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Association of single nucleotide variants of the *SLCO1B1* gene with the Gilbert syndrome phenotype

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ABSTRACT

The aim of the study is to investigate the association of rs2306283 and rs4149056 variants of the *SLCO1B1* gene with benign unconjugated hyperbilirubinemia.

Materials and methods. A case-control study design was employed. The group with the Gilbert syndrome (GS) phenotype comprised 414 individuals (mean age 36.7 ± 15.9 years, 49.8% men). The control group consisted of 429 individuals (mean age 38.5 ± 14.3 years, 52.2% men) randomly selected from DNA banks of MONICA project participants, young adults aged 25–44 years, and participants in a cross-sectional study of schoolchildren in Novosibirsk. Genotyping of the groups for nucleotide sequence variants rs2306283 and rs4149056 of the *SLCO1B1* gene was performed using real-time polymerase chain reaction.

Results. No statistically significant differences were found between the GS and control groups regarding the frequencies of genotypes and alleles of rs2306283 ($p > 0.05$). Carriers of the TT rs4149056 genotype were less common (OR = 0.67, 95% CI 0.51–0.89, $p = 0.005$), while carriers of the TC genotype were more prevalent (OR = 1.46, 95% CI 1.1–1.94, $p = 0.009$) in the GS group compared to the control group. The frequency of the C allele rs4149056 was higher in the GS group compared to the control group (OR = 1.35, 95% CI 1.07–1.7, $p = 0.012$). These differences persisted for carriers of the 6TA/7TA genotype but not for the 6TA/6TA and 7TA/7TA genotypes of rs3064744 in the *UGT1A* gene.

Conclusion. The single nucleotide variant rs2306283 of the *SLCO1B1* gene is not associated with benign unconjugated hyperbilirubinemia. The TC genotype and C allele of the single nucleotide variant rs4149056 of the *SLCO1B1* gene are the genotype and risk allele of Gilbert syndrome, while the TT variant genotype exhibits a protective effect against the development of the syndrome, particularly for carriers of the 6TA/7TA genotype of rs3064744 in the *UGT1A* gene.

Keywords: Gilbert syndrome, gene, rs2306283, rs4149056, *SLCO1B1*, unconjugated hyperbilirubinemia

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Conformity with the principles of ethics. All participants of the study signed an informed consent. The study was approved by the local Ethics committee of the Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (Protocol No. 4 of 14.02.2023).

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Ассоциация однонуклеотидных вариантов гена *SLCO1B1* с фенотипом синдрома Жильбера

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РЕЗЮМЕ

Цель исследования – проверка ассоциации rs2306283 и rs4149056 гена *SLCO1B1* с доброкачественной неконъюгированной гипербилирубинемией.

Материалы и методы. Дизайн исследования «случай – контроль». Группа с фенотипом синдрома Жильбера (СЖ) включала 414 человек (средний возраст 36,7 ± 15,9 лет, 49,8% мужчин). Группа контроля (429 человек, средний возраст 38,5 ± 14,3 лет, 52,2% мужчин) – случайная выборка лиц из банков ДНК участников проекта MONICA, скрининга молодых людей 25–44 лет и одномоментного исследования школьников г. Новосибирска. Генотипирование групп по вариантам нуклеотидной последовательности rs2306283 и rs4149056 гена *SLCO1B1* выполнено методом полимеразной цепной реакции в режиме реального времени.

Результаты. По частотам генотипов и аллелей rs2306283 не найдено статически значимых различий между группой СЖ и контрольной группой ($p > 0,05$). Носители генотипа TT rs4149056 встречаются реже (отношение шансов (ОШ) = 0,67, 95%-й доверительный интервал (95%ДИ) 0,51–0,89, $p = 0,005$), а носители генотипа TC чаще (ОШ = 1,46, 95%ДИ 1,1–1,94, $p = 0,009$) в группе СЖ по сравнению с контрольной группой, частота аллеля C rs4149056 больше в группе СЖ по сравнению с контрольной группой (ОШ = 1,35, 95%ДИ 1,07–1,7, $p = 0,012$). Полученные различия сохраняются для носителей генотипа 6TA/7TA, но не генотипа 6TA/6TA и 7TA/7TA rs3064744 гена *UGT1A*.

