Полиморфизм локуса SLC7A11-PCDH18 может быть новым генетическим фактором риска для ювенильного идиопатического артрита

Бакутенко И.Ю.[1], Гаврильчик И.Д.[1], Сечко Е.В.[2], Козыро И.А.[2], Чичко А.М.[2], Батян Г.М.[2], Сукало А.В.[2], Рябоконь Н.И.[1]

1 – Институт генетики и цитологии Национальной академии наук Беларуси, 220072, Республика Беларусь, г. Минск, ул. Академическая, 27

2 – Белорусский государственный медицинский университет 220116, Республика Беларусь, г. Минск, пр. Дзержинского, 83

Полиморфизм T>C rs13128867, расположенный между генами *SLC7A11* и *PCDH18*, первоначально описан как новый локус предрасположенности к болезни Кавасаки (БК) в китайской популяции. Частью нашего исследования по идентификации аллелей риска ювенильных аутоиммунных ревматических заболеваний был анализ связи между полиморфизмом rs13128867 и БК, ювенильным идиопатическим артритом (ЮИА), ювенильной системной красной волчанкой (ЮСКВ) у представителей европеоидной расы, проживающих в Беларуси.

В исследование было включено 675 детей и подростков, в том числе 289 пациентов в возрасте до 17 лет на момент начала заболеваний и 386 человек, которые не имели аутоиммунных, воспалительных или суставных заболеваний и служили клиническим контролем. Образцы геномной ДНК были генотипированы методом ПЦР в реальном времени. Сравнение случай-контроль было скорректировано по полу с целью уменьшения неравномерности гендерного распределения между группами, а значения *p* были скорректированы с использованием метода Бенджамини-Хохберга.

Частота минорного аллеля C rs13128867 в контрольной группе составила 17,6%, что соответствует другим европейским популяциям. Результаты анализа ассоциации полиморфизма rs13128867 с БК не совпали с данными, полученными в китайской популяции. Дальнейший анализ выявил ассоциацию минорного аллеля rs13128867 с ЮИА (OR = 1,50; 95% ДИ 1,11–2,03; p_{adj} = 0,027) и олигоартритом – наиболее распространенным подтипом ЮИА (OR = 1,67; 95% ДИ 1,17–2,39; p_{adj} = 0,016). Также наблюдалась тенденция к ассоциации минорного аллеля rs13128867 с ЮСКВ. Таким образом, результаты исследования впервые продемонстрировали, что полиморфизм rs13128867 *SLC7A11–PCHD18* может быть новым генетическим фактором риска ЮИА у пациентов европеоидной расы, однако для подтверждения этого факта необходимы дальнейшие исследования.

Ключевые слова: *SLC7A11, PCDH18*, rs13128867, генетический фактор риска, болезнь Кавасаки, ювенильный идиопатический артрит, ювенильная системная красная волчанка, аутоиммунные заболевания

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Polymorphism of the SLC7A11-PCDH18 locus may be a novel genetic risk factor for juvenile idiopathic arthritis

Bakutenko I.Y.[1], Haurylchyk I.D.[1], Sechko E.V.[2], Kozyro I.A.[2], Tchitchko A.M.[2], Batyan G.M.[2], Sukalo A.V.[2], Ryabokon N.I.[1]

1 – Institute of Genetics and Cytology, National Academy of Sciences of Belarus, 27 Akademicheskaya St., 220072 Minsk, Republic of Belarus

2 – Belarusian State Medical University 83 Dzerzhinski Ave., 220116 Minsk, Republic of Belarus

The rs13128867 (T>C) polymorphism located between *SLC7A11* and *PCDH18* genes was originally described as a new susceptibility locus for Kawasaki disease (KD) in the Chinese population. Focusing on the identification of risk alleles for juvenile-onset autoimmune rheumatic diseases, the presented paper aims to demonstrate the results of the study undertaken to investigate an association between the rs13128867 polymorphism and KD, juvenile idiopathic arthritis (JIA), and juvenile systemic lupus erythematosus (JSLE) in Caucasians living in Belarus.

In total, 675 children and adolescents under 17 at the onset of the disease were included in the study performed, and 386 out of them were without any autoimmune, inflammatory, or joint disorders and served as the clinical control. Genomic DNA samples were genotyped using the real-time PCR technique. Case-control comparison was adjusted for sex with a view of reducing uneven gender distribution between the groups, and p-values were adjusted with the Benjamini-Hochberg procedure.

