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HIGH INCIDENCE OF RARE *TGFB1* HAPLOTYPES IN CHILDREN WITH BILIARY ATRESIA

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Objective: to evaluate the occurrence of single nucleotide polymorphisms (SNPs) in transforming growth factor beta 1 (*TGFB1*) – rs1800469, rs1800470, rs1800471 – and their haplotypes in children with biliary atresia (BA). **Materials and methods.** We studied 106 pediatric liver recipients aged 4 to 150 (median 8) months, of whom 44 were boys, and 199 healthy individuals aged 32.7 ± 9.6 years, of whom 79 were boys. The indication for pediatric liver transplantation was BA. Genomic DNA was isolated from peripheral blood using a commercial QIAamp DNA Blood Mini Kit on a QIAcube automated analyzer. SNPs rs1800469, rs1800470, and rs1800471 in the *TGFB1* gene were determined by real-time polymerase chain reaction using TaqMan probes on a CFX96 amplifier. **Results.** In children with BA, the occurrence of the investigated SNPs in *TGFB1* was as follows: rs1800469 – 38% GG homozygotes, 50% AG heterozygotes and 12% AA homozygotes; rs1800470 – 39% AA, 44% AG, 17% GG; rs1800471 – 88% CC, 12% GC, 0% GG. The distributions of all the three SNPs followed the Hardy–Weinberg principle. For rs1800469 and rs1800470, the genotype and allele frequencies in children with BA did not differ from those in healthy individuals, whereas for rs1800471, the heterozygous GC genotype was three-fold more frequent in children with BA than in healthy individuals. Haplotype analysis showed the presence of 6 major combinations: 2 most frequent were present in a total of about 66% of patients and 91% of healthy individuals, each of the frequencies practically did not differ between the comparison groups. Significant differences were found in the frequency of 3 rarer haplotypes, A-A-C, G-G-C and G-A-G at position rs1800469, rs1800470, rs1800471, which were observed more frequently in patients with BA by 3.10 (CI 1.59 to 6.04) (p = 0.001), 3.10 (CI 1.55 to 6.17) (p = 0.0015), and 17.02 (CI 1.94 to 149.30) (p = 0.011) times, respectively, than in healthy individuals. **Conclusion.** In children with BA, the occurrence of CG heterozygotes in rs1800471 and the distribution of three rare haplotypes A-A-C, G-G-C and G-A-G of the rs1800469, rs1800470 and rs1800471 SNPs in the *TGFB1* gene significantly differs from that in healthy individuals. It is possible that carriage of rare genotypes and haplotypes of *TGFB1* may predispose to BA in children.

Keywords: congenital and hereditary liver diseases, biliary atresia, pediatric liver recipients, liver transplantation, rs1800469, rs1800470, rs1800471, polymorphism.

INTRODUCTION

Pediatric liver transplantation (LT) is the only effective treatment for end-stage liver disease. Biliary atresia (BA) is the most common cause of liver failure in young children (up to 50% of cases) [1–3].

The incidence of BA, a rare congenital liver pathology, varies by country, ranging from 5 to 11 children per 100,000 newborns. The incidence is higher in Japan and China than in Europe, and girls are more likely than boys to have it [4, 5].

It is unclear exactly what causes BA. In addition to genetic considerations, environmental factors such as viral infection, toxins, or circulatory disorders during the fetal and/or prenatal periods are currently considered. The action of risk factors on the liver leads to inflammatory obliteration of the extrahepatic bile ducts and causes characteristic lesions in the intrahepatic biliary tree. Cholestasis, which results from damage to the common bile duct, triggers a cascade of other pathological processes, including parenchymal inflammation, bile acid buildup and toxic effects, cytokine activation that causes hepatocellular injury and dysfunction, development of fibrosis, which eventually progresses to liver cirrhosis [6–8].

Children with BA have significantly decreased levels of transforming growth factor beta-1 (*TGFB1*), an anti-inflammatory and profibrogenic cytokine that is believed to play a crucial role in the processes of inflammation and fibrosis. Although the exact mechanism regulating the *TGFB1* content in biliary atresia has not been investigated, genetic determination of the cytokine level due to protein polymorphism may be one of the key factors [9–11].