Заключение. Однонуклеотидный вариант rs2306283 гена *SLCO1B1* не ассоциирован с доброкачественной неконъюгированной гипербилирубинемией. Генотип TC, аллель C однонуклеотидного варианта rs4149056 гена *SLCO1B1* являются генотипом и аллелем риска синдрома Жильбера, а генотип TT – протективный в отношении развития синдрома, прежде всего для носителей генотипа 6TA/7TA rs3064744 гена *UGT1A*.

Ключевые слова: синдром Жильбера, ген, rs2306283, rs4149056, *SLCO1B1*, неконъюгированная гипербилирубинемия

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INTRODUCTION

The most common genetic cause of benign unconjugated hyperbilirubinemia (Gilbert syndrome, GS) in adults is an increase in the number of TA repeats in the promoter of the *UGT1A1* gene (rs3064744) to 7 in the homozygous state (7TA/7TA). However, some individuals with clinical symptoms of GS do not have an increased number of TA repeats in the homozygous state (6TA/6TA), or are heterozygous carriers of the rs3064744 variant (6TA/7TA), which may indicate the contribution of other singlenucleotide gene variants to the development of pathology [1].

In a genome-wide association study on the Mayo Genome Consortium cohort, two loci were identified that are associated with total bilirubin levels – 2q37 (corresponding to the *UGT1A1* gene) and 12p12 (corresponding to the *SLCO1B1* gene) [2]. A meta-analysis of three genome-wide association studies showed a strong genetic effect on serum bilirubin levels of the *UGT1A1* gene and the 12p12.2 locus. At the same time, the peak signal in the 12p12.2 region was a variant of rs4149056 in the *SLCO1B1* gene, which leads to the replacement of the amino acid valine with alanine, which leads to a decrease in the activity of a carrier protein in the liver with a known affinity for bilirubin [3]. Therefore, we suggested that variants of the *SLCO1B1* gene may be associated with benign unconjugated hyperbilirubinemia. To test this hypothesis, we selected two variants of the *SLCO1B1* gene, rs2306283 and rs4149056, which were the most studied in relation to bilirubin concentration, hyperbilirubinemia.

MATERIALS AND METHODS

The study design is a case-control study. The group of people with the Gilbert syndrome (GS) phenotype (n = 414; average age 36.7 ± 15.9 years, 49.8% were men) was formed by gastroenterologists and included people with unconjugated hyperbilirubinemia who underwent a standard clinical examination. Individuals with known causes of unconjugated hyperbilirubinemia, except for genetic ones, were excluded from the group. DNA was isolated from venous blood using either phenol chloroform extraction or the express method (PREP-RAPID-GENETICS, DNA-Technology LLC, Moscow).

The control group (n = 429; average age 38.5 ± 14.3 years, 52.2% were men) was a random sample of individuals from DNA banks of participants in the MONICA project (Multinational MONItoring of trends and determinants in CArdiovascular disease), a screening of young people aged 25–44 years, and a cross-sectional study of schoolchildren in Novosibirsk. Information on the level of total or unconjugated bilirubin, liver and gallbladder diseases, and diagnosis of GS was not available for these studies, which is a limitation of this study since isolated cases of the diagnosed or undiagnosed GS may be present in the control group. The DNA of the individuals included in the control group was isolated from venous blood using phenol chloroform extraction. The GS group and the control group did not differ in terms of gender and age.

In previous studies, we determined the genotypes of the rs3064744 variant (the number of TA repeats in the promoter) of the *UGT1A1* gene for individuals included in the GS group and the control group. In the GS group, the distribution of genotypes according to rs3064744 of the *UGT1A1* gene was: 73.3% – 7TA/7TA, 20.3% – 6TA/7TA, 5.8% – 6TA/6TA, 0.2% – 5TA/7TA, 6TA/8TA, 7TA/8TA. In the control group, the distribution of genotypes according to rs3064744 of the *UGT1A1* gene was: 11.7% – 7TA/7TA, 42.9% – 6TA/7TA, 45.0% – 6TA/6TA, 0.2% – 5TA/6TA, 6TA/9TA.

