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Генетические факторы риска пищевой аллергии: обзор полногеномных исследований

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АННОТАЦИЯ

Обоснование. Пищевая аллергия является актуальной проблемой для общественного здравоохранения во всём мире: заболевание снижает качество жизни пациентов, повышает риск развития непрогнозируемых анафилактических реакций.

Цель — анализ генетических исследований в когортах пациентов с пищевой аллергией, направленных на оценку роли генетических факторов в развитии данной патологии.

Материалы и методы. Проведён анализ результатов полногеномных ассоциативных исследований по изучению влияния генетических факторов на развитие пищевой аллергии. В обзор включены оригинальные статьи, опубликованные в период с 01.01.2012 по 31.12.2021.

Результаты. Данный обзор позволил систематизировать данные о связи генетических вариаций, связанных с пищевой аллергией, в результате полногеномного скрининга. Из 8 анализируемых исследований максимальный эффект с развитием IgE-опосредованной пищевой аллергии на арахис установлен для варианта rs10018666 гена *SLC2A9* у европейцев. Для некоторых аллергенов найдены ассоциации со специфическими локусами: например, варианты rs9273440 (*HLA-DQB1*), rs115218289 (*ITGA6*), rs10018666 (*SLC2A9*) и другие являются уникальными для арахиса. Ассоциированные варианты связаны преимущественно с нарушениями врождённого/адаптивного иммунного ответа и функционирования эпителиального барьера, подтверждая их ведущую роль в развитии пищевой аллергии. Помимо ассоциаций с пищевой аллергией, большинство идентифицированных генов влияют на развитие других фенотипов аллергического марша, включая атопический дерматит, атопическую бронхиальную астму, аллергический ринит, а также неаллергических заболеваний (сахарный диабет 2-го типа, болезнь Паркинсона, инфаркт миокарда и др.).

Заключение. Суммируя результаты полногеномных ассоциативных исследований, необходимо отметить, что в развитии пищевой аллергии участвуют варианты, локализованные как в известных для атопии, так и во вновь выявленных локусах, не имеющих отношение к развитию других аллергических заболеваний. Особенности структуры пищевой сенсибилизации и недостаточность исследований по вопросам подверженности пищевой аллергии в России определяют направление дальнейших научных исследований в этой области.

Ключевые слова: пищевая аллергия; генетические факторы риска; однонуклеотидные полиморфные варианты; полногеномные ассоциативные исследования.

Как цитировать

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Genetic risk factors of food allergy: a review of genome-wide studies

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ABSTRACT

BACKGROUND: Food allergy (FA) is an urgent problem for public health worldwide. This disease reduces the quality of life of patients and increases the risk of developing unpredictable anaphylactic reactions.

AIM: Conduct an analysis of genetic studies in cohorts of patients with FA aimed at assessing the role of genetic factors in the development of this pathology.

MATERIALS AND METHODS: The results of genome-wide association studies aimed at studying the influence of genetic factors in FA development. The review includes original articles published for the period from January 1, 2012 to December 31, 2021.

RESULTS: This systematic review analyzed data on the relationship of genetic variations associated with FA. Eight studies were analyzed, and the maximum effect with the development of IgE-mediated FA on peanuts was found for the rs10018666 variant of the *SLC2A9* gene in Europeans. Some allergens associated with specific loci have been found, for example, variants rs9273440 (*HLA-DQB1*), rs115218289 (*ITGA6*), rs10018666 (*SLC2A9*), and others are unique to peanut. Associated variants are predominantly associated with disorders of the innate/adaptive immune response and functioning of the epithelial barrier, confirming their leading role in FA development. In addition to associations with FA, most of the identified genes affect the development of other "allergic march" phenotypes, including atopic dermatitis, bronchial asthma, allergic rhinitis, and non-allergic (type 2 diabetes mellitus, Parkinson's disease, myocardial infarction, and others) diseases.

CONCLUSIONS: Summarizing the results of genome-wide associative studies, it should be noted that the development of food allergies involves variants localized both in known atopic and newly identified loci that are not related to the development of other allergic diseases. The peculiarities of the structure of food sensitization and the lack of research on the susceptibility to food allergies in Russia determine the direction of further scientific research in this area.

Keywords: food allergy; genetic risk factors; single nucleotide polymorphisms; genome wide association studies.

