, necrotizing pancreatitis), the mortality rate in which, according to various data, varies from 7 to 50 %, depending on the severity and prevalence of the process, averaging 20-30 %. [4, P. 565–573]. With infected pancreatic necrosis, which occurs in 40-70 % of cases, with a severe course of the disease, the mortality rate reaches 85 %, and with fulminant pancreatitis up to 100 % [5, p. 373-379.]. e

The increase in the incidence of pancreatitis is due, on the one hand, the characteristics of the diet, increasing abuse of alcohol and its surrogates, the prevalence of gallstone disease and, as a consequence, the increase in the absolute number of patients, and on the other hand, improvement in clinical, laboratory and instrumental diagnosis of the disease [6, p. 247-250].

In this regard, it is of interest to study the etiopathogenetic factors of destructive forms of acute pancreatitis in order to predict it and to treat it early. A review of the data of the modern literature indicates that researchers pay close attention to the genetic risk factors for pancreatitis.

The first ideas of genetic determination of predisposition to pancreatitis were expressed in the middle of the twentieth century. [7, P. 247-250.]. The disease is characterized by periodic attacks of acute pancreatitis in the absence of known provoking factors, debuts in childhood and is found in at least two other family members. Thus, L. Le Bodic et al. [8, P. 1504-1510.], having studied 249 family members from eight generations, found that this nosology is inherited by an autosomal dominant type with incomplete (80 %) penetrance. These works marked the beginning of the study of genetic changes associated with pancreatitis.

In recent years, researchers have been paying attention to the genetic predisposition to severe forms of the disease [9, p. 20-25.]. In this case, molecular genetic research methods are used to identify groups of patients who are determined

to develop severe forms of acute pancreatitis with septic complications. Many studies are devoted to the identification of gene polymorphism in chronic and acute pancreatitis. When analyzing the factors affecting the development of chronic pancreatitis, mutations in the cystic fibrosis gene (CFTR-transmembrane regulator of cystic fibrosis conduction), a pancreatic secretory trypsin inhibitor, were revealed. The literature also describes other mutations in genes that affect the state of the pancreas-SPINK1 (serine protease inhibitor kazal type 1), genes responsible for the synthesis of alcohol dehydrogenase and alpha-1 – antitrypsin. In the development of severe forms of pancreatitis, the authors note the role of polyorphism in the genes of tumor necrosis factor-2 and TNF-alpha (tumor necrosis factor) and IL-8 in [10, P. 247-250.]. A method for determining the severity of acute idiopathic pancreatitis based on the detection of heterozygous mutations in the SPINK1, PRSS1 and CFTR genes is described [11, p. 169-177.].

One of the most studied here is the cationic trypsinogen gene PRSS1 – over the past 15 years, many mutations associated with both hereditary and idiopathic and alcoholic pancreatitis have been described (for example, R122H, N21I, R116C, N29T, R122C, E79K, etc.) [12, P. 247–250].

Interaction between trypsinogen isoforms in genetically determined pancreatitis: mutation E79K in cationic trypsin (PRSS1) causes increased transactivation of anionic trypsinogen (PRSS2) // Hum. Mutat. 2004. Vol. 23, No. 1. P. 22-31.]. All of them lead to an acceleration of the conversion of trypsinogen to trypsin, which triggers a cascade of enzymatic reactions and serves as the pathogenetic basis for acute recurrent pancreatitis [13, P. 8–15.].

Another equally important protein that regulates trypsin is a serine protease inhibitor of the Kazal‑1 type (SPINK1). Since the protection of the pancreas is provided by the balance between trypsin and its inhibitor, pancreatitis can develop not only with excessive activation of trypsinogen, but also with insufficient trypsin-binding ability of the inhibitor. In the case of damage to the SPINK1 gene, the inhibitory activity of the protein decreases, which leads to a violation of the inactivation of trypsin in the pancreatic tissue. Excess trypsin triggers the activation of other pancreatic enzymes with proteolytic necrosis of the gland tissue [4, P. 775–778.].