Genotyping of groups according to variants of the nucleotide sequences rs2306283 and rs4149056 of the *SLCO1B1* gene was carried out by real-time polymerase chain reaction using kits from NPF SINTOL LLC (Russia) on Light Cycler 96 (Roche, Switzerland/ Germany) (rs4149056) and CFX96 Touch Real-Time PCR Detection System (Bio-Rad, USA) (rs2306283).

Comparison of groups by frequencies of genotypes and alleles and calculation of a relative risk for a specific allele or genotype were carried out using cross tables, the Pearson chi-square criterion ($\chi 2$), and the exact two-sided Fisher criterion with Yates correction for continuity. The normality of the distribution of the level of total and unconjugated bilirubin was checked using the Kolmogorov – Smirnov test, and then the Kruskall – Wallis test and the Mann – Whitney test were used. Quantitative data are presented as median and interquartile range Me [Q_{25}–Q_{75}]; $p < 0.05$ was also used as the significance level.

All participants in the study signed a voluntary informed consent. The study was approved by the Ethics Committee of IIPM – Branch of IC&G SB RAS (Protocol No. 4 of 14.02.2023).

RESULTS

The obtained frequencies of genotypes and alleles of variants rs2306283 and rs4149056 of the *SLCO1B1* gene are presented in Table 1.

Table 1

The frequencies of genotypes and alleles of variants rs2306283 and rs4149056 of the *SLCO1B1* gene in the GS and control groups

Single nucleotide variant	Genotype/ allele	GS group		Control group		*p*
		n	%	*n*	%	
rs2306283	TT	181	43.7	184	42.9	0.25
	TC	148	35.7	173	40.3	
	CC	85	20.6	72	16.8	
	T	510	61.6	541	63.1	0.54
	C	318	38.4	317	36.9	
rs4149056	TT*	228	55.1	277	64.6	0.02
	TC*	164	39.6	133	31.0	
	CC	22	5.3	19	4.4	
	T	620	74.9	687	80.1	0.01
	C	208	25.1	171	19.9	

Note: *n* – number of individuals, *p* – significance of differences between groups. * – statistically significant differences when using the genotype 1 vs genotype 2 + genotype 3 model. No differences were found in the frequencies of rs2306283 genotypes and alleles between the GS group and the control group ($p > 0.05$) (Fig. 1).

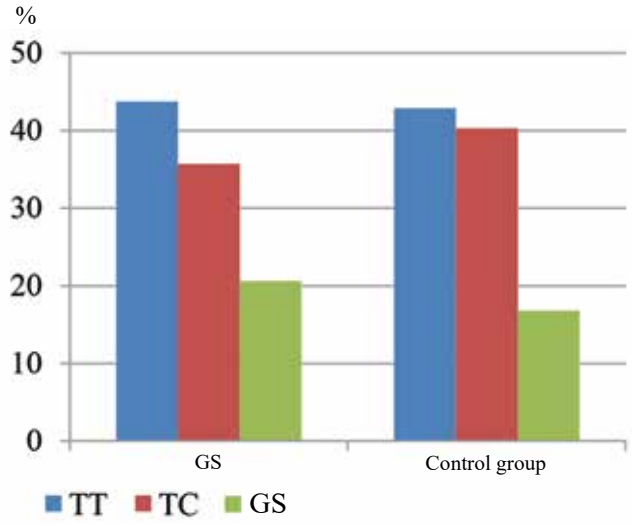

Fig. 1. The frequencies of rs2306283 genotypes of the *SLCO1B1* gene in the GS group and the control group

However, we found differences in the frequencies of rs4149056 genotypes ($p = 0.02$) between the two groups: carriers of the TT genotype were less common (TT vs TC+CC: odds ratio (OR) = 0.67, 95% CI 0.51–0.89, $p = 0.005$), and carriers of the TC genotype were more common (TC vs TT+CC: OR = 1.46, 95% CI 1.1–1.94, $p = 0.009$) in the GS group compared to the control group (Fig. 2). Significant differences were also found in allele frequencies. C allele was more frequent in the GS group (0.25) compared to the control group (0.2) (OR = 1.35, 95% CI 1.07–1.7, $p = 0.012$).

