



## POLYMORPHISM OF IL-8 CYTOKINE GENE IN PATIENTS WITH PANCREATOGENIC PERITONITIS

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**Цель.** Данное предварительное исследование проводилось с целью определения возможной связи генетического полиморфизма цитокина IL-8 (-251A/T) с его влиянием на варианты клинического течения и исхода острого панкреатита, осложненного панкреатогенным перитонитом.

**Материал и методы.** Данными для исследования были образцы ДНК из лейкоцитов периферической крови 143 человек: 83 пациента с острым панкреатитом, осложненным панкреатогенным перитонитом, 60 здоровых доноров без острого панкреатита в анамнезе как группа сравнения. Анализ полиморфизма гена цитокина IL-8 (-251A/T) выполнялся методом полимеразной цепной реакции с последующим анализом длины рестрикционных фрагментов (PCR-RFLP).

**Результаты.** Анализ частоты аллельных вариантов гена цитокина IL-8 (-251A/T) выявил, что в группе здоровых доноров доминирующим вариантом в 45% случаев были гетерозиготы (генотип A/T). При исследовании наблюдалась достоверно ( $p < 0,05$ ) повышенная частота носителей генотипа T/T в группе оперированных пациентов в сравнении с неоперированными пациентами. Это может свидетельствовать о прогностической связи генотипа T/T с неблагоприятным течением панкреатогенного перитонита ( $OR > 1$ ). Среди оперированных пациентов наблюдалась достоверно ( $p < 0,05$ ) сниженная частота носителей генотипа A/T в сравнении с неоперированными пациентами. Это может указывать на прогностическую связь генотипа A/T с благоприятным течением панкреатогенного перитонита ( $OR < 1$ ). Носители генотипа A/A регистрировались редко, что, возможно, связано с региональными особенностями генотипа пациентов.

**Заключение.** Это предварительное исследование предполагает, что определение генетического полиморфизма цитокина IL-8 (-251A/T) может быть информативным и служить как дополнительный критерий прогнозирования клинического течения и исхода панкреатогенного перитонита, а также указывать на степень нуждаемости в оперативном лечении. Однако возможная роль полиморфизма цитокина IL-8 (-251A/T) в клиническом течении панкреатогенного перитонита требует дальнейшего тщательно спланированного когортного исследования.

*Ключевые слова:* острый панкреатит, панкреатогенный перитонит, интерлейкин-8, полиморфизм генов, иммунный ответ, цитокины

**Objective.** This preliminary study was conducted to assess the possible association of IL-8 (-251A/T) polymorphism with clinical course and outcome of acute pancreatitis aggravated by pancreatogenic peritonitis.

**Methods.** Data for the study were DNA samples, received from the leucocytes of 143 humans: 83 patients with acute pancreatitis aggravated by pancreatogenic peritonitis, 60 healthy blood donors without acute pancreatitis in the anamnesis served as controls. IL-8 (-251A/T) polymorphism detection was made with polymerase chain reaction with further length analysis of the restriction fragments.

**Results.** The analysis of frequency of allelic variants of the cytokine gene IL-8 (-251A/T) revealed that genotype A/T was the dominant variant (45%) among healthy blood donors. Distribution of IL-8 (-251A/T) polymorphism among the patients with pancreatogenic peritonitis without and after surgical treatment is characterized by dominance of genotype T/T in group after surgical treatment ( $p < 0.05$ ). This may indicate association of genotype T/T and unfavorable clinical course of pancreatogenic peritonitis ( $OR > 1$ ). Among patients after surgical treatment genotype A/T was less often met in comparison with the group without it ( $p < 0.05$ ). This may indicate the association of genotype A/T and favorable clinical course of pancreatogenic peritonitis ( $OR < 1$ ). Genotype A/A was rarely registered, which may be due to regional peculiarities of the patient's genotype.

