INFLUENCE OF CYTOKINE GENE POLYMORPHISM OF TNF-A ON THE CLINICAL COURSE OF CHRONIC PANCREATITIS

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Abstract: *a significant contribution to the modern understanding of the pathogenesis of pancreatitis is made directly to the discovery of genes causing or contributing to the risk of developing the disease. In the pathogenesis of pancreatitis crucial role played by dysfunction of the cytokine cascade of genes that lead to the expression of a variety of key inflammatory mediators and promoting destructive and inflammatory changes of the pancreas. Necrosis Factor-α tumors (TNF- α) plays an important role in the normal regulation of differentiation, growth and metabolism of various cells, and at the same time - a potent proinflammatory cytokine. TNF-α modulates gene transcription and expression of growth factors and stimulates the synthesis of the proinflammatory interleukins -1 and - 6, main inductor generalized inflammatory responses in various organs and tissues including and in the pancreas. Our results suggest that the A allele and heterozygous genotype G / A polymorphism rs1800629 were significant predictors of increased risk of CP (P <0.05) and is a predictor of severe disease. Therefore, homozygous genotype G / G is a reliable protective marker with respect to the flow of development and severity of the disease (χ2 = 4.0; P = 0.04; OR = 0.5; 95% CI0.2408- 0.9927).*
Keywords: *Chronic Pancreatitis, gene TNF-α, genes polymorphism.*

ВЛИЯНИЕ ПОЛИМОРФИЗМА ГЕНА ЦИТОКИНА TNF- НА КЛИНИЧЕСКОЕ ТЕЧЕНИЕ ХРОНИЧЕСКОГО ПАНКРЕАТИТА

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Аннотация: *в патогенезе панкреатита важнейшую роль играет дисфункция генов цитокинового каскада, обуславливающая экспрессию различных ключевых медиаторов воспаления и способствующая деструктивно-воспалительным изменениям поджелудочной железы. Фактор некроза опухолей- (TNF-) играет важную роль в регуляции нормальной дифференцировки, роста и метаболизма различных клеток, и в то же время – мощный провоспалительный цитокин. TNF- модулирует экспрессию генов транскрипционных и ростовых факторов и стимулирует синтез провоспалительных интерлейкинов -1 и - 6, основного индуктора генерализованной воспалительной реакции в различных органах и тканях, в том числе, и в поджелудочной железе. Полученные нами результаты позволяют предположить, что аллель А и гетерозиготный генотип G/A полиморфизма rs1800629 являются значимыми предикторами повышенного риска развития ХП (P<0.05) и является прогностическим фактором тяжелого течения заболевания. Следовательно, гомозиготный генотип G/G является достоверным протективным маркером в отношении развития и тяжести течения данного заболевания (χ^2=4.0; P=0.04; OR=0.5; 95%CI0.2408- 0.9927).*
Ключевые слова: *хронический панкреатит, ген TNF-α, полиморфизм генов.*

A significant contribution to the modern understanding of the pathogenesis of pancreatitis is made directly to the discovery of genes causing or contributing to the risk of developing the disease [7]. In the pathogenesis of pancreatitis crucial role played by dysfunction of the cytokine cascade of genes that lead to the expression of a variety of key inflammatory mediators and promoting destructive and inflammatory changes of the pancreas [1, 4]. Necrosis Factor-α tumors (TNF- α) plays an important role in the normal regulation of differentiation, growth and metabolism of various cells, and at the same time - a potent proinflammatory cytokine [2, 6]. TNF-α modulates gene transcription and expression of growth factors and stimulates the synthesis of the proinflammatory interleukins -1 and - 6, main inductor generalized inflammatory responses in various organs and tissues including and in the pancreas [3, 5]. 116 DNA samples from patients with CP and 115 conditionally healthy donors were studied Total contact (control group). All patients underwent standard general clinical and basic biochemical analyzes, and they were divided into 2 groups of comparison (comparison group). The first subgroup accounted for 84 patients aged 48,4 ± 0,65 (subgroup 1). The second subgroup included 32 patients aged 62,9 ± 0,76 (subgroup 2).