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The cytokine *TGFB1* may exhibit varying degrees of expression and activity in tissues due to the significant variability of the *TGFB1* gene. The *TGFB1* gene currently has three single nucleotide polymorphisms (SNPs) that are believed to be the most important: rs1800469 or C(–509)T – substitution of cytosine for thymine in the promoter region resulting in altered binding to transcription factors; rs1800470 or T(+869)C – substitution of thymine by cytosine in codon 10, leading to replacement of leucine by proline in the cytokine itself; and rs1800471 or C(+915)G – substitution of cytosine by guanine in codon 25, leading to replacement of arginine by proline in the protein [12, 13].

We have previously shown that children with end-stage liver disease have a significantly higher frequency of rare haplotypes of SNPs rs1800469, rs1800470, and rs1800471 in the *TGFB1* gene than healthy individuals. The causes of end-stage liver disease in the cohort under study included various congenital cholestatic or metabolic diseases, as well as acquired cirrhosis or hepatitis. This made it impossible to evaluate the role of the *TGFB1* genetic polymorphism in the development of a particular disease and necessitated the study of more homogeneous (in terms of causes of the disease) patient groups [14].

The aim of the present study was to evaluate the occurrence of the three SNPs in the *TGFB1* gene – rs1800469, rs1800470, rs1800471 – and their haplotypes in pediatric liver recipients with BA.

Evaluation of the role of the TGFB1 genetic polymorphism in biliary atresia would advance our knowledge of the pathogenesis of the disease and allow to come up with new personalized prognostic and therapeutic approaches to the treatment of liver recipients who have been diagnosed with this condition.

MATERIALS AND METHODS

The study included 106 pediatric liver recipients aged 4 to 150 (median, 8) months (44 boys and 62 girls) and 199 healthy individuals aged 32.7 ± 9.6 years (78 boys and 120 girls). The indication for pediatric LT was BA.

BA was diagnosed based on clinical, laboratory and instrumental studies. The examination included laboratory diagnostics, abdominal ultrasound scan and magnetic resonance cholangiopancreatography (MRCP). The activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase (ALP), bilirubin, albumin, total protein were determined. Biochemical parameters revealed signs of cholestasis – increased levels of transaminases, direct bilirubin, and alkaline phosphatase. Ultrasound evaluated the state of intrahepatic bile ducts. MRCP allowed to verify the diagnosis and to specify the anatomy of bile ducts. Morphological methods of investigation were performed at the pathological anatomy department of Shumakov National Medical Research Center of Transplantology and Artificial Organs (department headed by Dr. N.P. Mozheiko (MD)) and included macroscopic description and histologic examination of patients' liver samples.

All patients included in the study underwent living related LT, after which they received double or triple immunosuppressive therapy consisting of tacrolimus, corticosteroids and mycophenolate. Routine examination and treatment of patients were performed in accordance with the clinical guidelines of Shumakov National Medical Research Center of Transplantology and Artificial Organs.

Genomic DNA was isolated from peripheral blood using a commercial QIAamp DNA Blood Mini Kit on automatic analyzer QIAcube™ (Qiagen, Germany) according to the manufacturers' protocols. Polymorphic variants rs1800469 (G>A), rs1800470 (A>G), rs1800471 (G>C) of the TGFB1 gene were tested by real-time polymerase chain reaction using TaqMan probes (Applied Biosystems, USA) on a CFX96™ amplifier (Bio-Rad, USA) according to the manufacturer's instructions.

Statistical processing of the study results was performed using the Microsoft Excel program. Genotype distribution frequencies of the studied SNPs and haplotype structure were analyzed using the SNPstats program [15]. To confirm the independent distribution of alleles in the studied polymorphisms, their compliance with the Hardy–Weinberg principle was checked. The allele frequency was calculated as a percentage using the formula: Allele frequency = ((2 × number of homozygotes) + number of heterozygotes)) / 2 × total number of individuals. Pearson's chi-square test was used to compare the frequencies of genotypes or individual alleles in different groups. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated to quantitatively represent the strength of influence of a possible genotype on a trait. The critical value of the significance level was taken as 0.05.

The protocol of this study was approved by the local ethics committee of Shumakov National Medical Research Center of Transplantology and Artificial Organs. Before participating in the study, patients or their guardians signed a written informed consent, which is kept in their medical records.

RESULTS

In pediatric liver recipients diagnosed with BA (hereinafter referred to as the "BA group") and in healthy adults (control group, hereinafter referred to as "healthy"), genotyping was performed and the occurrence of the 3 most significant TGFB1 gene SNPs – rs1800469, rs1800470, and rs1800471 – were analyzed (Fig.).

As can be seen in Fig., the frequencies of genotypes and alleles of two SNPs – rs1800469 (Fig., a) and rs1800470 (Fig., b) – in children with BA and in healthy individuals are virtually identical.

