NEW POTENTIAL GENETIC PREDICTORS OF AUTOIMMUNE ADRENAL INSUFFICIENCY

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AIM search for new genetic predictors of autoimmune adrenal insufficiency (AAI).
MATERIALS AND METHODS: In n=54 patients with AAI (isolated and as part of type 2 autoimmune polyglandular syndrome (APS-2; group 1)) and n=32 healthy individuals (group 2) we analyzed polymorphisms in *IL28B* (rs12979860, rs8099917), *TLR9* (rs5743836, rs352140), *TLR2* (rs5743708).
RESULTS: In group 1, compared with group 2, a predominance of CT genotype of rs12979860 polymorphism of *IL28B* (p=0.024), and T allele of rs5743836 polymorphism of *TLR9* (p=0.044) was revealed. The allele C of rs5743836 polymorphism of *TLR9* (p=0.044) was more common in group 2 than in group 1. With respect to other genotypes, alleles and haplotypes, no significant differences (or differences at the level of statistical trend) were found between groups 1 and 2.
CONCLUSION: Thus, it is possible that the CT genotype according to the polymorphic locus rs12979860 of the IL28B gene and the allele T of the rs5743836 polymorphism of the TLR9 gene are prognostic markers that increase the likelihood of developing AAI due to violation the peripheral immune tolerance (IT), whereas the allele C of the rs5743836 polymorphism of the TLR9 gene performs a protective role in this disease in the Russian population.

KEYWORDS: toll-like receptors; interferon-lambda receptor; Addison's disease; polymorphisms.

INTRODUCTION

The most common (up to 90% or more) cause of the primary adrenal insufficiency (1-AI) is autoimmune destruction of the adrenal cortex – autoimmune adrenal insufficiency (AAI). In about 50% of cases, AAI is combined with autoimmune damage of other (one or more) peripheral endocrine glands and various organ-specific non-endocrine diseases of autoimmune origin in the framework of autoimmune polyglandular syndromes (APS) type 1 or 2 (APS-1 and -2 respectively). APS-1 is a monogenic disease with an autosomal recessive type of inheritance due to a mutation in the gene of the autoimmune regulator AIRE. APS-2 most often manifests in adulthood. The predisposition to isolated AAI and AAI in the framework of APS-2 is determined by variants of the genes of the Human Leukocyte Antigens system encoding Major Histocompatibility Complex class II molecules [1]. However, genetic factors that determinethe development of pathology are not fully understood. Identification of new genetic predictors of AAI and APS-2 is required for timely detection and treatment of autoimmune lesions in target organs, predicting the course of the disease, and conducting preventive measures [2]. It is possible that other genetic markers play role in modulating the risk determined by HLA class II genes, in particular, in genes encoding receptors (for example, toll-like receptors (TLR): TLR2 and TLR9) and cytokines (for example, interferon (IFN)-λ: IL28B) involved in the immune response, as well as environmental factors.

TLRs are expressed by innate immune cells and provide protection against bacterial infections through rapid induction of an inflammatory response. The induction of inflammation in adrenal tissue during acute or chronic bacterial or viral infection is often accompanied by an increase in TLR expression, which may be involved in the pathogenesis of AAI. Thus, TLR2 and TLR9 mediate a pronounced systemic or local cytokine response with the release of such proinflammatory cytokines as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α. Also, TLR ligands directly cause apoptosis of adrenocortical cells and contribute to hemorrhages in the adrenal glands in animal models [3].

In addition, the cytokine interferon (IFN)-λ, which belongs to type III IFN and implements a response to viral infections, may be involved in the pathogenesis of AAI. The IFN-λ signaling pathway is carried out through a heterodimeric receptor complex (IFN-λR) consisting of IFN-λR1 (IL-28Ra; expressed by the adrenal cortex) and IFN-λR2 (IL-10Rß) chains [4]. IFN-λ is encoded by the IL28B gene [5].

