THE ROLE OF SOME XENOBIOTIC BIOTRANSFORMATION GENES SNP IN THE DEVELOPMENT OF ACUTE PANCREATITIS

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Genetically determined features of the xenobiotic biotransformation system play an important role in the development of acute pancreatitis (AP) and its complications. The aim of this study was to assess the contribution of 3 SNPs (CYP1A1 -1293 T>C rs1048943, CYP2E1 -1293 G>C rs3813867 and ABCB1 -3435 G>A rs1045642) to the development of AP and its complications. DNA samples were collected from 547 unrelated patients with AP (154 women and 393 men; mean age 48.9 ± 13.1 years) undergoing therapy at surgery departments of Kursk and 573 unrelated individuals without gastrointestinal diseases (161 women and 412 men; mean age 47.8 ± 12.1 years). The polymorphisms were genotyped by PCR using TaqMan probes for allele discrimination. Infected pancreatic necrosis (IPN) was observed in 97 patients; 101 patients developed a pseudocyst (PC); 111 patients had a peripancreatic necrosis (PN). AP was the most common in the carriers of the А allele in ABCB1 G>A (p = 0.0008). The carriers of the G/G genotype rarely developed both AP (p = 5·10^-4) and its complications: IPN (p = 0.03), PN (p = 0.036), PC (p = 0.04). The carriers of the G/C–C/C CYP2E1 G>C (rs3813867) genotypes who had no long-term history of alcohol abuse rarely developed AP (p = 0.03). The carriers of the G/C CYP2E1 (rs3813867) genotype tended to develop pseudocysts (p = 0.050). AP was more frequently complicated by IPN (p = 0.009), PN (p = 0.003) and PC (p = 0.003) in the carriers of the C/C CYP1A1 T>C (rs1048943) genotype. A milder course of AP was typical for the carriers of the G/G ABCB1 G>A (rs1045642) genotype; a more severe course was characteristic of the carriers of the C/C CYP1A1 T>C (rs1048943) genotype.

Keywords: acute pancreatitis, xenobiotic biotransformation enzyme genes, genetic polymorphism, rs1045642, rs1048943, rs3813867

Author contribution: Samgina TA conceived and designed the study, conducted clinical and molecular-genetic tests, analyzed and interpreted the obtained data, and wrote the manuscript; Nazarenko PM supervised surgical treatment and postoperative care at Kursk City Clinical Hospital № 4 and recruited patients for the study; Polonikov AV supervised genetic testing; Lazenarenko VA supervised the study.

Compliance with ethical standards: the study was approved by the Ethics Committee of Kursk State Medical University (Protocol № 3 dated March 11, 2013). The patients gave informed consent to participate.

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In recent years, there has been a lot of research into the contribution of environmental chemicals and disrupted proc oxidant-antioxidant balance to the development of acute pancreatitis (AP). For example, acute nonbiliary pancreatitis has been associated with smoking [1]; smokers and alcohol abusers with AP have been shown to be at increased risk for necrotizing pancreatitis [2]. Despite numerous research efforts, though, genetic mechanisms underlying predisposition

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ЗНАЧЕНИЕ ОДНОНУКЛЕОТИДНОГО ПОЛИМОРФИЗМА НЕКОТОРЫХ ГЕНЫ СИСТЕМЫ БИОТРАНСФОРМАЦИИ КСЕНОБИОТИКОВ В РАЗВИТИИ ОСТРОГО ПАНКРЕАТИТА

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Генетически детерминированные особенности функционирования системы биотрансформации ксенобиотиков играют важную роль в развитии острого панкреатита (ОП) и его осложнений. Целью работы было определить вклад однонуклеотидных полиморфизмов генов CYP1A1 -1293 T>C rs1048943, CYP2E1 -1293 G>C rs3813867 и ABCB1 -3435 G>A rs1045642 в развитие ОП и его осложнений. Образцы ДНК получали от 547 неродственных больных ОП (154 женщины и 393 мужчины; средний возраст составил 48,9 ± 13,1, находившихся на стационарном лечении в хирургических отделениях города Курска и 573 неродственных индивида без заболеваний ЖКТ (161 женщина и 412 мужчин; средний возраст — 47,8 ± 12,1). Генотипирование полиморфизмов изучаемых генов выполняли методом ПЦР путем дискриминации аллерелей с помощью TaqMan-зондов. У 97 пациентов развился инфицированный панкреатоневроз (ИП), у 101 — панкреонекроз (ПК), у 111 — гнойно-некротический перипанкреатит (ГНП). Установлено, что у носителей аллеля А гена ABCB1 G>A (rs1045642) чаще развивался ОП (p = 0,0008), у носителей генотипа G/G редко развивался как ОП (p = 5·10^-4), так и его осложнения: ИП (p = 0,003), ГНП (p = 0,003). Отсутствие длительного злоупотребления алкогольными напитками у носителей генотипов G/C–C/C CYP2E1 G>C (rs3813867) редко приводило к развитию ОП (p = 0,03), у носителей генотипа G/C CYP2E1 (rs3813867) ОП было более частым, чем у носителей генотипа C/C CYP1A1 T>C (rs1048943) (p = 0,050), чаще возникала псевдокиста. У носителей генотипа C/C CYP1A1 T>C ОП чаще осложнялся ИП (p = 0,009), ГНП (p = 0,003), ПК (p = 0,003). В целом, для носителей генотипов G/G ABCB1 G>A (rs1045642) было характерно более легкое течение ОП, тяжелое течение было характерно для носителей C/C CYP1A1 T>C (rs1048943).