At the same time, significant differences were found in the distribution of rs1800471 genotypes (Fig., c): the

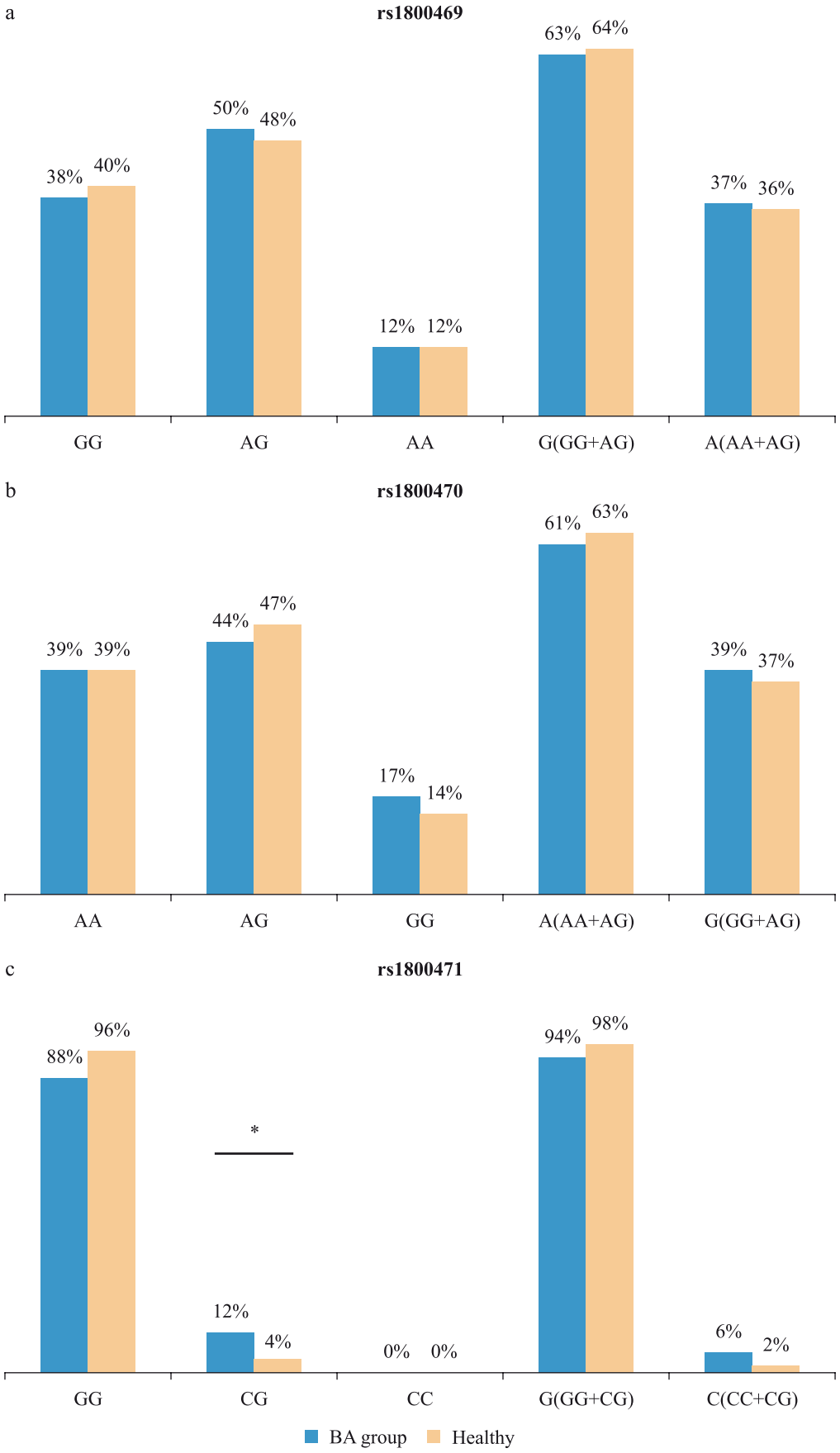

Fig. Distribution of genotypes and alleles of the TGFB1 gene SNPs – rs1800469 (a), rs1800470 (b) and rs1800471 (c) – in children with biliary atresia and in healthy individuals, * $p < 0.05$

heterozygous CG genotype was more than 3 times more frequent in children with BA than in healthy individuals (p = 0.014).