The rs13128867 minor C allele frequency in the control group was found to be 17.6% that is close to other European populations. At the same time, an associative analysis of the rs13128867 polymorphism with KD did not replicate the data known for the Chinese population. Further analysis revealed an association between the rs13128867 minor allele with JIA (OR = 1.50, 95% CI 1.11-2.03, p_{adj} = 0.027) and oligoarthritis – the most common JIA subtype (OR = 1.67, 95% CI 1.17-2.39, p_{adj} = 0.016). A tendency to association of the rs13128867 minor allele and JSLE was also observed. Thus, the study results demonstrated for the first time that the *SLC7A11–PCHD18* rs13128867 polymorphism may be a novel genetic risk factor for JIA in Caucasian patients. However, a further investigation into the rs13128867 polymorphism is strongly required.

Key words: *SLC7A11, PCDH18*, rs13128867, genetic risk factor, Kawasaki disease, juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, autoimmune diseases.

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Corresponding author: Nadezhda I. Ryabokon; **e-mail:** n.ryabokon@igc.by
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Introduction

Autoimmune diseases are a heterogeneous group of chronic diseases affecting various tissues and systems due to the loss of immune tolerance. The social significance of these disorders is high, since up to 3–5% of the world's population, including children and persons of working and reproductive ages, suffers from autoimmune diseases [1] and usually requires continuing therapy. While exact causes of autoimmunity are poorly understood, they may include external (infections, traumas, UV, some drugs etc.), as well as genetic factors. With regards to the latter, it is hard to identify certain genetic alterations directly leading to autoimmune diseases due to their polygenic nature. Therefore, many genome-wide association studies (GWAS) were conducted to determine genetic loci underlying an autoimmune response and a risk of autoimmune disease development. Unfortunately, there are not so many results of GWAS and other genotyping studies of multifactorial diseases that were reproduced in different ethnic populations. This confirms the need for genomic research involving various populations to identify genetic risk factors for autoimmune diseases.

On the other hand, it is well-known that many of the discovered risk alleles or genotypes are not specific for one disease and are shared among different multifactorial disorders, including autoimmune diseases. This phenomenon is described as genetic overlap [2]. It means that well-documented alleles for one disorder may be a risk factor for the other belonging to the same heterogeneous group of diseases.

In our research, we focused on finding risk alleles for juvenile-onset autoimmune rheumatic diseases. Juvenile idiopathic arthritis (JIA) is among them due to the fact that it is the most frequently occurring autoimmune rheumatic disease in children. Less common disorders of this group, such as juvenile systemic lupus erythematosus (JSLE) and Kawasaki disease (KD, also known as mucocutaneous lymph node syndrome), were also of our interest. All of them are characterized by malfunctions of different components of the immune system that is important for understanding of a possible role of gene variants in the pathogenesis of autoimmune diseases. The relevance of assessing a genetic predisposition to these diseases and their early molecular diagnosis are determined by the severity of these diseases, as well as a high probability of their rapid progression resulting in organ changes and disability.

Our focus fell on the rs13128867 polymorphism located between *SLC7A11* and *PCDH18* genes on chromosome 4 being described as a new susceptibility locus for KD in the original GWAS of the Chinese population [3]. At the same time, the role of these genes or their polymorphisms in the development of autoimmune diseases has not yet been elucidated.

Our study aimed to determine the frequency of rs13128867 polymorphic variants in the Belarusian population and analyze their relationship with juvenile rheumatic diseases, including KD, JIA, and JSLE.

Subjects and methods

Participants and samples. Our case-control study involved children and adolescents under 17 at the onset of the disease and was approved by the Ethics Committee of

the Belarusian State Medical University (Minsk) in accordance with the Declaration of Helsinki. Parents of all the participants signed informed consent. Subjects of the case and control groups were involved in the study in the course of their treatment in 2012-2021 at the clinical bases of the 1st Department of Childhood Diseases of the Belarusian State Medical University. In total, 675 Caucasian children and adolescents living in Belarus were included into the study; 386 out of them had no autoimmune, inflammatory, or joint disorders and served as the clinical control; 202 patients were diagnosed with JIA, 38 patients with JSLE, and 49 with KD in accordance with the international diagnostic criteria [4–6]. For the JIA group, the Steinbrocker functional capacity rating was used to assess the disease severity (from class I with no joint restrictions to class IV with maximal functional disability). The participants were not related to each other and had no other autoimmune diseases or malignancies. Basic demographic and clinical details of the case and control groups are summarized in **Table 1**.

