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Acute Pancreatitis And Cationic Trypsinogen Gene Polymorphism In The Uzbek Population

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Abstract

This article examines the impact of the Arg122His polymorphism in the PRSS1 gene on the incidence of acute pancreatitis. In the mechanism of acute pancreatitis development, environmental factors play an important role alongside genetic factors. Ethnic differences in the frequency distribution of alleles and genotypes of this gene's polymorphic variant were identified. Further advancement of molecular genetic research through studying the genetic basis of pancreatitis is crucial for developing new diagnostic methods and determining treatment strategies with an individualized approach to each patient.

Keywords: Acute pancreatitis, cationic trypsinogen (PRSS1), gene polymorphism.

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1. Introduction

Acute pancreatitis is considered a significant problem in modern medicine. Despite advances in treatment approaches for this disease, the incidence of acute pancreatitis is steadily increasing. In terms of its growth rate, acute pancreatitis surpasses all other acute abdominal conditions [1, 4, 5]. Alongside the rise in the number of patients with acute pancreatitis, there is a trend towards an increased proportion of fatal cases. The persistently high mortality rate from acute pancreatitis is due to the disease's complex, multilevel pathogenesis, and some mechanisms underlying these pathological reactions remain unclear [2, 4, 6].

The development of the disease is influenced by genetic predisposition, the complex interaction of multiple genes, and various environmental factors. The genetic mechanisms involved in the development of pancreatitis and its complications are currently insufficiently studied. To date, a number of mutations have been identified that are considered major factors in hereditary predisposition to pancreatitis. For example, a mutation in the cationic

trypsinogen gene (PRSS1) makes trypsinogen resistant to autolysis and prone to premature autoactivation, which can lead to genetically determined acute pancreatitis. A mutation in the pancreatic secretory trypsin inhibitor gene (SPINK1) impairs the inactivation of trypsin in pancreatic tissue, which leads to the activation of pancreatic enzymes, proteolytic necrosis of pancreatic tissue, and lysis of venule walls [3, 7].

Although a small number of studies on the genetic aspects of pancreatitis have been published, a spectrum of genetic polymorphisms suitable for the comprehensive diagnosis of pancreatitis has not been established in clinical practice. The literature often contains contradictory information regarding the role of a particular polymorphism in the pathogenesis of pancreatitis and the importance of its detection. Discrepancies also exist between the findings of European and Asian research centers. Therefore, identifying the optimal diagnostic spectrum of genetic polymorphisms is crucial for the timely prediction of acute pancreatitis development.

The aim of our study was to predict and improve treatment outcomes for acute pancreatitis by assessing the clinical significance of polymorphisms in the cationic trypsinogen (PRSS1) gene.

2. Methods

This study was conducted at the surgical department of Tashkent State Medical University. To address these problems, we analyzed the diagnostic and therapeutic measures in 68 patients hospitalized with acute pancreatitis of various etiologies. For this study, we formed standardized groups based on age and sex, according to the diagnostic and treatment methods used. The patients were divided into two groups: the main group (n=68), consisting of patients with clinical signs of acute pancreatitis; and the control group (n=70), consisting of healthy individuals in whom the Arg122His polymorphism in the PRSS1 gene was studied.

The control group consisted of 38 healthy men (n=38) and 32 women (n=32) aged 25 to 66 years (mean age 56.7±8.4). The age of the patients in the main group ranged from 29 to 75 years (mean age 57.3±9.3). Of these, 37 (52.2%) were women and 31 (47.8%) were men. Thus, the compared groups were comparable in terms of sex (main group: 31 men, 37 women; control group: 38 men, 32 women; $\chi 2=0.018$, $p=0.89$) and age (57.3±9.3 and 56.7±8.4; $t=0.417$, $df=136$, $p=0.677$), and did not differ significantly from each other in these parameters ($p>0.05$).

A diagnosis of acute pancreatitis was established based on the combination of at least two of the following criteria, after excluding other surgical pathologies: a typical clinical presentation (severe, girdle-like pain not relieved by antispasmodics; uncontrolled vomiting; a history of alcohol or spicy food consumption, or cholelithiasis, etc.); characteristic ultrasound findings (enlargement, decreased echogenicity, and indistinct borders of the pancreas; presence of free fluid in the abdominal cavity); and hyperenzymemia (hyperamylasemia or hyperlipasemia) at levels three or more times the upper limit of normal.

Samples for genetic typing were obtained from whole peripheral venous blood. The material was collected using vacuum tubes with the anticoagulant EDTA-K3 coated on the inner wall. DNA was isolated from whole blood leukocytes using the "DNA-Express-Blood" reagent kit manufactured in Russia (LLC NPF "Litekh," Moscow).