Possible immunopathological effects of IFN-λ on adrenal cortex cells have been studied in adrenocortical carcinoma. In particular, IFN has been proven to have a cytotoxic effect on adrenocortical carcinoma cells and enhance IFN-γ-induced chemokine secretion. In addition, IFN-λ is known to mediate an increase in the expression of class I MHC molecules, which enhances the presentation of viral peptides and the destruction of infected cells by cytotoxic T lymphocytes. Such a mechanism may contribute to the development of an autoimmune process in predisposed individuals. Thus, IFN-λ increases the presentation of P450c21 peptides on MHC class I molecules of adrenocortical cells, thereby contributing to the initiation of immune autoaggression reactions [4].

Given the involvement of TLR2, TLR9 and IFN-λ in the pathogenesis of AAI, it seems advisable to study the association of the corresponding genes with the risk of developing the disease.

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AIM

search for new genetic predictors of autoimmune adrenal insufficiency (AAI).

MATERIALS AND METHODS

Study participants

The active single-stage case-control study included patients with isolated AAI and as part of APS-2 and conditionally healthy individuals. Patients were recruited into groups based on compliance with the inclusion criteria and in the absence of exclusion criteria (Tables 1; 2).

The study included 86 participants who were divided into the groups:

-1: patients with manifest AAI as part of APS-2 and with isolated AAI (n=54);

-2: conditionally healthy without AI and AIDs (n=32).

The participants analyzed polymorphic markers in the *IL28B* (rs12979860 and rs8099917), *TLR9* (rs5743836 and rs352140) and *TLR2* (rs5743708) genes.

Table 1. Inclusion and exclusion criteria

Inclusion and exclusion criteria	Group with AAI	Group of healthy people
Inclusion criteria[1]		
Male or female	+	+
Age ≥18	+	+
Elevated levels of antibodies to 21-hydroxylase and	+	-
Verified, in accordance with international clinical guidelines, the diagnosis is 1-AI	+	-
Normal levels of aldosterone, renin, adrenocorticotropic hormone; cortisol in the morning (06:00-10:00) or during a test with insulin hypoglycemia ≥ 500 nmol/l[2]	-	+
Exclusion criteria[3]		
The presence of a relative with non-autoimmune hereditary 1-AI	-	+
Mutation of the *AIRE* gene and/or the presence of at least two components of APS-1	+	-
Severe, life-threatening conditions: decompensation of chronic heart failure, chronic kidney disease C3b and more, pulmonary and hepatic insufficiency (according to physical examination and laboratory test results)	+	+
Pathology of the immune system (congenital immunodeficiency conditions; according to the survey data and provided medical documentation)	+	+
The presence of autoimmune diseases, including potential and latent forms (according to the survey data and provided medical documentation, screening examination)	-	+
The presence of malignant oncological diseases, including in the anamnesis (according to the data provided by the medical documentation)	-	+
Type 2 diabetes (according to the survey data and provided medical documentation, screening examination)	-	+
Surgical interventions on the pituitary gland (according to the survey data and provided medical documentation)	-	+
Hypopituitarism (including partial) of any origin (according to the survey data and provided medical documentation)	-	+
Treatment with glucocorticoids, including in the anamnesis (according to the survey data and provided medical documentation)	-	+
Taking enzyme inhibitors (mitotan, ketoconazole, methirapone, etomidate, aminoglutetimide, rifampicin, phenytoin), including in the anamnesis (according to the survey data and provided medical documentation)	-	+
Damage to adrenal tissue, including in the anamnesis (according to the survey data and provided medical documentation): surgical interventions; hemorrhage; against the background of infiltrative diseases (hemochromatosis, amyloidosis, sarcoidosis); infections (tuberculosis, mycoses, histoplasmosis, cytomegalovirus, syphilis, African trypanosomiasis); the presence of adrenal gland formations	-	+

[1] «+» — the presence of a criterion is mandatory for inclusion in the study, «-» — the absence of a criterion is mandatory for inclusion in the study.

[2] When the morning cortisol level was <500 nmol/L (n=17 participants), an insulin hypoglycemia test was performed.

[3] «+» — the presence of the criterion is the basis for being excluded from the study, «-» — the presence of a criterion is not a reason for being excluded from the study.

Notes: AAI — autoimmune adrenal insufficiency; 1-AI — primary adrenal insufficiency; APS-1 — autoimmune polyglandular syndrome type 1.