DNA extraction and genotyping. Venous blood samples were collected in EDTA-containing tubes (Sarstedt, Germany). Then DNA extraction from blood samples was conducted according to the standard phenol-chloroform protocol. Further, DNA samples were quantified, diluted to 100 ng/μl, and stored at -20°C before genotyping. Genotype status was determined by the real-time PCR using the following oligos: Fw 5'AGAAAAAAATAAATAATCCTGTGACT, Rv 5'GAAAGTACAAGGCAAGAAGAG, PrC 5'FAM-AGCCGAAAATCCTCCTAACA-BHQ1, PrT 5'ROX-AGCTGAAAATCCTCCTAACAC-BHQ2 (Primetech ALC, Minsk, Belarus). Real-time PCR and allelic discrimination were performed using the QuantStudio 5 system (Applied Biosystems, Singapore).

Statistical analysis. Categorical variables are expressed as percentages and frequencies, and age data are presented as the mean ± standard error (SE). The χ^2 test and the Mann–Whitney U-test were used to compare gender and age differences between the case and control groups. For these purposes, IBM SPSS Statistics 22 was used. The exact Hardy-Weinberg equilibrium test and the association analysis were performed using the statistical package SNPassoc for R v4.0.3. An allele or genotype association with the disease was evaluated by the odds ratio (OR) with a 95% confidence interval (95% CI). Since most autoimmune diseases have a strong sex bias and the case groups in our study significantly ($p<0.05$) differed from the control by gender (**Table 1**), the case-control association analysis performed was gender-adjusted to reduce uneven gender distribution between the groups. Also, there was a significant age difference ($p<0.05$) between case and control groups (**Table 1**). Nevertheless, taking into account the small sample sizes in our study, age adjustment was not applied to avoid false effects. In order to steer away from a multiple testing problem, *p*-values were adjusted (p_{adj}) with the Benjamini-Hochberg correction, and $p_{adj} < 0.05$ was considered significant.

Results

The Hardy-Weinberg equilibrium was confirmed for rs13128867 genotype frequencies in all the groups under

Table 1

Clinical and demographic characteristics of study groups

Group or subgroup	Number of patients	Females, %	Age at disease onset, mean ± SD, years	Age at study, mean ± SD, years
Clinical control	386	40.7	-	14.6 ± 2.35
JIA, including subtypes:	202	64.4*	6.9 ± 4.92	9.8 ± 4.88*
Oligoarthritis	118	68.6	5.8 ± 4.48	8.9 ± 4.70
Polyarthritis, RF positive	4	75.0	13.1 ± 1.31	15.0 ± 0.0
Polyarthritis, RF negative	31	64.5	7.0 ± 3.72	11.0 ± 4.25
Systemic arthritis	20	50.0	4.3 ± 4.54	7.1 ± 4.96
Psoriatic arthritis	2	100	15.5 ± 0.71	17.0 ± 0.0
Enthesitis-related arthritis	14	21.4	14.0 ± 1.96	14.9 ± 2.13
Undifferentiated arthritis	13	84.6	10.2 ± 4.1	11.3 ± 4.6
KD	49	20.4**	2.5 ± 2.46	3.1 ± 2.75*
JSLE	38	89.5*	11.9 ± 3.11	13.6 ± 2.84**

Note. JIA – juvenile idiopathic arthritis; RF – rheumatoid factor; KD – Kawasaki disease; JSLE – juvenile systemic lupus erythematosus; * – $p < 0.001$ and ** – $p < 0.05$ compared with the clinical control.

study. The minor C allele frequency of rs13128867 in the clinical control was found to be 17.6% that corresponded to the data for European populations, showing large variation in allele frequency, from 15.9 to 23.4% according to the dbSNP database [7].

The distribution of rs13128867 genotypes and alleles between the control and patient groups is demonstrated in **Table 2**. A comparison analysis showed that the rs13128867 C allele is associated with susceptibility to JIA (OR = 1.50, 95% CI 1.11-2.03, p_{adj} = 0.027), and homozygous CC genotype carriers have a tendency (p_{adj} = 0.085) to the JIA development. The analysis of the most common JIA subtypes (**Table 3**) revealed that the rs13128867 C allele is strongly correlated with oligoarthritis (OR = 1.67, 95% CI 1.17-2.39, p_{adj} = 0.016), while other JIA subgroups (polyarthritis and systemic JIA) with smaller sample sizes did not allow us to derive corresponding conclusions.