Data analysis was performed using STATISTICA software, version 6.0, in compliance with the principles and requirements for statistical processing of data in biological and medical research.

3. Results And Discussion

The PRSS1 gene is located on the long arm of chromosome 7 (locus 7q34) and consists of 5 exons that encode cationic trypsinogen (or trypsinogen 1). Cationic trypsinogen constitutes two-thirds of the total trypsinogen in the pancreas. To date, more than 20 different mutations in the PRSS1 gene have been described, most of which, in heterozygous form, lead to the development of an autosomal dominant variant of pancreatitis. In this part of the study, we investigated the Arg122His polymorphism of the PRSS1 gene.

The study began by assessing whether the studied groups conformed to the Hardy-Weinberg equilibrium. The frequency distribution of genotypes for the gene polymorphism in patients with acute pancreatitis and in the general sample of the Uzbek population was found to be in Hardy-Weinberg equilibrium ($p > 0.05$).

Analysis of the genotype and allele frequency distribution in the control group showed that the frequency of the Arg allele was 99.3%, and the frequency of the His allele was 0.7%. Individuals homozygous for the Arg allele (Arg/Arg genotype) constituted 98.6% (n=69) of the group, while heterozygotes (Arg/His genotype) accounted for 1.4% (n=1). The homozygous His/His genotype was not observed in either the patient or control groups (Table 1).

Table 1

Analysis of the study results on the influence of the Arg122His polymorphism in the PRSS1 gene on the incidence of acute pancreatitis

Polymorphism		Allele, genotype	Main group (n=68)		Control group (n=70)		χ^2, p, OR (95% CI)
			n	%	n	%	
Arg122His in the PRSS1 gene	Allele	Arg	133	97,8	139	99,3	χ^2= 1,1, p =0,3; OR= 0,32 (0,03- 3,1)
		His	3	2,2	1	0,7	
	Genotype	Arg/Arg	65	95,6	69	98,6	χ^2= 1,1, p =0,3; OR= 0,31 (0,03- 3,1)
		Arg/His	3	4,4	1	1,4	
		His/His	0	0	0	0.0	

The results of the analysis, based on a study of polymorphic markers of the PRSS1 gene (Arg122His), showed that the association with the allele (χ2= 1.1, p =0.3; OR= 0.32 (0.03-3.1)) and the probability of an effect by genotype were not statistically significant. This indicates a virtually complete absence of a role for the PRSS1 (Arg122His) genotype polymorphism in the genesis of acute pancreatitis.

However, when these indicators were studied separately only in patients with alcoholic (alimentary) etiology, different results were obtained (Table 2).

Table 2

Analysis of the study results on the influence of the Arg122His polymorphism in the PRSS1 gene on the incidence of alcoholic (alimentary) acute pancreatitis

Polymorphism		Allele, genotype	Main group (n=68)		Control group (n=70)		χ^2, p, RR, OR (95% CI)
			n	%	n	%	
Arg122His in the PRSS1	Allele	Arg	55	94,8	139	99.3	χ^2= 4,12, p =0,042; RR=2,64 (1,44-4,9); OR= 7,6 (0,77- 3,1)
		His	3	5,2	1	0.7	
	Ge no	Arg/Arg	26	89,7	69	98,6	

		Arg/His	3	10,3	1	1,4	χ^2= 3,84, p =0,0499; RR=2,6 (1,4-5); OR= 7,4 (0,74- 74,1)
		His/ His	0		0	0	

The results obtained show that although the PRSS1 gene polymorphism (Arg122His), which is the main focus of this study, is not a significant factor in the overall development of acute pancreatitis, it does play a statistically significant role ($p<0.05$) in acute pancreatitis of alcoholic (alimentary) etiology.

At the genotype level of the PRSS1 (Arg122His) gene polymorphism, the main group with acute pancreatitis of alcoholic etiology consisted of 26 (89.7%) Arg/Arg homozygotes and 3 (10.3%) Arg/His heterozygotes. A comparison with the control group showed that the risk of acute pancreatitis of alcoholic etiology is significantly higher ($\chi2=3.84$, $p=0.0499$), with a 2.6-fold higher relative risk (RR) and a 7.4-fold higher odds ratio (OR).

According to the results, the risk of acute pancreatitis of alcoholic etiology also showed high values at the allele level: the risk was significantly high ($\chi2=4.12$, $p=0.042$), the relative risk (RR) was 2.64 times higher, the odds ratio (OR) was 7.6 times higher, the risk in the exposed group was 75%, the risk in the unexposed group was 28.4%, and the overall risk was 29.3%.

