# The Role of Genes Regulating Inflammatory Mediators in the Etiopathogenesis of Chronic Pancreatitis

**1. Akhmedova Nigora Akbarovna**

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[1] Tashkent Medical Academy

**Annotation**: This article presents the general information about chronic pancreatitis and promotes the historical development of the genetic approach of chronic pancreatitis etiopathogenesis. In addition, the role of genes that regulate inflammatory mediators such as cytokines and chemokines is discussed with the integration of examples from numerous researches.

**Keywords:** pancreatitis, chronic pancreatitis, CP, genes, cytokine, genetic component, hereditary, mutation, PRSS1, SPINK I, trypsin, CFTR, enzyme, N34S, R67C, CD14, genotype, protein, interleukin.

Chronic pancreatitis (CP) is a difficult clinical and surgical condition. Despite advances in the diagnosis and treatment of CP, the illness continues to cause serious consequences and, in rare cases, death. Alcohol intake and cholelithiasis are the two most common etiological causes of chronic pancreatitis. It should be remembered, however, that only 10% of individuals who misuse alcohol develop chronic pancreatitis. Simultaneously, CP can develop in people without the presence of evident inciting elements - this is known as idiopathic pancreatitis, which accounts for 10-30% of all chronic pancreatitis cases. A pronounced structural restructuring, sclerosis, and fibrosis of the pancreatic parenchyma is the pathomorphological basis for the development of chronic pancreatitis, which leads to a violation of the gland's outflow of secretion, an increase in pancreas size, and, often, compression of the parapancreatic structures. There are several clinical manifestations of CP:

1. Compression of the common bile duct with the development of obstructive jaundice syndrome;

2. Compression of the portal vein with the development of portal hypertension syndrome;

3. Compression of the duodenum with the development of duodenostasis (some of the more complicated clinical forms of CP).

Not all changes in the epidemiology of chronic pancreatitis over the past decade can be explained by social and economic factors in society. Changing environmental conditions can affect the receptivity of the human body by both endogenous and exogenous factors. The study of the etiology of chronic pancreatitis revealed that among the possible factors there is a genetic component. Despite the fact that the significance of genetic factors for various forms of pancreatitis, especially the chronic form, and the population frequency of this kind are not clear, the established cases of genetic predisposition have made it possible to take important steps in understanding the molecular mechanisms of the development of pathology. Talking about the role of genes in the etiopathogenesis of chronic

pancreatitis, we can identify that genetic mutations that induce fermentopathies, which, therefore, cause chronic recurring inflammation, are one of the known risk factors for the development of CP. As a result, both acute and chronic pancreatitis appear to be complex diseases in the majority of instances. The function of genetic elements in the etiology was discovered to be a kind of hereditary pancreatitis. Hereditary pancreatitis is an autosomal dominant inheritance pattern with an 80 percent penetrance rate. To date, the literature has amassed a substantial quantity of molecular genetic data on genes whose mutations are a predisposition factor for both well-established hereditary pancreatitis and pancreatitis of different etiologies, including idiopathic pancreatitis. Despite the fact that many writers acknowledge the importance of hereditary variables, there are few specific research on the genetic components of pancreatitis in the literature.

In the middle of the twentieth century, the first hypotheses on hereditary susceptibility to pancreatitis were presented. Then they started discussing about inherited chronic pancreatitis for the first time. Recurrent incidents of acute pancreatitis without known triggering causes define the condition, which first appears in childhood and affects at least two additional family members. Thus, L. Le Bodic et al. discovered that this nosology is inherited in an autosomal dominant way with partial (80%) penetrance after studying 249 family members over eight generations.

These studies set the groundwork for future research into genetic alterations linked to pancreatitis. The PRSS1 cationic trypsinogen gene is one of the most investigated here; various mutations related with hereditary, idiopathic, and alcoholic pancreatitis have been identified during the last 15 years (for example, R122H, N21I, R116C, N29T, R122C, E79K and etc.). All of them cause an increase in the rate of trypsinogen to trypsin conversion, which sets off a chain of enzymatic processes and is the pathogenetic basis for acute recurrent pancreatitis.

To date, the primary mutations that cause hereditary pancreatitis, idiopathic pancreatitis, and perhaps additional kinds of pancreatitis have not been found. In the present research, mutations in the cationic trypsinogen (PRSSI), trypsinogen inhibitor (SPINK I), and cystic fibrosis transmembrane regulatory protein (CFTR) genes are regarded the key determinants of hereditary pancreatitis risk. Many occurrences of juvenile pancreatitis appear to be caused by mutations in cationic trypsinogen. Adult chronic pancreatitis is linked to CFTR mutations. However, these genes are only linked to a small percentage of pancreatitis instances and cannot account for the remainder. In the majority of instances, the documented genetic abnormalities in pancreatitis are linked to a malfunction of the pancreatic enzyme activation system. In the large spectrum of pancreatic enzymes, *trypsin* (EC 3.4.2.4) holds a unique place. The point is that human trypsin is unusual in that it has the ability to autoactivate and activate practically all other proteolytic enzymes in a cascade.