No differences were found in the rs13128867 variant distribution among the JIA patients with the low (class I) and moderate (class II) severity of the disease assessed using the Steinbrocker functional classification (data not shown). Higher severity (class III and IV) cases were quite rare in our study. Also, no obvious differences in rs13128867 frequencies were found between males and females, as well as between different age groups with JIA.

The JSLE group (**Table 2**) demonstrated a tendency (p_{adj} = 0.078) to a more frequent occurrence of the rs13128867 C allele and genotypes compared with the control. The low statistical significance of these data is likely to be due to a small number of patients in the JSLE group involved in our analysis, and this requires a further study of rs13128867 in JSLE patients to confirm our preliminary observation.

In contrast to our data on JIA and JSLE, as well as KD-related data for the Chinese population [3], no significant differences in rs13128867 allele and genotype frequencies were identified between the KD and control groups (**Table 2**). This demonstrates the importance of genetic research involving ethnically different populations.

Table 2

Comparison of the rs13128867 genotype and allele frequencies in the case and control groups

Genotype / allele	Clinical control (n=386)	KD (n=49)			JSLE (n=38)			JIA (n=202)		
	%	%	OR [95% CI]	p_{adj}	%	OR [95% CI]	p_{adj}	%	OR [95% CI]	p_{adj}
CC	2.6	4.1	1.44 [0.30-6.86]	0.661	5.3	2.50 [0.46-16.63]	0.485	6.9	2.57 [1.10-6.04]	*0.085*
TC	30.1	28.6	0.90 [0.47-1.75]	0.765	42.1	1.75 [0.86-3.58]	0.301	34.7	1.28 [0.88-1.85]	0.301
CC+TC	32.6	32.7	0.96 [0.48-1.79]	0.901	47.4	1.96 [0.97-3.96]	*0.094*	41.6	1.49 [1.04-2.15]	*0.089*
C	17.6	18.1	1.01 [0.58-1.76]	0.971	26.4	1.83 [1.01-3.34]	*0.078*	**24.4**	**1.50 [1.11-2.03]**	**0.027***

Note. JIA – juvenile idiopathic arthritis; JSLE – juvenile systemic lupus erythematosus; KD – Kawasaki disease; * – statistically significant data (p_{adj} < 0.05).

Table 3

rs13128867 polymorphism among the most frequent subtypes of JIA

Genotype / allele	Clinical control (n=386)	Oligoarthritis (n=118)			Polyarthritis (n=35)			Systemic arthritis (n=20)		
	%	%	OR [95% CI]	p_{adj}	%	OR [95% CI]	p_{adj}	%	OR [95% CI]	p_{adj}
CC	2.6	**8.5**	**3.25 [1.27-8.30]**	**0.046***	8.6	3.86 [0.98-15.29]	0.125	0.0	0	0.322
TC	30.1	35.6	1.33 [0.85-2.08]	0.216	31.4	1.08 [0.51-2.31]	0.833	35.0	1.26 [0.49-3.24]	0.639
CC+TC	32.6	*44.1*	*1.66 [1.07-2.56]*	*0.069*	40.0	1.41 [0.69-2.90]	0.523	35.0	1.12 [0.44-2.88]	0.816
C	17.6	**26.2**	**1.67 [1.17-2.39]**	**0.016***	24.3	1.56 [0.86-2.82]	0.229	17.5	1.00 [0.42-2.36]	0.998

Note. JIA – juvenile idiopathic arthritis; * – statistically significant data (p_{adj} < 0.05).

Discussion

As far as we know, this study is the first to describe the *SLC7A11–PCHD18* rs13128867 (T>C) polymorphism in the Caucasian patients with autoimmune rheumatic diseases such as KD, JA, and JSLE. The specified diseases were studied in the Belarusian population of children in comparison with the clinical control consisting of children without any autoimmune, inflammatory, or joint disorders. Here, we report about the minor C allele of rs13128867 demonstrating an association with susceptibility to JIA, and a tendency to association with JSLE. We also showed that the rs13128867 polymorphism is associated with a risk of particularly common oligoarticular JIA. At the same time, no association with age, gender, or JIA severity was observed. Moreover, mucocutaneous lymph node syndrome (or KD) did not show any obvious association with the rs13128867 polymorphism in our study, and thus, we were not able to confirm the aforementioned GWAS data obtained for the Chinese population [3].