Table 2. List of studies for laboratory screening

Estimated parameters	Patients with suspected AAI	Persons presumably without AID and AI
Assessment of inclusion criteria		
Determination of the level of antibodies to 21-hydroxylase		
Blood test for antibodies to 21-hydroxylase	+	+
Diagnosis of primary adrenal insufficiency		
Blood test for cortisol, aldosterone, renin, adrenocorticotropic hormone	-	+
Blood test for sodium, potassium	-	+
Insulin hypoglycemia test (selectively)[1]	-	+
Diagnostics of autoimmune diseases (and predisposition to them): thyroid gland, type 1 diabetes/ latent autoimmune diabetes of adults, hypergonadotropic hypogonadism of autoimmune genesis, hypoparathyroidism		
Blood test for glycated hemoglobin, glucose, IAA, ICA, AT to GAD, IA2 and ZnT8	-	+
Blood test for total Ca, ionized Ca, P, parathyroid hormone (if Ca levels change)	-	+
Blood test for thyroid stimulating hormone, antibodies to thyroid peroxidase, thyroglobulin, thyroid stimulating hormone receptor (if thyroid stimulating hormone level decreases)	-	+
Blood test for LH, FSH, testosterone — in men	-	+
Blood test for LH, FSH, estradiol — in women with irregular menstrual cycles	-	+
Evaluation of exclusion criteria		
Exclusion of other immune system disorders		
General clinical blood test	+	+
Exclusion of severe organ pathology		
Blood test for aspartate aminotransferase, alanine aminotransferase, total protein, creatinine	+	+

[1]If morning cortisol level <500 nmol/L (n=15 participants).
Notes: AAI — autoimmune adrenal insufficiency; GAD — glutamate decarboxylase; ICA — antibodies to pancreatic islet cells; IAA — antibodies to insulin; IA2 — tyrosine phosphatase; ZnT8 — zinc transporter 8; Ca — calcium; P — phosphorus; LH — luteinizing hormone; FSH — follicle-stimulating hormone.

Research methods

Clinical examination

All participants were examined by a physician-researcher for compliance with the inclusion criteria and identification of possible exclusion criteria. The initial examination scheme included collection of anamnestic data, including the presence of acute and chronic diseases. The day, month and year of the start and end of the recruitment period for this study: 10.05.2018-10.02.2021.

Laboratory examination

Blood was collected into vacuum tubes with inert gel and ethylenediaminetetraacetic acid from the cubital vein 08–10 am in a fasting state. The obtained samples were centrifuged using an Eppendorf 5810R centrifuge at 4°C at 3000 rpm for 15 minutes and then put into operation. Biochemical blood testing was performed on an Architect plus C 4000 analyzer (Abbott Diagnostics, USA). Determination of the TSH level (using standard kits (Abbott Diagnostics, USA)) was carried out by the immunochemiluminescence method on the Architect 2000 analyzer. The levels of LH, FSH, estradiol, and testosterone were determined by the chemiluminescent immunoassay method on the Vitros ECi 3600 automatic analyzer (Ortho-Clinical Diagnostics). Aldosterone and renin levels were measured by the immunochemiluminescent method on the DiaSorin Liaison analyzer (DiaSorin SpA, Italy). ACTH and cortisol in the blood were determined by the immunochemical method on the automated Cobas 6000 system (Roche, Germany). Determination of DHEA-S, PTH, AT to rTSH and TG was carried out on the electrochemiluminescence analyzer Cobas 6000 (Roche, Germany), AB to TPO — by the chemiluminescence immunoassay method on the automatic analyzer Architect i2000 (Abbott). Determination of AB to P450c21, ZnT8, IA-2, GAD, ICA, IAA was carried out by the ELISA method using commercial kits: BioVendor, Czech Republic (AT to P450c21), Medipan, Germany (AT to ZnT8, IA-2, ICA), EUROIMMUN, Germany (AT to GAD), Orgentec Diagnostika, Germany (IAA). The reference intervals (RI) for blood parameters were: glucose — 3.1–6.1 mmol/l, total Ca — 2.15–2.55 mmol/l, ionized Ca — 1.03–1.29 mmol/l, P — 0.74–1.52 mmol/l, aldosterone — 69.8–1085.8 pmol/l, renin — 2.8–39.9 mIU/l, ACTH — 7.2–63.3 pg/ml, DHEA-S — 1.65–11 μmol/l (for women 18–39 years old), 0.26–6.68 μmol/l (for women ≥40 years old), 1.2–13.4 μmol/l (for men 18–54 years old), 0.44–6.76 μmol/l (for men ≥55 years old), TSH — 0.25–3.5 mIU/l, PTH — 15–65 pg/ml, LH — 2.6–12.1 U/l