Mutations in the SPINK1 gene are found in 20-23% of patients with hereditary pancreatitis, which is several times higher than the frequency of the disease in the general population [15, P. 324–329.]. In the study of Yu. A. Kucheryavy, SPINK1 mutations were detected in all forms of chronic pancreatitis, except for autoimmune. The most common mutations of this gene associated with idiopathic chronic pancreatitis are N34S (replacement of asparagine with serine in codon 34) and P55S [16, P. 675-681.]. Mutations of the serine protease inhibitor, Kazal type 1 gene, in patients with idiopathic chronic pancreatitis // Am. J. Gastroenterol. 2002. Vol. 97, No. 5. P. 1133-1137.]. It is also shown that such genetic damage is a factor predisposing to alcoholic pancreatitis [17, P. 687–692]. Other mutations of the SPINK1 gene were also detected: R67C, R65Q, Y1092X, M1T, intron mutations c. 27deIC and C. 871G>A. The phenotypic manifestations of these genetic changes

have not yet been studied due to their low frequency [4]. In a study by Witt and Luck, it was shown that the M1T mutation is located in the starting codon of the gene, disrupts the synthesis of the trypsin inhibitor, and is inherited autosomal dominant with high penetrance [18, P. 2716–2717.].

O. Kiraly et al. [Kiraly O., Boulling A., Witt H. [et al]. Signal peptide variants that impair secretion of pancreatic secretory trypsin inhibitor (SPINK1) cause autosomal dominant hereditary pancreatitis //Hum. Mutat. 2007. Vol. 28, No. 5. P. 469–476.] New mutations were found in the first exon of the SPINK1 gene that damage the secretory signaling peptide: c. 41T4G (p.L14R) and c.36G4C (p.L12F). Both mutations were found in families with autosomal dominant inheritance of pancreatitis. Mutation p.L14R initiates rapid intracellular degradation of the trypsin inhibitor, reducing its secretion. The authors attributed these mutations not to the modifiers of the disease, but to its immediate cause.

However, the genetic status is of great importance: for example, in the presence of mutations in the genes of the pancreatic secretory trypsin inhibitor (PSTI/SPINK1) or the cystic fibrosis gene (CFTR), the risk of developing pancreatitis increases by 50 times, and if a patient with such mutations also abuses alcohol — by 200 times. The maximum risk (by a factor of 1000) was observed in a combination of genetic and environmental factors (mutation of the cationic trypsinogen PRSS1 gene and alcohol abuse or smoking) [19, 346–350.].

In Finland, only 50% of patients with the R122H mutation of the PRSS1 gene were found to have hereditary pancreatitis [Raty S., Babu M., Pelli H. et al. Human cationic trypsinogen (PRSS1) and trypsinigen inhibitor gene (SPINK1) mutation screening in a Finnish hereditary pancreatitis family. 38th Eur. Pancr. Club. 2006. 1. P34.], similar data were obtained in Europe and in the United States And vice versa, according to Keiles S., 49% of patients with pancreatitis of various etiologies have at least one mutant allele of the PRSS1, PSTI/SPINK or CFTR genes [20, 221-227.]. Among 94 patients with AP, the Italian authors found only 1 mutation (N34S) of the PSTI/SPINK1 gene and did not detect any mutation of the PRSS1 gene [Perri F., Piepoli A., Stanziale P. et al. Mutation analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the cationic trypsinogen (PRSS1) gene, and the serine protease inhibitor, Kazal type 1 (SPINK1) gene in patients with alcoholic chronic pancreatitis // Eur. J. Hum. Genet. 2003. 11. 687–692.]. Considering that among the four patients with pancreatitis with genetic mutations, not a single person abuses alcohol [21, 42-47], the authors believe that the genetic basis of increased sensitivity to alcohol or the modulation of the inflammatory response of the pancreatic tissues in response to its effects remains unknown.

The cystic fibrosis transmembrane regulator (CFTR) gene is the third most common among genes with mutations associated with the development of pancreatitis [22, P. 467-474.]. CFTR is a cyclic adenosine monophosphate-sensitive anionic channel in the apical membrane of epithelial cells of some organs, including the pancreatic ducts, that controls the transport of chlorine and bicarbonates. Many of its mutations are known [23, P. 1133-1137.]. Some of them completely disrupt the functioning of the protein and cause severe clinical manifestations, others only reduce

its function [24, 134-138.]. The most severe CFTR mutations are found in cystic fibrosis, a hereditary autosomal recessive disease characterized by damage to the endocrine glands [25,1229–1256.].