Ключевые слова: острый панкреатит, гены ферментов биотрансформации ксенобиотиков, генетический полиморфизм, rs1045642, rs1048943, rs3813867

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CYP2E1 genes are associated with increased activity

The transmembrane protein ABCB1 is a member of the subfamily of broad-specificity ATP-dependent drug/xenobiotic transporters. This protein inhibits accumulation of narcotic drugs in multidrug resistant cells and often mediates resistance to antitumor medications. ABC genes constitute 7 different subfamilies. The ABCB1 protein is a member of the MDR/TAP subfamily; the gene encoding this protein is located on the chromosomal region 7q21.12. ABCB1 is primarily expressed in the testes, muscle, intestine, stomach and pancreas. There have been studies of its role in the development of colorectal cancer [3, 4] but no statistically significant associations have been reported.

The role of this gene in AP has never been investigated.

So far, the cytochrome P450 oxidase system remains the most well-studied. It comprises CYP1, CYP2 and CYP3 enzyme families responsible for the metabolism of foreign compounds in mammals.

It is reported that polymorphisms of the P450, CYP1A1 and CYP2E1 genes are associated with increased activity of enzymes in patients with pancreatitis [5]. The researchers conclude that CYP1A1 is the most implicated in pancreatitis; it triggers the proteinase cascade, promoting DNA replication and tissue proliferation, generates oxygen radicals, forms reactive intermediates during xenobiotic metabolism, and can activate various carcinogens.

It is known that CYP1A1 (aromatic ligand-dependent aryl hydrocarbon hydroxylase) converts polycyclic aromatic hydrocarbons into highly active mutagenic metabolites in the first phase of xenobiotic biotransformation. The gene encoding the key enzyme is localized in codon 462 of the cytochrome molecule (Ile462Val); substitution in codon 462 of the cytochrome molecule (Ile462Val); this polymorphism and alcohol-induced pancreatitis in AP [10, 11]. The researchers conclude that CYP1A1 is the most important of the factors that influence the development of AP; 2) age of 18–80 years; 3) the absence of biliary pathology, such as gallstones, pancreas divisum and pancreatic injury, including injuries due to surgery/endooscopic manipulations; 4) no previous history of pancreotoxic drugs (hypothiazid, NSAIDs, steroid anti-inflammatory drugs), the absence of autoimmune disorders, infections, allergies (to paints and varnishes), pregnancy/ menopause-related endocrine pathology, diseases of neighboring gastrointestinal organs; 5) no family history of AP. Patients who did not meet the inclusion criteria were excluded from the study.

AP was diagnosed using the AP classification developed by the Russian Society of Surgeons in 2014, which is based on the Atlanta-92 classification and its modifications proposed by the International Association of Pancreatology in collaboration with the International Acute Pancreatitis Classification Working Group in Cochin in 2011 [16, 17]; the patients underwent a standard examination, as well as laboratory (complete blood count and biochemistry) and instrumental (US and MRI of the pancreas, EGD) tests.

The patients were also asked about their lifestyle, including addictions such as smoking and alcohol abuse regarded as the major risk factors for AP [18, 19].

The participants were distributed into two groups depending on the amount of weekly consumed alcohol: 1) consumption below 200 g ethanol a week; 2) consumption above 200 g ethanol a week. This threshold is the median value (grams of pure ethanol) of the maximum weekly alcohol intake considered safe in many countries [20]. Another two groups were formed based on the frequency of alcohol consumption: 1) 1 or 2 days a month or less often; 2) 1 day a week or more often. Also, the participants were divided into two groups based on the total duration of alcohol consumption: 1) less than 10 years; 2) 10 years or more.