Table 3. Characteristics of the study participants

Group		Participants				
		n	Age (years)	Gender (female / male)		
				n	%	Ratio
1	Isolated AAI + APS-2	54	19-72	43/11	80/20	3,9:1
2	Conditionally healthy	32	18-60	24/8	75/25	3:1

Notes: AAI – autoimmune adrenal insufficiency; APS-2 – autoimmune polyglandular syndrome type 2.

(for women), 2.5–11 U/L (for men), FSH — 1.9–11.7 U/L (for women), 1.6–9.7 U/L (for men), estradiol — 97–592 pmol/L (for women), testosterone — 11–28.2 mmol/L (for men), AB to P450c21 <0.4 U/ml, TPO — 0–5.6 IU/ml, TG — 0–115 IU/ml, rTSH 0–1.75 IU/l, GAD — 0–10 U/ml, IA2 — 0–10 U/ml, ZnT8 — 0–15 U/ml, ICA — 0–1 U/ml, IAA — 0–10 U/ml, alanine aminotransferase — 0.0–55.0 U/L, aspartate aminotransferase — 5.0–34.0 U/L, creatinine — 50–98 mmol/L, potassium — 3.5–5.1 mmol/L, sodium — 136–145 mmol/L, erythrocytes — 3,8–5,2*1012 cl/L (for women), 4,3–5,8*10^{12} cl/l (for men), white blood cells — 3,4–10,8*10^{9} cl/L (for women), 3,9–10*10^{9} cl/L (for men), hemoglobin — 112–153 g/l (for women), 132–172 g/l (for men), platelets — 152–372*10^{9} cells/l. The laboratory-accepted RI for blood cortisol (outside the insulin hypoglycemia test) was 171–536 nmol/L. Basal blood cortisol level (outside the insulin hypoglycemia test) ≥500 nmol/l excluded manifest AI (both 1- and 2-). Basal cortisol level <140 nmol/l in combination with ACTH >126.6 pg/ml confirmed manifest primary glucocorticoid deficiency. A biochemical blood test was performed on an Architect plus C 4000 analyzer (Abbott Diagnostics, USA), and a general blood test (with mandatory assessment of the level of leukocytes and platelets) was performed on an automatic analyzer Sysmex XE-2100 D, Sysmex, Japan.

Determination of glycated hemoglobin was carried out in capillary blood using an automatic biochemical analyzer D10 (BioRad Laboratories, USA) and a kit from the same manufacturer according to the standard method. The HbA1c level of up to 6% was considered normal.

Analysis of polymorphic markers

DNA was isolated using a commercial Ribosorb kit (InterLabService, Russia). Next, the following polymorphic markers were studied by real-time polymerase chain reaction (PCR-RT): rs12979860 and rs8099917 in the *IL28B* gene, rs5743708 in the *TLR2* gene, rs5743836 and rs352140 in the *TLR9* gene. The analysis of polymorphic markers in the *IL28B* gene was carried out using commercial kits, according to the attached instructions (Syntol, Russia). To evaluate the polymorphic markers rs5743836 in the *TLR9* gene and rs5743708 in the *TLR2* gene, an adapted technique was used with commercial kits from Litech (Russia) and a «Kit for PCR-RT in the presence of the intercalating dye SYBR Green I» (Syntol, Russia). The polymorphic marker rs352140 in the *TLR9* gene was studied using reagents from the «Set of reagents for PCR-RT» (Syntol, Russia) and specially synthesized primers and probes (Syntol, Russia). PCR-RT was performed on devices manufactured by DNA Technology (RF): «DT-96», «DTprime 4» and «DTprime 5».

Statistical analysis of the research results

Data were analyzed with STATISTICA v. 13 (TIBCO Inc., USA). The frequency was calculated for categorical data. We used the chi-square test and the Chi-square test with Yates' correction in the comparison between the presence and absence of polymorphic variants. A two-tailed value of $p<0.05$ was taken to indicate statistical significance. To correct the problem of multiple hypothesis testing, the Bonferroni correction was used. After applying the correction, the p values in the range between the calculated and 0.05 were interpreted as a statistical tendency.