The hexapeptide is separated from the trypsinogen during autoactivation. Enterokinase of the brush border of the small intestine, which occurs naturally, or trypsin itself can operate as an endopeptidase that induces the separation of such an oligopeptide from trypsinogen and its conversion to trypsin. In addition to autoactivation, trypsin has the potential to autolysis, or autodegradation, which happens when a molecule is broken at a specified point. A trypsin inhibitor can control trypsin activity (SPINK II). Trypsin is a somewhat complicated molecule with two globular domains. These domains create an amino acid recognition center when they connect, which is placed in a small space between them. Two amino acids in the substrate molecule, arginine and lysine, are identified at the active site, and trypsin cleaves the polypeptide chain there.

The two trypsin domains are connected by an amino acid chain on the other side of the molecule from the active site and the trypsin inhibitor binding site. The active core of this enzyme is ensured by the spatial structure of the enzyme. Pancreatic trypsin inhibitor penetrates between trypsin's two domains and blocks the molecule's active site. The position 122 of arginine on the amino acid chain connecting the domains has been determined. It is this amino acid that is cleaved by trypsin and other trypsin-like

enzymes during autolysis. The domains are split as a result, and the active center is destroyed. The synthesis of digestive enzymes in an inactive form - in the form of proenzymes (zymogens), the localization of the enteropeptidase activation enzyme outside the pancreas, and a low concentration of calcium ions are all mechanisms that protect the pancreas from autodegradation when the pancreatic digestive cascade is triggered by trypsin. Enzyme synthesis and activation are separated by space: proenzymes are generated in the acinar cell and reach the duodenum, where they are activated. So, based on the information available, a hypothesis has been made that if the pancreas' function is disrupted by a genetic mutation, trypsin can readily trigger pancreatic autolysis, leading to the development of AP or CP.

The N34S missense mutation was detected in the 3rd exon of the secretory trypsin inhibitor's gene with the highest frequency in individuals with CP, according to the investigations. It's worth noting that the N34S mutation was discovered with two intron mutations: IVS1–37T > C and IVS3–69insTTTT, and a similar collection of mutations (N34S + IVS1–37T > C + IVS3–69insTTTT) has been found in a number of nations. In patients with idiopathic CP, alcoholic CP, and tropical calcific CP, mutation N34S was found in 20-23 percent of patients, and in the latter group, the frequency of mutation detection reached 50 percent. The following can be used to support the idea that the N34S mutation has a key role in the development of CP:

a)  data based on theoretical computer analysis (Chou-Fosman and Robson-Garnier) indicating that the N34S mutation can affect the structure of the nearby active site and reduce the biological function of the RIT;

b)  the frequency of the N34S mutation in patients with CP is significantly higher than in individuals without symptoms of CP;

c)  the frequency of CP in homozygous twins with the N34S mutation reaches 98 percent, implying the presence of an inherited recessive trait.

In a subsequent study by M. Hirota et al. (2003) in Japan revealed the presence of two more mutations in the 4th exon of the secretory trypsin inhibitor gene. One of the identified new mutations, R67C, has not previously been encountered in similar studies in other countries in patients with CP. Based on the data obtained, the authors concluded that the R67C mutation may be typical only for the Japanese.

According to the results of this investigation, there were no significant differences in the frequency of mutations in the CFTR, SPINK1, and PRSS1 genes across the comparison groups. Furthermore, it was shown that a variation in the alcohol dehydrogenase gene is most likely one of the reasons that predisposes to a difficult course of chronic pancreatitis.

In conclusion, we may conclude that pancreatitis is transforming our understanding of the illness as a whole because to genetic research on its heredity. Genetic pancreatitis was once thought to be an uncommon genetic condition and the genes regulating inflammatory mediators were not considered to have any major role in the etiopathogenesis of chronic pancreatitis. However, a review of current studies and genetic research shows that hereditary pancreatitis is considerably more frequent than previously considered. Taking everything into account, we may infer that there is an undeniable link between certain genes, such as PRSS1, SPINK I, CFTR, abnormalities and specific types of chronic pancreatitis. However, many research findings are conflicting, and there are few studies on the effects of many mutations in pancreatic destructive-inflammatory illnesses.

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