Samples of the patients' whole venous blood (5-10 ml) were collected into plastic EDTA-containing (0.5M) test tubes. Then, the samples were frozen and stored at –20 °C until further DNA isolation. DNA was isolated using a standard two-step phenol-chloroform extraction and precipitation in ethanol. First, white blood cells were lysed. Briefly, the white blood cell pellet obtained by centrifuging the sample twice with a sodium phosphate buffer (pH = 7.8) was lysed in the solution containing a TE-buffer, proteinase K and 0.4% sodium dodecyl sulfate (SDS) for 12 h at 42 °C. Then, genomic DNA was isolated from the obtained cell lysate. The first step was extraction in phenol and 10 mM Tris-HCl (pH = 8.0), the second, in phenol and chloroform (1:1); in the final step, extraction was performed in chloroform only. Genomic DNA was precipitated in ice-cold 96% ethanol, air-dried and dissolved in the TE-buffer. Then, the DNA concentration was measured. The obtained DNA was frozen at –20 °C until genotyping.

Genotyping of CYP1A1 -462 T>C rs1048943, CYP2E1 -1293 G>C rs3813867 and ABCB1 -3435 G>A rs1045642.

**METHODS**

DNA samples were collected from 547 unrelated inpatients with AP (154 women and 393 men) undergoing therapy at surgery departments of Kursk in 2012–2015 and 573 unrelated individuals without gastrointestinal diseases (161 women and 412 men). The mean age of the patients was 48.9 ± 13.1 years, the mean age of the healthy controls, 47.8 ± 12.1 years. The following inclusion criteria were applied: 1) the established diagnosis of AP; 2) age of 18–80 years; 3) the absence of biliary pathology, such as gallstones, pancreas divisum and pancreatic injury, including injuries due to surgery/endooscopic manipulations; 4) no previous history of pancreotoxic drugs (hypothiazid, NSAIDs, steroid anti-inflammatory drugs), the absence of autoimmune disorders, infections, allergies (to paints and varnishes), pregnancy/ menopause-related endocrine pathology, diseases of neighboring gastrointestinal organs; 5) no family history of AP. Patients who did not meet the inclusion criteria were excluded from the study.

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RESULTS

No associations were established between the risk of AP and the alleles/genotypes of the polymorphic genes encoding the enzymes involved in xenobiotic biotransformation and antioxidant defense (the codominant model) (Table 1).

The carriers of the A allele in ABCB1 G>A (rs1045642) were at increased risk for AP, unlike the carriers of the G/G genotype, who were at low risk for this condition.

AP was rarely observed in the carriers of the G/C–C/C CYP2E1 G>C (rs3813867) genotypes who did not have a long history of alcohol abuse (Table 2).

Infected pancreatic necrosis occurred more frequently in the carriers of the C/C CYP1A1 T>C (rs1048943) genotype than in the carriers of the G/G ABCB1 G>A (rs1045642) genotype (Table 3).

Pancreatic pseudocysts were observed in the carriers of the C/C CYP1A1 T>C (rs1048943) and G/C CYP2E1 (rs3813867) genotypes more often than in the carriers of the G/G ABCB1 G>A rs1045642 genotype (Table 4).

Table 1. The analysis of the associations between the risk of AP and the alleles/genotypes of the polymorphic genes encoding the enzymes involved in xenobiotic biotransformation and antioxidant defense (the codominant model)

| Gene (SNP ID) | Genotype, allele | Healthy individuals (n=573) | Patients (n=547) | p | OR (95%CI) |
|---------------|-----------------|-----------------------------|-----------------|---|-----------|
| CYP1A1 -462 T>C (rs1048943) | T/T | 507 (91.0) | 489 (90.2) | 0.07 | 1.00 |
| | T/C | 49 (8.8) | 46 (8.5) | | 0.97 (0.64–1.48) |
| | C/C | 1 (0.2) | 7 (1.3) | | 7.26 (0.89–59.21) |
| CYP2E1 -1293 G>C (rs3813867) | G/G | 532 (95.0) | 513 (94.0) | 0.46 | 1.00 |
| | G/C | 22 (3.9) | 29 (5.3) | | 1.37 (0.78–2.41) |
| | C/C | 6 (1.1) | 4 (0.7) | | 0.69 (0.19–2.46) |
| ABCB1 -3435 G>A (rs1045642) | A/A | 158 (28.3) | 183 (33.5) | 5·10^-4 | 1.00 |
| | G/A | 269 (48.2) | 284 (52.0) | | 0.91 (0.70–1.19) |
| | G/G | 131 (23.5) | 79 (14.5) | | 0.52 (0.37–0.74) |
| A | 0.52 | 0.6 | 0.0008 | 1.33 (1.13–1.58) |