When the CFTR is damaged, the transport of bicarbonates into the lumen of the duct is most disturbed, which leads to a decrease in the hydrogen index of pancreatic juice, and as a result, causes a violation of the solubilization of proteins and the transport of zymogenic granules. Equally important, acidification of the environment also contributes to the auto-activation of trypsinogen and disrupts the inactivation of trypsin [26, 134-138.]. Nevertheless, clinical manifestations of acute pancreatitis are found only in 1-2% of patients with cystic fibrosis [27, 86-95.]. Data from some studies have suggested that some mutations in the CFTR gene can play a role in pancreatic lesions and without the development of cystic fibrosis [28, 178-181]. Persons with less severe mutations that do not cause cystic fibrosis, in which the secretory function of the organ is preserved, are susceptible to pancreatitis [29, P. 951-952.]. This is attributed to the fact that most of the pancreatic tissue that supports the inflammatory process is preserved in such people [30, P. 609-620.]. In their study, J. Okcenga et al. [Ockenga J., Stuhrmann M., Ballmann M. [et al]. Mutations of the cystic fibrosis gene, but not cationic trypsinogen gene, are associated with recurrent or chronic idiopathic pancreatitis // Am. J. Gastroenterol. 2000. Vol. 95, No. 8. P. 2061-2067.] showed that CFTR mutations are associated with chronic and acute recurrent pancreatitis. Among patients with idiopathic chronic pancreatitis, such mutations were found in 45 %, and among patients with repeated attacks of acute pancreatitis – in 38 % of cases [31, P. 372–381].

Chymotrypsin C is an enzyme of the pancreas that specifically cleaves the Leu81–Glu82 peptide bond in the cationic trypsinogen molecule, thus performing its degradation. This provides a second line of protection for organ tissue from prematurely activated trypsinogen after the trypsin inhibitor SPINK1. Since the corresponding cleavage sites are present in the molecules of anionic trypsinogen and mesotrypsin, chymotrypsin C probably provides their degradation, although there is no experimental confirmation of this yet [32, 1238-1246.]. It is suggested that CTRC mutations that reduce the activity of the enzyme or disrupt its synthesis may lead to the development of pancreatitis as a result of reduced degradation of excess trypsin [33, P. 78–82.].

Two CTRC mutations-microdeletions p. K247_R254del and p.R254W, located in exon 7, are the most common polymorphic variants found in 3.3% of patients with idiopathic chronic pancreatitis in the European population. They were also detected in 2.9 % of people suffering from alcoholic pancreatitis, which exceeded the indicator for patients with alcoholic liver disease without damage to the pancreas, which is 0.7 %. These data indicate the role of CTRC mutations in the formation of predisposition to alcoholic pancreatitis.

Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis // Nat. Genet. 2008. Vol. 40, No. 1. P. 78-82.] also demonstrated that tropical pancreatitis can be caused by CTRC polymorphism. The authors identified its mutations in 14.1 % of patients with the tropical form of

chronic pancreatitis and only in 1.2 % of healthy individuals in India. The previously described mutations p. K247_R254del and p.R254W were not detected. Some authors have diagnosed tropical pancreatitis in carriers of the c.180C>T mutation, also seen in the French population [34, 889-894.], others noted the p.V235I mutation as the most frequent variant of polymorphism among patients from India (4.9 % of the examined) [35, 1602–1606.].

The calcium - sensing receptor (CASR) plays a key role in calcium homeostasis and is expressed in many tissues involved in its metabolism, including the cells of the pancreatic acinuses and ducts [36, 705-711.]. The gene encoding the calcium-sensitive receptor is located in the long arm of the third chromosome. To date, more than 70 mutations of this gene have been described, including heterozygous inactivating mutations that cause familial hypocalciuric hypercalcemia (SGH), which is considered a benign disease accompanied by an increase in the level of calcium in the blood plasma. The data that SSG is often accompanied by recurrent pancreatitis suggested a common genetic cause of the two pathologies [37, 675–680.].