**Conclusions.** This preliminary study suggests that the identification of genetic polymorphism of IL-8 (-251A/T) may be informative and serve as an additional criterion to predict both the clinical course and outcome of pancreatogenic peritonitis; it may also specify indications for surgical treatment. However, the possible role of IL-8 (-251A/T) cytokine polymorphism in the outcome of pancreatogenic peritonitis requires further carefully planned cohort investigations.

*Keywords:* acute pancreatitis, pancreatogenic peritonitis, interleukin-8, gene polymorphism, immune response, cytokines

### Научная новизна статьи

Проведен анализ частоты встречаемости аллельных вариантов гена цитокина IL-8 (-251A/T) у пациентов с различными вариантами течения панкреатогенного перитонита. Наблюдалась повышенная частота носителей генотипа T/T и сниженная частота носителей генотипа A/T в группе оперированных пациентов в сравнении с неоперированными пациентами. Определение генетического полиморфизма цитокина IL-8 (-251A/T) может служить дополнительным критерием прогнозирования клинического течения и исхода панкреатогенного перитонита, а также указывать на степень нуждаемости в оперативном лечении.

### What this paper adds

The frequency of allelic variants of the IL-8 (-251A/T) cytokine gene was analyzed among the patients with different variants of pancreatogenic peritonitis. There was an increased frequency of carriers of the T/T genotype and a reduced frequency of carriers of the A/T genotype in the group of the operated patients in comparison with the unoperated patients. The determination of the genetic polymorphism of IL-8 cytokine (-251A/T) can serve as an additional criterion for predicting the clinical course and outcome of pancreatogenic peritonitis, and also indicate the extent of need for surgical treatment.

### Introduction

According to modern concepts, acute pancreatitis (AP) is a multifactorial polyethiological disease with complex multicomponent pathogenesis [1]. The urgency of research problems of diagnosis and prognosis of the AP course of is due to the fact that, according to the Center for Medical Statistics of the Ministry of Health of Ukraine, it is established that for 2006-2013 hospitalization rates in case of AP increased by 11.6%, and the postoperative mortality rate for this period was 14.0-10.8%, indicating a downward trend, but exceeding the global values [2]. Despite the improvement of diagnostic methods, the success of modern intensive care and surgical treatment, lethality in complicated forms of AP is according to different data from 25 to 85% without a significant downward trend [3]. Inflammation of the pancreas and peripancreatic tissue, peritoneal exudation and progression of the intestinal paresis lead to the development of pancreatogenic peritonitis with subsequent increase in intra-abdominal pressure, which may contribute to the development of the multiple organ dysfunction [4, 5, 6]. The initial phase of AP development is characterized by premature intracellular activation of proteolytic, and then other enzymes (elastase, phospholipase A2). United localization with lysosomal enzymes leads to the destruction of pancreatic tissue [7]. The pancreatic response to the stimulus is non-specific, independent of the factor inducing the pathological process and is realized by the synthesis and secretion of a large number of inflammatory mediators (IL-1, IL-6, IL-8, IL-10, TNF-) into the blood. The imbalance between the mediators of inflammation leads to a "cytokine storm" and multiple organ failure [8, 9, 10, 11, 12].

Multicentre studies indicate the relationship of polymorphism of the IL-8 gene (-251AT) to the probability of AP development, namely the carriage of heterozygote A/T is associated with an increased risk of AP development [13]. At the same time, monocenter studies on small groups give different

variants of genetic polymorphism of IL-8 (-251AT) with the risk of developmental probability and variants of AP course [14, 15]. Possible reasons for the data discrepancy are the features of the patients' genotypes of the regions studied.

In international publications, data on the possible association of IL-8 gene (-251AT) polymorphism with various forms of acute pancreatitis complicated by pancreatogenic peritonitis with the possibility of predicting the clinical course and outcome of the disease are not presented.

**Objective.** This preliminary study was conducted to assess the possible association of IL-8 cytokine (-251A/T) polymorphism with clinical course and outcome of acute pancreatitis aggravated by pancreatogenic peritonitis.