Comparison of TNF-α frequencies of alleles and genotypes of rs1800629 polymorphism of the gene among patients with CP and comparison groups conducted by the "case-control".

At the initial stage we studied the diagnostic efficiency of polymorphism rs1800629 TNF-α gene to predict the pancreatitis risk. -SE performance sensitivity and specificity - SP genetic marker rs1800629 gene TNF-α in the combined group were equal to 0.22 and 0.85 respectively, and the evaluation of AUC was equal to 0.54 (P = 0.1). As in the combined group CP patients, patients in subgroups A and B parameters also strongly deflected sideways and specificity in both cases were equal when SP = 0.85 SE = 0.56 and 0.12, respectively. The calculated values of predictive efficiency (AUC = 0.56 and 0.49, respectively) in these subgroups also indirectly indicate not a very high level of efficiency Classifier polymorphism G-308A TNF-α gene as an independent genetic marker at a statistically significant values (P = 0.06 and P = 0.7, respectively).

In the study of the role of a specific gene polymorphism on the development and progression of the disease process, there are many serious problems. In some cases, evaluation of gene effects on the risk of developing the disease is complicated by the existence of differing in ethnic or population groups of alleles and genotypes. Therefore, each individual population should be examined both in the nature and level of polymorphism susceptibility to multifactorial diseases, including HP.

In the studied sample as a whole is marked predominance of the G allele frequency and the corresponding genotypes. The highest frequency is homozygous genotype G / G. A characteristic feature is the lack of distribution of genotypes homozygous for the allele A in all samples examined. As it is known, in the ontogeny age redistribution of carriers of polymorphism genotypes in the population with the elimination of it unfavorable genotypes carriers and a corresponding increase of other carriers. The absence of homozygous A / A (associated with high levels of expression of the gene), is a characteristic and may indicate a specific developmental effects of different genotypes.

In the studied group of patients and control of the actual distribution of the wild genotype G / G significantly reduced compared with the theoretical (0.78 / 0.79 and 0.85 / 0.86, respectively), and the expected distribution of the heterozygous genotype G / A not significantly reduced (0.2 / 0.22 and 0.14 / 0.15, respectively).

In the next stage of the work we assessed the state of genetic diversity polymorphism rs1800629 gene TNF-α, by calculating the relative deviation index (D) of the observed heterozygosity expected. observed heterozygosity (Hobs), expected heterozygosity (Hexp) and the index of deviation from Hobs Hexp (D) were calculated.

The groups studied the actual value of allelic diversity varied Hobs = 0,15 in the control group and from Hobs = 0,12 (subgroup B) to Hobs = 0,26 (subgroup A) among CP patients. Expected allele frequency diversity Hexp = 0,14 varied in the control group and from Hexp = 0,12 (subgroup B) = 0.23 to H0 (subgroup A) among CP patients. The calculated level of heterozygosity in both groups is very low, and the rate of the index relative deviation D is to the right of 0, then there is a positive (D> 0). The revealed fact indicates higher frequency of heterozygotes evidence in relation to the expected heterozygotes

Thus, the distribution of allele frequencies and genotype polymorphism rs1800629 gene TNF-α, in a community sample, and in the group of patients with CP corresponds to the RCE. Both samples were characterized by high values of frequencies of wild-G / G genotype and the relatively low level of heterozygosity and genetic variability, respectively. Relatively low heterozygosity Hexp = 0.22 and the absence of the mutated genotype A / A, is probably the result of natural selection, ie, genotypes containing the mutant allele A may partially eliminated under certain adverse conditions.

Studying the distribution of genotypes and alleles of the polymorphism rs1800629 TNF-α gene in patients and control groups, as can be seen from Tables 8-11, a comparative analysis of genotype distribution and allele frequencies - rs1800629 TNF-α gene between the total group of patients with CP and the control group was not no statistically significant difference (P> 0.05).

Thus, functionally unfavorable allele A statistically significant prevailed in HP patients compared with the control group (11.2% vs. 7.4%) and a favorable allele of the G, on the contrary, was more common in the control group compared with the patients (92.6% vs. 88.8%).