Table 2. The impact of alcohol abuse on the development of AP in the presence of alcohol-induced pancreatitis in the carriers of the studied polymorphisms

| Genotype | Healthy individuals (n=573) | Patients (n=547) | OR (95%CI) | p | Risk factor (r^2) |
|----------|-----------------------------|-----------------|-----------|---|-----------------|
| CYP2E1 (rs3813867) | G/G | 119 (90.8) | 173 (96.6) | 0.34 | (0.13–0.94) |
| | G/C–C/C | 12 (8.2) | 6 (3.4) | 4 (3.9) | 0.03 | 1.27 (0.35–4.62) |

Note: *p* — significance threshold in the analysis of interactions between SNPs and the risk factor; the risk factor (r^2) is long-term alcohol abuse (over 10 years).
Table 3. The analysis of the associations between the risk of infected pancreatic necrosis and the genotypes of the studied polymorphisms (the most significant models)

| Gene (SNP ID) | Genotype, allele | Control (n = 573) | Patients with IPN (n = 97) | \( p^2 \) | \( \psi \) OR (95%CI) |
|---------------|-----------------|------------------|---------------------------|---------|----------------|
| CYP1A1 -462 T>C rs1048943 | T/T-T/C | 556 (99.8%) | 93 (96.9%) | 0.0098 | 1.00 |
| | C/C | 1 (0.2%) | 3 (3.1%) | | 15.65 (1.61–152.54) |
| ABCB1 -3435 G>A rs1045642 | A/A-G/A | 427 (76.5%) | 82 (85.4%) | 0.0361 | 1.00 |
| | G/G | 131 (23.5%) | 14 (14.6%) | | 0.54 (0.30–0.99) |

Table 4. The analysis of the associations between the risk of peripancreatic necrosis and the genotypes of the studied polymorphisms (the most significant model)

| Gene (SNP ID) | Genotype, allele | Control (n = 573) | Patients with PC (n = 101) | \( p^2 \) | \( \psi \) OR (95%CI) |
|---------------|-----------------|------------------|---------------------------|---------|----------------|
| CYP1A1 -462 T>C rs1048943 | T/T-T/C | 556 (99.8%) | 97 (96%) | 0.0035 | 1.00 |
| | C/C | 1 (0.2%) | 4 (4%) | | 18.36 (2.03–166.52) |
| CYP2E1 -1293 G>C rs3813867 | G/G-G/C | 538 (96.1%) | 92 (91.1%) | 0.0510 | 1.00 |
| | G/C | 22 (3.9%) | 9 (9.9%) | | 2.43 (1.07–5.56) |
| ABCB1 -3435 G>A rs1045642 | A/A-G/A | 427 (76.5%) | 86 (85.2%) | 0.0411 | 1.00 |
| | G/G | 131 (23.5%) | 15 (14.8%) | | 0.55 (0.30–0.99) |

Table 5. The analysis of the associations between the risk of peripancreatic necrosis and the genotypes of the studied polymorphisms (the most significant model)

| Gene (SNP ID) | Genotype, allele | Control (n = 573) | Patients with PN (n = 111) | \( p^2 \) | \( \psi \) OR (95%CI) |
|---------------|-----------------|------------------|---------------------------|---------|----------------|
| CYP1A1 -462 T>C rs1048943 | T/T-T/C | 556 (99.8%) | 106 (96.4%) | 0.0037 | 1.00 |
| | C/C | 1 (0.2%) | 4 (3.6%) | | 18.00 (1.99–163.22) |
| ABCB1 -3435 G>A (rs1045642) | A/A-G/A | 427 (76.5%) | 94 (85.5%) | 0.0371 | 1.00 |
| | G/G | 131 (23.5%) | 16 (14.6%) | | 0.56 (0.31–0.98) |

CONCLUSIONS

This study aimed at assessing the contribution of SNPs of some xenobiotic biotransformation genes to the development of AP in the residents of Kursk region has detected a few associations between the studied genotypes and the risk for AP and its complications, as well as established the trigger effect of the risk factors on the disease in the carriers of certain genotypes. Based on the analysis of genetic factors, including polymorphic variants of the genes coding for xenobiotic biotransformation enzymes, one can predict the risk of AP and the severity of its clinical course. This opens new opportunities for early diagnosis and timely prevention of the disease. Research into genetic polymorphisms might help to predict the outcomes of the disease and develop personalized approaches to its treatment and prevention.

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