P. Felderbauer et al. [Felderbauer P., Hoffmann P., Einwachter H. [et al]. A novel mutation of the calcium sensing receptor gene is associated with chronic pancreatitis in a family with heterozygous SPINK1 mutations // BMC Gastroenterol. 2003. Vol. 3. P. 34.] studied a family with cases of SGH and chronic pancreatitis. In patients with SGH, a sporadic mutation L173P (518T>C) in the CASR gene was found, causing the replacement of leucine with proline in the extracellular domain of the protein. The same patients suffered from recurrent attacks of acute pancreatitis, which allowed the authors to suggest the presence of a predisposition to chronic pancreatitis in individuals with this mutation. They explain the possibility of such a relationship by the fact that hypercalcemia causes premature activation of trypsinogen, which serves as a trigger factor for pancreatitis. This is confirmed by data on the increased incidence of pancreatitis in individuals with primary hyperparathyroidism (1-19 %), accompanied by an increase in the level of calcium in the blood due to the homozygous CASR mutation. However, P. Felderbauer et al. [Felderbauer P., Hoffmann P., Einwachter H. [et al]. A novel mutation of the calcium sensing receptor gene is associated with chronic pancreatitis in a family with heterozygous SPINK1 mutations // BMC Gastroenterol. 2003. Vol. 3. P. 34.] found that neither parathyroidectomy nor treatment with bisphosphonates led to the expected improvement in the patients ' condition.

Due to the fact that proinflammatory and regulatory cytokines play an important role in the pathogenesis of acute pancreatitis, many studies have been conducted in recent years to study the role of polymorphism of genes encoding this group of proteins.

So, the researchers ' attention was attracted by the CD14 protein. It exists in two forms: membrane, present on the surface of monocytes, macrophages, neutrophils, and soluble, circulating in the bloodstream. CD14 recognizes lipopolysaccharide molecules and plays an important role in immune responses by stimulating the cytokine-induced response of cells to the appearance of

lipopolysaccharide [38, 1312–1322]. Two most common polymorphisms of the CD14 gene were identified, differing in position: -260 and -651. A. Masamune et al. [39, P. 225-233.], assessing the relationship between polymorphic variants of the CD14 promoter region and pancreatic diseases in the Japanese population, found that the frequencies of the genotype –260C/T and –651C / T did not differ between healthy and patients with acute or chronic pancreatitis. Similarly, S. H. Rahman et al. did not reveal the predominance of any polymorphic variant of CD14 in patients with acute pancreatitis.

The effect of the CD14 genotype on the risk of alcohol‑induced pancreatitis was also studied. Y. Chao et al. [40, P. 6043-6048.] registered a higher frequency of alleles –260C among patients with alcoholic acute pancreatitis than among healthy or suffering patients. pancreatitis of a different etiology. Another group of researchers, on the contrary, excluded the influence of CD14 polymorphism on the likelihood of developing alcoholic or biliary acute pancreatitis [41, P. 56–61.].

In addition to the CD14 protein, among the cytokines that may predispose to the development of pancreatitis, polymorphic variants of tumor necrosis factor‑α continue to be studied. This protein plays the role of the main mediator of the immune response to the appearance of endotoxins. Two major polymorphic variants of the tumor necrosis factor‑α gene occur when guanine is replaced with adenosine at positions -308 and -238 of the promoter region.

Despite the assumptions, these mutations occur with the same frequency among healthy and patients with acute pancreatitis [42, P. 229-234.], showed that the –308A/G mutation of this gene does not increase the risk of acute pancreatitis (similar results were obtained for the –238G/A variant).

Many polymorphic variants have been found for interleukins. The –174C/C genotype of interleukin‑6 has been shown to be associated with acute biliary pancreatitis [43, P. 295-301.]. Genotype-251A/T of interleukin-8, according to some data, is more common in patients with pancreatitis, and according to others-is present with the same frequency in both patients and healthy. No differences in the frequency of different variants of the interleukin‑10 genotype (–1082A/G, –819T/C, and –592A/C) and interleukin‑6 (–174G/C) were found [44, P. 542–548.].

Polymorphism of genes of other cytokines, such as transforming growth factor-β1 and gamma-interferon, according to various authors, does not play a role in the development of chronic pancreatitis, as well as alcohol‑induced pancreatitis. The latter is also indicated for tumor necrosis factor-α and interleukin-10 [45, P. 162-171.]. There is evidence of the role of the heat shock protein HSP70‑2 gene polymorphism in the development of pancreatitis. Thus, the mutant G-allele HSP70-2 is found with much greater frequency among patients with acute and chronic pancreatitis [46, P. 414-419.]. However, polymorphic variants of this gene are not involved in the appearance of alcoholic chronic pancreatitis [47, P. 1721–1727.].

The above indicates an undeniable relationship between certain gene mutations and certain forms of acute and chronic pancreatitis. However, many research data are

contradictory, and studies on the combinations of mutations in destructive-inflammatory diseases of the pancreas are very few.

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