According to the odds ratio, the risk of CP in carriers of mutant A allele polymorphism rs1800629 TNF-α gene in a 1.6-fold higher ($\chi 2 = 2.0$; P = 0.1; OR = 1.6; 95% CI0.8334- 3.001) compared to the G allele carriage.

The frequency distribution of genotypes of G / G, A / G and A / A patients in the study group and was not statistically different from the control group. The main frequency of these patients genotypes was 77.6%, 22.4% and 0.0%, whereas in the control group, 85.2%, 14.8% and 0.0% respectively. Comparative statistical analysis of the frequency distribution of the unfavorable genotype A / G polymorphism rs1800629 gene TNF-α also showed no statistically significant differences in the group combined patients and controls (22.4% and 14.8%, respectively; $\chi 2 = 2.2$; P = 0.1; OR = 1.7; 95% CI0.848- 3.271). As can be seen, adverse homozygous genotype A / A is associated with a high concentration of cytokines was not detected in both groups.

However, a comparative analysis of allele frequencies of occurrence depending on the clinical stage of KP, we have a tendency prevailing prevalence of the mutant allele in the absence of significant differences. A allele was more common in patients with severe patients with a severe form of CP than controls (13.1% vs 7.4%; $\chi 2 =$

3.6; P = 0.06; OR = 1.9; 95% CI 0.969- 3.678). The predominance of the number of carriers of the mutant allele investigated in this subgroup of patients may indicate the existence of a pathogenetic link between this genetic polymorphism and HP.

frequency distribution genotype G / G, A / G and A / A polymorphism rs1800629 TNF-α gene in a subset of patients with severe CP was 73.8%, 26.8% and 0.0%, respectively (85.2% in the control group, 14.8% and 0.0%). Statistical analysis showed a significant increase in the frequency of the genotype A / G patients (26.8%) compared with the control group (14.8%). According to the odds ratio, the risk of developing a severe form of CP in the presence of the genotype significantly increased more than 2 times ($\chi2 = 4.0$; P = 0.04; OR = 2.1; 95% CI1.007- 4.154). In addition, it revealed a significant protective effect of homozygous G / G genotype with respect to the development of CP ($\chi2 = 4.0$; P = 0.04; OR = 0.5; 95% CI0.2408- 0.9927).

The frequency of allele A and G polymorphism rs1800629 TNF-α gene in the investigated sub-group B were as follows: 93.7% and 6.2%. The frequency of occurrence of the mutant allele "G" in this subgroup did not differ statistically compared with control group ($\chi2 = 0.1$; P = 0.7; OR = 0.8; 95% CI 0.2709, 2.576). The frequency distribution of genotypes of the polymorphic variant also showed no significant differences between the main group and the comparison group in the total sample (P> 0.05). Such ambiguity of the data regarding the role of the gene rs1800629 TNF-α in determining susceptibility to CP and the clinical course may be an indication that the gene serves as a key regulator gene, whose phenotypic effect against HP pathogenesis slightly expressed.

There were no differences in the distribution of allele frequencies and genotype polymorphism rs1800629 TNF-α gene compared to A and B subgroups (P> 0.05). However, there was a trend to an increase in the frequency of carriage "mutant" alleles and genotypes of this polymorphism in the subgroup of A, in the differences between these were close to the level of statistical significance ($\chi2 = 2.1$; P = 0.1; OR = 2.3; 95% CI0. 7472, 6,837 and $\chi2 = 2.5$; P = 0.1; OR = 2.5; 95% CI0.78-7.884). This trend confirms the hypothesis as a whole in favor of the functional impact of adverse allele and genotypic variants of this gene on the formation and progression of CP.

Thus, our results suggest that the A allele and heterozygous genotype G / A polymorphism rs1800629 were significant predictors of increased risk of CP (P <0.05) and is a predictor of severe disease. Therefore, homozygous genotype G / G is a reliable protective marker with respect to the flow of development and severity of the disease ($\chi2 = 4.0$; P = 0.04; OR = 0.5; 95% CI0.2408- 0.9927).

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