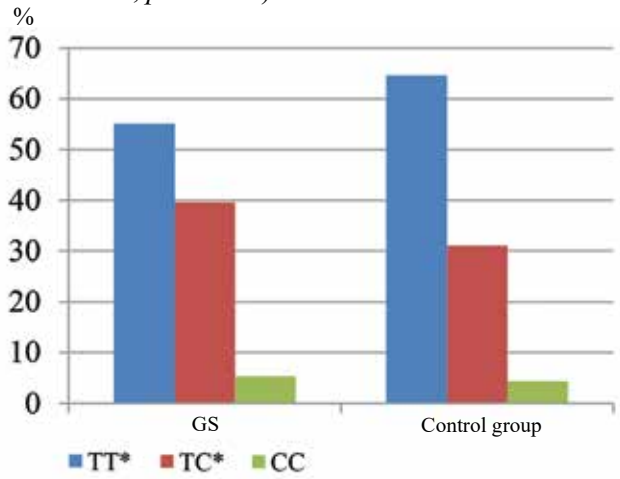

Fig. 2. The frequencies of rs4149056 genotypes of the *SLCO1B1* gene in the GS group and the control group

When dividing the GS group and the control group by genotypes of the rs3064744 variant of the *UGT1A1* gene (excluding rare genotypes 5TA/7TA, 6TA/8TA, 5TA/6TA, 6TA/9TA, 7TA/8TA) into three subgroups – carriers of the genotype 6TA/6TA, 6TA/7TA, and 7TA/7TA – significant differences in the frequencies of the rs4149056 genotype of the *SLCO1B1* gene were only observed in the subgroup of the 6TA/7TA genotype carriers ($p = 0.005$). In carriers of the 6TA/7TA rs3064744 genotype of the *UGT1A1* gene, the TT rs4149056 genotype of the *SLCO1B1* gene is protective against GS (TT vs TC+CC: OR = 0.41, 95% CI 0.24–0.71, $p = 0.002$), while the TC genotype and the C allele are the genotype and allele that increase risk of GS (TC vs TT+CC: OR = 2.36, 95% CI 1.35–4.14, $p = 0.004$; C vs T: OR = 1.91, 95% CI 1.23–2.97, $p = 0.005$, respectively).

There was no association between the genotypes of the rs4149056 variant and the concentration of total or unconjugated bilirubin ($p > 0.05$, Table 2).

Table 2

The concentration of total and unconjugated bilirubin based on the genotype rs4149056, *Me* (Q_{25}–Q_{75}), umol/l

Genotype rs4149056	Total bilirubin	Unconjugated bilirubin
TT	36.8 (27.0–31.3)	30.0 (20.6–35.0)
TC	35.0 (26.2–40.2)	27.9 (20.5–33.6)
CC	36.8 (27.9–40.2)	30.1 (21.3–40.2)

The concentration of total or unconjugated bilirubin with which the association was searched is a randomly detected concentration with which the patient went to see a doctor. During the life of patients, more severe hyperbilirubinemia could be observed. The average concentration of total bilirubin in the GS group was 36.9 umol/l (27.2–42.2), and unconjugated bilirubin level was 29.9 umol/l (21.0–36.1). At the same time, there is a statistically significant difference in the concentration of bilirubins based on the genotypes of the variant rs3064744 of the *UGT1A1* gene. The concentration of total ($p < 0.01$) and unconjugated ($p < 0.01$) bilirubin is higher in carriers of the *UGT1A1* gene genotype 7TA/7TA rs3064744 compared to carriers of the genotypes 6TA/6TA and 6TA/7TA (carriers of rare genotypes were not included in the calculations) (Table 3). Thus, even the randomly detected concentration of total and unconjugated bilirubin is higher in carriers of the 7TA/7TA rs3064744 genotype of the *UGT1A1* gene, which suggests that if there was an association of bilirubin concentration with the genotypes of the rs4149056 variant, it would have been detected.

Table 3

The concentration of total and unconjugated bilirubin based on the genotype rs3064744 of the *UGT1A1* gene, *Me* (Q_{25}–Q_{75}), umol/l

Genotype rs3064744	Total bilirubin	Unconjugated bilirubin
7TA/7TA	38.2 (28.1–44.6)	31.1 (22.2–37.9)
6TA/6TA + 6TA/7TA	31.7 (22.2–37.9)	24.9 (18.5–28.7)

DISCUSSION

The *SLCO1B1* gene (solute carrier organic anion transporter family member 1B1, 12p12.1) encodes a transmembrane receptor specific to liver cells, which mediates the sodium-independent absorption of numerous endogenous compounds, including bilirubin, and participates in the excretion of medicinal compounds, such as statins, bromosulfophthalein, and rifampicin from the blood into hepatocytes [4].