However, the published data and the results obtained in the course of our study are descriptive and cannot shed light on the mechanisms of relationships between rs13128867 and a risk of autoimmune disease development. Besides, there was hardly any evidence until recently allowing to build a hypothesis accounting for such a relationship.

The rs13128867 polymorphism is located in the chromosome 4 region between *SLC7A11* and *PCDH18* genes. The *SLC7A11* gene encodes the SLC7A11 protein (also known as xCT), one of the members of the anionic amino acid transport system known as the cystine-glutamate antiporter (system Xc^-), and specific for cystine transportation in exchange for glutamate export. The *PCDH18* gene encodes a member of protocadherins and its function is not yet known.

According to GTEx (https://gtexportal.org/), there is no evidence that rs13128867 affects the expression or splicing of any known genes, including *SLC7A11* and *PCDH18*. At the same time, the eQTLGen database (https://www.eqtlgen.org/cis-eqtls.html/) shows that the rs13128867 T>C polymorphism may be associated with an increased expression of *SLC7A11* in blood samples. However, a high false discovery rate (FDR=0.35) from the Blood eQTL database (https://genenetwork.nl/bloodeqtlbrowser/) does not fully confirm this and may indicate that there is a need for further studies investigating the effect of this polymorphism on the expression of genes.

On the other hand, the chromosome region between *SLC7A11* and *PCHD18* genes has at least 9 long noncoding RNAs (https://www.ncbi.nlm.nih.gov/variation/view/). Their function is still unclear, but some of them may serve as regulator molecules for protein-coding mRNAs, such as *SLC7A11-AS1*, that inhibits the translation of *SLC7A11* mRNA [8]. Thus, the information available that could have shed light on the possible functional activity of the rs13128867 T>C polymorphism is contradictory.

At the same time, accumulated evidence suggests that attention should be directed to a possible role of the SLC7A11 protein in immune and inflammatory processes. Solute carrier transporters are proposed to be called the metabolic gatekeepers of immune cells due to their critical importance in mediating immune cell homeostasis (reviewed in [9]). Among them, glutamate transporter Xc^- is a major way of the intracellular transport of cystine, a precursor for the biosynthesis of powerful antioxidant glutathione. Therefore, a particularly important role of Xc^- in the regulation of macrophage immune functions through maintaining redox state and oxidative stress protection is suggested [9]. Overall, redox regulation is seen as a necessary part of immunometabolism, and glutathione participates in regulation of innate immunity and inflammation (reviewed in [10]). As regards immune cells, the functional activity of T cells is also associated with increased glutathione biosynthesis [10]. Moreover, SLC7A11 is involved in the proliferation of regulatory T (T_{reg}) cells, since the release of glutamate stimulates T_{reg} proliferation and activity [11]. Importantly, T_{reg} cells participate in maintaining self-tolerance and preventing an autoimmune reaction [12]. They are also necessary for controlling inflammation, and it was demonstrated that T_{reg} cell proliferation through the stimulation of the *SLC7A11* expression attenuates such autoimmune disease as multiple sclerosis [13]. It is important to note that JIA and JSLE, demonstrating in our study the association or a tendency for association with the rs13128867 variant instead of KD, have a common feature in the form of the impaired function of T_{reg} cells [14,15] that was even proposed to correct with the low doses of IL-2 [14,16]. Thus, the results of our study may suggest the involvement of the rs13128867 polymorphism in autoimmunity through downregulation of cystine-glutamate transport and/or T_{reg} cell functionality.

Conclusions

Our study conducted on the Belarusian population did not demonstrate the association between the *SLC7A11–PCHD18* rs13128867 (T>C) polymorphism and KD in Caucasian children. Thus, the results of this study did not replicate the data known for the Chinese population. At the same time, the study first revealed the association of rs13128867 with susceptibility to JIA in general and oligoarthritis (the most common subtype of JIA) in particular. A tendency to association with JSLE was also observed. Thus, we demonstrated that the *SLC7A11–PCHD18* rs13128867 polymorphism may be a novel genetic risk factor for JIA. However, further investigations are required to confirm our observations and study the molecular mechanisms of rs13128867

variants, as well as non-specificity of this polymorphism for JIA or its relation with other autoimmune diseases.

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