Analysis of allele distribution equilibrium in accordance with the Hardy–Weinberg principle revealed no significant deviations for any of the studied SNPs in both children with BA and in healthy individuals.

To assess the differences in the distribution of genotypes in children with BA and in healthy individuals in different allelic gene interaction models: codominant, dominant, recessive, and over dominant, genotype frequencies, odds ratios, and error bars were calculated for each SNPs (Table 1).

The results presented in Table 1 show that for SNPs rs1800469 and rs1800470, there are no significant differences in the frequency distribution of genetic variants in children with BA and in healthy individuals in any of the allelic gene interaction models.

For SNP rs1800471, there were significant differences in the distribution of genotypes in the only possible codominant model: the CG genotype was more frequent in children with BA than in healthy individuals, OR 3.15 (CI 1.24–7.97), p = 0.014.

The polymorphic areas being examined are found in a single gene, can be inherited in a linked manner [14] and form haplotype combinations that are stable in inheritance.

The distribution of haplotypes rs1800469, rs1800470, and rs1800471 in the study sample was analyzed using the SNPstats program. Table 2 shows the observed haplotypes in decreasing order of frequency of occurrence, frequencies for comparison groups, OR between patients and healthy controls, and the error value.

The result (Table 2) shows that there were 6 major combinations in the studied groups, two of which were the most frequent and were cumulatively present in 66% of children with BA and 91% of healthy individuals. Each of these frequencies did not differ significantly between the children and healthy individuals. The occurrence of haplotype #5, G-G-G, also did not differ significantly between the comparison groups.

At the same time, there were notable differences in the distribution of three rarer haplotypes among the groups under study: #3, #4, and #6 (G-G-C, A-A-C, and G-A-G). Haplotypes #3 and #4 were shown to be three times more prevalent in BA patients than in healthy in the individuals, whereas haplotype #6 was found to be 17 times more prevalent.

DISCUSSION

BA is a complex disease with an unclear etiology; it is likely caused by environmental and/or genetic risk factors. Genetic polymorphism of the key anti-

Table 1

Distribution of the TGFB1 polymorphism in children with biliary atresia and in healthy individuals in different allelic gene interaction models

SNPs/Model	Genotype	Frequency (% of BA)	Frequency (% of healthy)	OR (95% CI)	P value
rs1800469					
Codominant	GG	38.5	40.4	1.00	0.94
	AG	50.0	48	1.09 (0.66–1.82)	
	AA	11.5	11.6	1.04 (0.47–2.31)	
Dominant	GG	38.5	40.4	1.00	0.74
	AG-AA	61.5	59.6	1.08 (0.67–1.76)	
Recessive	GG-AG	88.5	88.4	1.00	0.98
	AA	11.5	11.6	0.99 (0.47–2.08)	
Over dominant	GG-AA	50.0	52.0	1.00	0.74
	AG	50.0	48.0	1.08 (0.67–1.74)	
rs1800470					
Codominant	AA	38.8	39.4	1.00	0.66
	AG	43.7	47.0	0.94 (0.56–1.59)	
	GG	17.5	13.6	1.30 (0.64–2.64)	
Dominant	AA	38.8	39.4	1.00	0.92
	AG-GG	61.2	60.6	1.02 (0.63–1.67)	
Recessive	AA-AG	82.5	86.4	1.00	0.38
	GG	17.5	13.6	1.34 (0.70–2.57)	
Over dominant	AA-GG	56.3	53.0	1.00	0.59
	AG	43.7	47.0	0.88 (0.54–1.41)	
rs1800471					
Codominant	CC	88.3	96.0	1.00	0.014*
	CG	11.7	4.0	**3.15 (1.24–7.97)**	

* p < 0.05.

Table 2

Distribution of the TGFB1 haplotypes in children with BA and in healthy individuals

S/N	Nucleotide in position			Frequency (%)		Odds ratio (95% CI)	P value
	rs1800469	rs1800470	rs1800471	BA	Healthy		
1	G	A	C	45.94	58.85	1.00	–
2	A	G	C	19.63	31.74	1.02 (0.67–1.57)	0.92
3	G	G	C	15.79	3.69	**3.10 (1.59–6.04)**	0.001*
4	A	A	C	12.76	3.72	**3.10 (1.55–6.17)**	0.0015*
5	G	G	G	4.15	1.75	2.31 (0.73–7.36)	0.16
6	G	A	G	1.73	0.25	**17.02 (1.94–149.30)**	0.011*

* $p < 0.05$.

inflammatory and profibrotic cytokine TGFB1 may be one of the causes.