Ethical approval

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethics committee of the Endocrinology Research Centre, Ministry of Health of Russia, Moscow, Russia (protocol No. 8 and date of approval 25 April 2018).

Written informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

RESULTS

The characteristics of those included in the study are presented in Table 3.

Our study revealed a predominance at the level of statistical tendency in group 1 (patients with AAI) compared to group 2 (conditionally healthy) of the CT genotype of the polymorphic marker rs12979860 of the *IL28B* gene, as well as the T allele of the rs5743836 polymorphism of the *TLR9* gene. In contrast, the frequencie of the C allele of the rs5743836 polymorphism of the *TLR9* gene was statistically significantly higher in group 2 than in group 1 (Table 4). With respect to other genotypes, alleles and haplotypes, no significant differences (or differences at the level of statistical trend) were found between groups 1 and 2 (Tables 4, 5).

DISCUSSION

In our study in patients of group 1 with AAI, no significant differences in the distribution of genotypes and alleles were found among the markers of the *TLR2* (s5743708) and *TLR9* (rs352140) genes. Of the two polymorphic loci of the *IL28B* gene studied (rs8099917 and rs12979860), an association with the risk of developing the disease was found only in relation to rs12979860. Thus, at the level of a statistical trend, an increase in the frequency of occurrence of the heterozygous CT genotype for this marker was found in patients with AAI of group 1. In addition, at the level of statistical trend, the predominance

Table 4. Distribution of allele and genotype frequencies in the studied single nucleotide polymorphisms and the result of the analysis of their associations with group 1

Polymorphisms	Alleles/genotypes	Frequencies		p*, χ^2
		Gr. 1	Gr. 2	
		n_{pat} = 54	n_{pat} = 32	
		n_{all} = 108	n_{all} = 64	
IL28B rs12979860	Allele C	0,676	0,766	0,211
	Allele T	0,324	0,234	
	CC	0,444	0,656	0,057
	CT	***0,463***	***0,219***	***0,024***
	TT	0,093	0,125	0,912**
IL28B rs8099917	Allele T	0,787	0,828	0,513
	Allele G	0,213	0,172	
	TT	0,611	0,688	0,621
	TG	0,352	0,281	0,499
	GG	0,037	0,031	0,641**
TLR2 s5743708	Allele A	0,120	0,031	0,085**
	Allele G	0,880	0,969	
	AA	0,000	0,000	–
	AG	0,241	0,063	0,070**
	GG	0,759	0,938	0,070**
TLR9 rs5743836	**Allele T**	***0,870***	***0,750***	***0,044***
	Allele C	***0,130***	***0,250***	
	TT	0,741	0,563	0,089
	TC	0,259	0,375	0,259
	CC	0,000	0,063	0,263**
TLR9 rs352140	Allele G	0,426	0,516	0,254
	Allele A	0,574	0,484	
	GG	0,167	0,250	0,348
	GA	0,519	0,531	0,909
	AA	0,315	0,219	0,337

Notes: Gr. – group; pat. – patients; all. – alleles.
* Threshold p_0 = 0.003 (after applying the Bonferroni correction: 19 hypotheses). Differences at the level of statistical tendency are highlighted in bold and italic fonts.
** with Yates correction.

of the allele T of the rs5743836 polymorphism of the *TLR9* gene was revealed in group 1 compared with group 2, whereas in group 2, compared with group 1, the allele C of the same polymorphism. Thus, it is possible that the CT genotype according to the polymorphic locus rs12979860 of the *IL28B* gene and the allele T of the rs5743836 polymorphism of the *TLR9* gene are prognostic markers that increase the likelihood of developing AAI due to violation the peripheral immune tolerance (IT), whereas the allele C of the rs5743836 polymorphism of the *TLR9* gene performs a protective role in this disease in the Russian population.

The CT genotype of the polymorphic marker rs12979860 of the *IL28B* gene and the allele T of the rs5743836 polymorphism of the *TLR9* gene can be considered as new predictors of the development of AAI due to a violation of peripheral IT.