Both of the studied variants belong to the missense variants resulting in the substitution of amino acids in the amino acid sequence of the protein (rs2306283 – c.388A>G, p.Asn130Asp; rs4149056 – c.521T>C, p.Val174Ala).

The obtained frequencies of rare alleles of the studied variants in the control group do not differ from the GnomAD data: the frequency of the rare allele C rs2306283 according to GnomAD data for the European population is 0.37, rs4149056 is 0.2.

The rs2306283 variant according to ClinVar is benign for GS, and Rotor syndrome. It has been shown that the expression of the SLCO1B1 protein is significantly associated with the rs2306283 variant [5]. Studies of the rs2306283 variant have been conducted regarding changes in the metabolism of certain drugs (statins, sorafenib, rocuronium and others) [6–10]. In China, an association of rs2306283 with the risk of pulmonary tuberculosis was found in a group of women [11]. The association of rs2306283 with hyperbilirubinemia was not detected in newborns in China [12]. Our study also did not find an association of the rs2306283 variant with the GS phenotype.

According to ClinVar, the rs4149056 variant is benign for Rotor syndrome, pathogenic for GS, and is related to the metabolism of simvastatin, atorvastatin, and rosuvastatin. There is evidence that the rs4149056 variant reduces the transport activity of the SLCO1B1 protein, which increases the plasma concentration of a number of substances whose transport is associated with this protein [13]. Numerous studies have been conducted on the association of the rs4149056 variant with the development of statin-induced myopathy [14, 15]. In Korea, the relationship of the variant with the pharmacokinetics of rifampicin used in the treatment of tuberculosis has been shown [16]. Carriers of the rs4149056 C allele have an increased risk of bleeding compared to carriers of the TT genotype when taking the drug edoxaban [17]. A study on patients with HIV infection showed the effect of rs4149056 on the concentration of lopinavir (an antiretroviral drug) [18]. Another study found an association between the level of SLCO1B1 protein, allele C and genotype TC rs4149056 with exudative age-related macular degeneration [19]. A Chinese study revealed the association of the CC genotype and C allele of rs4149056 with the risk of pulmonary tuberculosis in women [11]. According to a large meta-analysis in 2009, rs4149056 affects the level of total bilirubin, explaining about 1% of the variability [3]. However, a study in Chile did not find a correlation between rs4149056 and total bilirubin levels or the phenotype of the GS [20].

According to our data, the allele with rs4149056 is a risk allele for unconjugated hyperbilirubinemia, which was also observed in a study in newborns with neonatal hyperbilirubinemia in India. In this case-control design study, carriers of rare alleles of the studied variants, including the rs4149056

variant, were more common in the case group compared to the control group. At the same time, the carriage of more than three of the studied variants (rs4124874, rs8175347 of the *UGT1A1* gene, rs2306283 and rs4149056 of the *SLCO1B1* gene) was also more common in the case group, and the average levels of total bilirubin in the blood and the need for phototherapy increased with the number of coexpressed variants [21]. The association between rs4149056 of the *SLCO1B1* gene and neonatal hyperbilirubinemia was also shown in Chinese newborns: carriers of the CC genotype had a higher risk of neonatal hyperbilirubinemia compared to carriers of other genotypes [22]. According to our data, the TC genotype is a risk genotype for benign unconjugated hyperbilirubinemia.

CONCLUSION

Thus, according to the results of the study, the single nucleotide variant rs2306283 of the *SLCO1B1* gene is not associated with benign unconjugated hyperbilirubinemia. The TC genotype and allele C of the single nucleotide variant rs4149056 of the *SLCO1B1* gene are the genotype and allele with a risk for GS. The TT genotype of the *SLCO1B1* gene is conditionally protective against the development of the syndrome, primarily for carriers of the 6TA/7TA rs3064744 genotype of the *UGT1A* gene.

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