### Methods

The study is preliminary and the design of the experiment is a study of a series of cases recruited in the study in accordance with the real capabilities of the research team. To study the polymorphic variants of the cytokine IL-8 (-251AT), DNA samples from the peripheral blood leukocytes were obtained from 143 patients. The main group was represented by the Caucasoid population of the North-Eastern region of Ukraine and was formed from 83 patients with AP complicated by pancreatogenic peritonitis in the first period of the disease (up to 14 days after the onset of the disease). Patients were on inpatient treatment in the ME "Sumy City Clinical Hospital 5". This group included 51 males (61.4%) and 32 females (38.6%), the average age was 53.3 years. The comparison group consisted of 60 healthy donors – Caucasians without AP in the anamnesis, who by sex, age and ethnic origin were comparable to the main group. The diagnosis of pancreatogenic peritonitis was verified on the basis of clinical, laboratory and instrumental examinations. Ultrasound examination (US) allowed determining the presence of effusion in the abdominal cavity, as well as assessing the condition of the pancreas

and adjacent structures. Survey radiography of the abdominal cavity permitted to reveal the phenomenon of intestinal paresis as a consequence of the development of dynamic intestinal obstruction. All patients underwent standard laboratory tests: a clinical analysis of blood and urine, a biochemical blood test, the level of urine diastase was determined. Assessment of the severity of the patients' condition was carried out on the APACHE II scale on admission and after 24 hours. The indication for conducting surgical interventions was the clinical picture of pancreatogenic peritonitis and the presence of more than 500 ml of fluid in the abdominal cavity according to ultrasound. Also, a biochemical study of peritoneal effusion was performed to verify the enzyme character of the effusion. The patients with purulent-septic complications of AP were not included in the study due to the lack of doubt about the severity of the condition and indications for conducting surgical interventions.

Ethical principles reflected in the Constitution of Ukraine and the Helsinki Declaration of the World Medical Association (2013) were fundamental while working with patients. All diagnostic studies were conducted only after the patients received a full explanation of the purpose of the study and with their written consent.

The analysis of polymorphic variants of the cytokine IL-8 (-251A/T) was performed on the basis of the laboratory of the molecular and genetic studies of Sumy State University in accordance with the requirements of the Ethics Board when conducting research involving a human subject. The polymerase chain reaction (PCR) method was used, followed by the analysis of the restriction fragments length (PCR-RFLP). Genotyping was carried out by the method of restrictive analysis of amplification products of the genome region. For the amplification, specific primers of the company "Metabion" (Germany) were used. PCR was performed in the GeneAmp PCR System 2700 thermocycler ("Applied Biosystems", USA). The restriction products were separated with the horizontal electrophoresis (0.13A; 200V) for 25 minutes and DNA was visualized using the transilluminator ("Biocom", RF).

## Statistics

The study calculated relative statistical indicators, namely the relative magnitude of the structure, which indicates the proportion (specific gravity) of the constituent parts in their total result and were represented as a percentage. The determination of the statistical significance of the difference in the obtained data was carried out after checking the normality of the distribution of the results in the groups. To assess the reliability of differences between groups, nonparametric methods of statistical analysis were used: Pearson's chi-squared test ( $\chi^2$ ) and the Fisher's exact test. The calculations were carried out using the 2x2 contingency tables. The level of statistical significance was considered reliable providing that  $p < 0.05$ . The analysis of the association of polymorphisms with a predisposition to different variants of AP course was carried out using the OR-odds ratio with a 95% confidence interval calculation (CI-confidence interval) for it. At  $OR > 1$ , it was believed that the relationship between the factors compared is direct (a risk factor). At  $OR < 1$ , it was believed that the relationship between the factors being compared is inverse (the stability factor).

## Results

Analysis of the polymorphism of the IL-8 gene (-251A/T) showed that in the comparison group, heterozygotes (genotype A/T) prevailed in 45.0%, homozygotes for the main allele (genotype T/T) were 36.6%, homozygotes for minor allele (genotype A/A) – 18.4%. The results of the study of polymorphism of IL-8 (-251A/T) among patients with different forms of AP are presented in Table 1.