Consequently, while the Arg122His polymorphism in the PRSS1 gene does not significantly affect the overall incidence of acute pancreatitis, it is highly likely to be involved in the onset of acute pancreatitis of alcoholic (alimentary) etiology.

One of the main aspects of our research was to study the influence of the gene polymorphisms under investigation on the morphological type of acute pancreatitis.

First, we studied the influence of the PRSS1 (Arg122His) gene polymorphism on the morphological type of acute pancreatitis (Table 3).

Table 3

Influence of the PRSS1 (Arg122His) Gene Polymorphism on the Morphological Type of Acute Pancreatitis

Groups	Genotype frequency, %			Allele frequency, %	
	Arg/Arg	Arg/His	His/His	Arg	His
Healthy (n=70)	69 (98,6%)	1 (1,4%)	0	139 (99,3%)	1 (0,7%)
Acute edematous pancreatitis (n=45)	44 (64,7%)	1 (1,5%)	0	89 (65,4%)	1 (0,7%)
Sterile and purulent pancreonecrosis (n=23)	21 (30,9%)	2 (2,9%)	0	44 (32,4%)	2 (1,5%)

P*	χ^2=0,1; p=0,75; RR=1,2, OR=1,6	χ^2=0,1; p=0,75; RR=1,2, OR=1,6
P**	χ^2=2,93; p=0,09; RR=2,9, OR=6,6	χ^2=2,88; p=0,09; RR=2,8, OR=6,3
P***	χ^2=1,51; p=0,22; RR=2,1, OR=4,2	χ^2=1,48; p=0,22; RR=2, OR=4

p* - difference between healthy individuals and patients with acute edematous pancreatitis; p** - difference between healthy individuals and patients with sterile and infected pancreatic necrosis; p*** - difference between patients with acute edematous pancreatitis and patients with sterile and infected pancreatic necrosis.

According to the results in Table 3, differences were shown between the morphological types of acute pancreatitis for the PRSS1 (Arg122His) gene polymorphism. The probability of acute edematous pancreatitis did not differ significantly at the genotype and allele level ($\chi2$=0.1; p=0.75; RR=1.2, OR=1.6; Risk in Exposed=50%, Risk in Unexposed=38.9%, Overall Risk=39.1% and $\chi2$=0.1; p=0.75; RR=1.2, OR=1.6; Risk in Exposed=50%, Risk in Unexposed=39%, Overall Risk=39.1%). Nevertheless, the odds of this condition were 1.6 times higher (OR), and the diagnostic value was 50%. Furthermore, there were practically no differences observed between the genotype and allele.

The study of the probability of sterile and infected pancreatic necrosis in the context of the PRSS1 (Arg122His) gene polymorphism at the genotype and allele levels also did not yield statistically significant results ($\chi2$=2.93; p=0.09; RR=2.9, OR=6.6). However, it was found that the probability indicators for sterile and infected pancreatic necrosis were somewhat higher than for acute edematous pancreatitis (OR=6.6; Risk in Exposed=66.7% vs. OR=1.6; Risk in Exposed=50%).

A comparative study of the PRSS1 (Arg122His) gene polymorphism in acute edematous pancreatitis versus sterile and infected pancreatic necrosis yielded low significance indicators at both the genotype and allele levels ($\chi2$=1.51; p=0.22; RR=2.1, OR=4.2; Risk in Exposed=66.7%, Risk in Unexposed=32.3%, Overall Risk=33.8% and $\chi2$=1.48; p=0.22; RR=2, OR=4; Risk in Exposed=66.7%, Risk in Unexposed=33.1%, Overall Risk=33.8%).

Based on the foregoing, it can be concluded that the PRSS1 (Arg122His) gene polymorphism has a statistically significant effect on the development of acute pancreatitis ($p<0.05$) but does not have a significant effect on its morphological forms ($p>0.05$). However, it does increase the odds of necrotic changes severalfold (OR=6.6).

4. Conclusion

Thus, environmental factors, alongside genetic factors, play an important role in the mechanism of acute pancreatitis development. To date, the role of the PRSS1 (Arg122His) gene polymorphism, which is involved in the mechanism of pancreatitis development, has been established. Ethnic differences have been identified in the distribution of allele and genotype frequencies of this gene's polymorphic variant. Further advancement of molecular genetic research through the study of the genetic basis of pancreatitis is crucial for developing new diagnostic methods and determining treatment strategies with an individualized approach for each patient. The PRSS1 (Arg122His) gene polymorphisms we studied have varying effects on the development of acute pancreatitis, its contributing factors (such as alcohol), and the course of the disease. Moreover, the PRSS1 (Arg122His) gene polymorphism plays a statistically significant role in the development of acute pancreatitis in cases of alcoholic pancreatitis.

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