The present study shows that in pediatric liver recipients diagnosed ITH biliary atresia, the frequency of polymorphic variants of the TGFB1 gene and its haplotypes differs significantly from that of healthy individuals.

The occurrence of SNPs rs1800469, rs1800470, and rs1800471 of the TGFB1 gene in healthy individuals, as reported in our work, is consistent with the Hardy–Weinberg principle and agrees with the findings by other authors and with the data presented in the NCBI database (US biotechnology information database) for the European population [16–18].

The distribution of the three *TGFB1* SNPs in children with BA also matches the Hardy–Weinberg equilibrium; the occurrence of genotypes and alleles rs1800469 and rs1800470 is the same as in healthy individuals, whereas the heterozygous CG genotype is three times more common in biliary atresia for rs1800471. The OR for the heterozygous CG genotype rs1800471 in children with BA in the codominant allelic gene interaction model averages 3.15 (CI 1.24–7.97) when compared to the healthy cohort, which may indicate a predisposition to the development of biliary atresia in those with this genotype. Given that there were only a few patients with the CG genotype in the study group, more research using a greater sample size is required.

Cytokine *TGFB1* is involved in the regulation of many key cellular processes, such as immune response, healing, apoptosis, and others; therefore, a significant impairment of its function may be incompatible with life [19]. It is possible that individual single nucleotide substitutions may have little effect on protein function, whereas a combination of several SNPs may be of clinical significance. As a result, we contrasted the haplotype frequencies of the three SNPs in children with BA and in healthy individuals.

The two most frequent haplotypes (G-A-C and A-G-C) were observed in 66% of children with BA and in 91% of healthy individuals, and the prevalence of each haplotype was not significantly different between the compared groups. Statistically significant differences were found in the distribution of 3 rare haplotypes (G-G-C, A-A-C, and G-A-G), which were generally found in 30% of children with BA and in 8% of healthy individuals. Children with BA were found to have rare haplotypes on average 3–17 times more often than healthy individuals, which may indicate that bearers of these haplotypes are predisposed to BA.

To date, no studies of the *TGFB1* genetic polymorphism in young children with BA in the Russian or other populations have been reported. In our previous work, we analyzed the distribution of *TGFB1* gene polymorphism in 225 children in the end-stage of liver failure as a result of various liver diseases, including BA [14]. The TGFB1 genetic polymorphism in young children with BA in the Russian or other populations has not yet been the subject of any published research. The distribution of *TGFB1* gene polymorphisms in 225 children with end-stage liver failure due to a variety of liver diseases, including BA, was examined in our earlier study.

Summarizing the results obtained in this study on the occurrence of polymorphic variants of the *TGFB1* gene and its haplotypes in children with BA and in healthy individuals, we can conclude that the *TGFB1* polymorphism plays a role in the development of BA in children. Therefore, the idea that genetic risk factors play a role in BA is supported by our findings.

The genetic hypothesis is supported by several facts such as familial cases of BA or data showing that 10–20% of children with BA also have other internal organ anomalies. In addition, full genome studies in Chinese and European patients with BA have identified the *XPNPEP1*, *ADD3*, and *PKD1L1* genes, presumably of functional significance for the development of BA. BA can now be regarded as a ciliopathy because of the intense interest generated in the past decade by data on multiple mutations in the genes that control the function of the ciliary apparatus (villi) of cholangiocytes in BA patients [7, 20, 21].

At the same time, it can be said that BA is a complex, heterogeneous disease that may be a common outcome of various disorders, given the abundance of data on its association with cytomegalovirus or human papillomavirus infection, as well as with the toxic effects of environmental factors during pregnancy [22].

CONCLUSION

BA, a rare congenital liver pathology, is most likely caused by environmental and/or genetic factors. The current study compared the distribution of the three most significant *TGFB1* polymorphisms – rs1800469, rs1800470 and rs1800471 – and its haplotypes in children with BA and in healthy individuals. Heterozygous CG genotype rs1800471 was shown to be three times more common in children with BA, while haplotypes G-G-C, A-A-C, and G-A-G (corresponding to rs1800469, rs1800470, and rs1800471) are three to seventeen times more common in these children than in the healthy cohort. This finding suggests that children carrying the CG genotype rs1800471 and haplotypes G-G-C, A-A-C or G-A-G corresponding to rs1800469, rs1800470 and rs1800471 of the TGFB1 gene may be at risk of developing BA.

The authors declare no conflict of interest.

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