The results of the study of polymorphism of IL-8 (-251A/T) among patients with the destructive forms of AP (25 clinical observations), who had indications for surgical intervention (11 patients) in comparison with the non-operated patients (14 patients) are presented in Table 2.

In the analysis of polymorphism of IL-8 (-251A/T) in patients with pancreatogenic peritonitis, the reliably increased ( $p < 0.05$ ) frequency of carriers of the T/T genotype was registered in the

Table 1

**Distribution of carriers of polymorphic variants of IL-8 cytokine among patients with various forms of acute pancreatitis**

Type of polymorphism	Comparison group, n=60		Acute pancreatitis			
	n	%	Edematous form, n=58		Destructive form, n=25	
			n	%	n	%
T/T	22	36.6	22	37.9	8	32
A/T	27	45.0	25	43.1	15	60
A/A	11	18.4	11	19	2	8

Table 2

**Distribution of carriers of polymorphic variants of IL-8 cytokine among patients with destructive forms of acute pancreatitis**

Type of polymorphism	Comparison group, n=60		Destructive form of AP			
	n	%	Non-operated, n=14		Operated, n=11	
			n	%	N	%
T/T	22	36.6	1	7.1*	7	63.6*
A/T	27	45.0	11	78.6**	4	36.4**
A/A	11	18.4	2	14.3	0	0

Note: \*,\*\* – the significance of differences ( $p < 0.05$ , the criteria of  $\chi^2$  and Fisher were used).

group of operated patients in comparison with the non-operated patients ( $OR > 1$ ). Among the operated patients, a reliably reduced ( $p < 0.05$ ) frequency of carriers of the A/T genotype was observed in comparison with the non-operated patients ( $OR < 1$ ). Carriers of the minor allele (genotype A/A) among patients who had indications for surgical interventions were not recorded.

### Discussions

In this preliminary study, the genetic polymorphism of the cytokine IL-8 (-251A/T) was studied in relation to its possible effect on the course variants and the outcome of pancreatogenic peritonitis among the patients with different forms of AP of the North-Eastern region of Ukraine. The design of the experiment was a study of a series of cases, recruited in the study in accordance with the real capabilities of the research team. The distribution of allelic variants of the IL-8 cytokine was characterized by the dominance of the A/T genotype in the comparison group. Among the operated patients, carriers of the T/T genotype were more likely ( $p < 0.05$ ) more often than among the non-operated patients with pancreatogenic peritonitis. This may indicate a prognostic connection of the T/T genotype with the adverse course of pancreatogenic peritonitis ( $OR > 1$ ). Among the operated patients, a reduced frequency of carriers of the A/T genotype was observed ( $p < 0.05$ ) in comparison with the non-operated patients. This may indicate a prognostic link between the genotype A/T and the favorable course of pancreatogenic peritonitis ( $OR < 1$ ). Carriers of the A/A genotype were rarely registered, which may be due to regional peculiarities of the patient's genotype.

The obtained data on the possible effect of genetic polymorphism of IL-8 cytokine (-251A/T) on the course of the course and outcome of AP complicated by pancreatogenic peritonitis, as well as on the occurrence of the need for surgery, do not coincide with the conclusions about the prognosis of development and severity of the AP course, obtained by other researchers in similar size groups

of patients. Possible causes of discrepancies in data are the characteristics of the patient's genotype in the regions studied. The results obtained are indicative, and this study should be continued and expanded in order to obtain more accurate results.

### Conclusions

This preliminary study suggests that the identification of genetic polymorphism of IL-8 cytokine (-251A/T) may be informative and serve as an additional criterion to predict both the clinical course and outcome of AP complicated by pancreatogenic peritonitis; it may also specify indications for surgical treatment. However, the possible role of IL-8 (-251A/T) cytokine polymorphism in the outcome of pancreatogenic peritonitis requires further carefully planned cohort investigations.

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### Conflict of interest

The authors declare that they have no conflict of interest.

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