Hyperactivation of certain TLRs, in particular TLR9, has been experimentally proven in the pathogenesis of autoimmune thyroiditis [3, 6]. TLR2 and TLR9 have been shown to cause activation of antigen-presenting cells and induction of TNF-α production by them when binding to the products of apoptosis of beta cells of the pancreas, and thus contributing to the activation of an autoimmune response with the development of DM1 [6].

The well-known association of a number of autoimmune diseases (AIDs), including systemic lupus erythematosus (SLE), DM1, autoimmune thyroiditis (AIT), with viral infections, as well as possible induction of the autoimmune process against the background of IFN therapy, assumes the participation of IFN-λ in these processes. The role of IFN-λ in the autoimmune process in DM1 and AIT has been described earlier [4].

Table 5. Distribution of haplotype frequencies in the *IL28B* and *TLR9* genes and the result of the analysis of their associations with group 1

Polymorphisms	Haplotypes	Frequencies		p*, χ^2
		Gr. 1	Gr. 2	
		n_{pat} = 54	n_{pat} = 32	
IL28B rs12979860-rs8099917	CCTT	0,407	0,625	0,051
	CCTG	0,019	0,031	0,718**
	CCGG	0,019	0,000	0,790**
	CTTT	0,185	0,063	0,206**
	CTTG	0,278	0,156	0,197
	CTGG	0,000	0,000	–
	TTTT	0,019	0,000	0,790**
	TTTG	0,056	0,094	0,815**
	TTGG	0,019	0,031	0,718**
TLR9 rs5743836-rs352140	TTGG	0,130	0,063	0,536**
	TTGA	0,333	0,375	0,695
	TTAA	0,278	0,125	0,167**
	TCGG	0,037	0,125	0,267**
	TCGA	0,185	0,156	0,733
	TCAA	0,037	0,094	0,542**
	CCGG	0,000	0,063	0,263**
	CCGA	0,000	0,000	–
	CCAA	0,000	0,000	–

Notes: Gr. – group; pat. – patients.
* Threshold p_0 = 0.003 (after applying the Bonferroni correction: 15 hypotheses).
** with Yates correction.

According to the literature, the association of rs352140 polymorphism of the *TLR9* gene with the risk of developing SLE [7] and rs5743708 polymorphism of the *TLR2* gene with atopic dermatitis was found [8]. The role of *IL28B* gene polymorphisms in AIDs has been studied in patients with autoimmune hepatitis (no association was found) [9] and in lupus nephritis (allele T of polymorphism rs8099917, allele C of polymorphism rs12979860 and other genetic markers are associated with the risk of developing the disease) [10]. However, similar studies have not been conducted on AAI before.

Our data suggest involvement of IFN-λ and TLR9 in the immunopathogenesis of AAI. The results obtained can become the basis for the development of models for predicting the development of AAI. Due to the lack of statistical significance after adjusting for the multiplicity of comparisons (with respect to all genetic markers studied in this study), unambiguous conclusions cannot be drawn in our study. Taking into account the small number of samples, which is a limitation of the study, it is necessary to continue the accumulation and analysis of data on a large cohort of patients with AAI due to violation of peripheral IT in Russian and other populations. It should be noted that the study aimed at analyzing the frequency of genotypes and alleles of polymorphisms of the *TLR2, TLR9* and *IL28B* genes was conducted for the first time not only in the Russian population, but also worldwide.

CONCLUSION

The search for new approaches for therapeutic effects and prevention of the development of the primary AI remains relevant.

The frequencies of genotypes and alleles of polymorphisms of the *TLR2, TLR9* and *IL28B* genes in a cohort of patients with primary adrenal insufficiency of autoimmune origin were studied for the first time in the world. Based on the data obtained, the CT genotype of the rs12979860 polymorphism of the *IL28B* gene and the allele T of the rs5743836 polymorphism of the *TLR9* gene are proposed as a new possible genetic predictors of hypocorticism due to a violation of peripheral immune tolerance. It is necessary to accumulate data to clarify the identified associations, including in other populations.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Declaration of interest. There is no conflict of interest

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All authors approved the final version of the article before publication and agreed to be responsible for all aspects of the work, which implies proper study and resolution of issues related to the accuracy or integrity of any part of the work.

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