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BACKGROUND

Food allergy (FA) is a recent public health problem worldwide. It reduces the quality of life of patients and increases the risk of unpredictable anaphylactic reactions [1]. Literature data revealed a trend toward an increase in FA prevalence worldwide. The prevalence rates of FA in different countries varied from 1%–5% in Europe and the USA to 10% in Australia [2, 3]. Most often, this pathology presents in infancy and early childhood [2, 3]. In the USA, significant allergens in the pediatric population are peanuts, milk, shellfish, and hazelnuts, and those in China include chicken eggs, milk, fish, shrimp, and soy [3, 4]. In the Russian Federation, the incidence of FA is 1.2% in children aged 7–10 years, and the main food allergens are fish, apples, eggs, carrots, hazelnuts, and peanuts [4]. Moreover, FA plays a significant role in the onset of atopic march and the further development of allergic diseases such as atopic dermatitis, asthma, and allergic rhinitis in older children [5–7].

The prevalence of FA among urban residents is higher than those among rural areas and increases with the level of the country's urbanization [8]. Globally, the incidence of anaphylactic reactions is steadily increasing, i.e., the hospitalization rate for anaphylactic shock caused by food triggers is increasing [9, 10].

According to accumulated data, both environmental factors and genetic predisposition significantly contributed to FA development [11]. According to several twin studies, the heritability for FA varies from 15% to 82% [12–14]. The wide range of heritability indicates that the genetic component contributes significantly to disease development and can be modified by the influence of environmental components; thus, studies of genetic factors involved in FA development are important in each region.

Genome-wide association studies (GWAS) make it possible to determine the relationship between genetic variations and a particular trait. For example, recently, through GWAS, new genetic loci that were associated with FA development have been identified [15]. In addition to GWAS, numerous studies have used an approach based on individual candidate genes for disease pathogenesis.

This systematic review aimed to analyze the GWAS of FA and evaluate the role of genetic factors in FA development.

MATERIALS AND METHODS

Methodology

Literature data on the results of epidemiological cross-sectional studies aimed at understanding the influence of genetic factors on FA development were analyzed. The literature search was performed in databases of PubMed and eLibrary, which catalog biomedical scientific literature. This review includes original articles published from January 1, 2012, to December 31, 2021.

Algorithm of analysis

The first stage involved a primary search for publications by keywords and titles. The following keywords were used in the PubMed search: "food allergy," "genetic risk factors," "single nucleotide polymorphism," "genome-wide association study," and "candidate gene association study." The eLibrary search was conducted using the following keywords: "FA," "genetic markers," "genetic risk factors," and "gene polymorphism." At this stage, 415 articles from PubMed, and 13 articles from eLibrary were screened.

In the second stage, data of publications obtained during the initial search were analyzed; 355 papers that did not contain data on genetic markers associated with FA development and duplicates were excluded. No articles in the Russian language matched the search criteria. Finally, 73 publications have been selected for further analysis at this stage.

In the third stage, the full texts of 73 publications were thoroughly evaluated. Reviews, comparative clinical studies, retrospective studies, etc., were excluded at this stage. Based on the results of the third stage of the review, eight publications containing data on the results of epidemiological studies that meet the inclusion criteria were included in the analysis. The inclusion criteria were as follows: comprehensiveness of the study design, including sample characteristics, selection criteria, and study design (genome-wide association search), and availability of data on genetic risk factors for FA development. The publications search algorithm is shown in Fig. 1.

RESULTS

Characteristics of epidemiological studies

This review presents the results of the eight cross-sectional studies conducted between 2012 and 2021 that aimed at searching for genome-wide associations (Table 1). In these studies, genetic markers associated with FA development were found at various gene loci.

Regarding methodology, several studies were cross-sectional randomized trials (n=4) [16–19], and the rest were case–control studies (n=4) [20–23]. The studies were performed in different age groups: children (n=3), adults (n=5), and family samples (n=1). The studies included samples with different ethnic groups of both European (n=5) and Asian (n=3) ancestry and mixed samples, such as Mexican-American.

The most extensive in terms of the number of participants was the cross-sectional study conducted in Japan, with a total number of 11,379 people aged 18–55 years; however, its drawbacks were associated with the screening nature of FA diagnosis, based on a questionnaire, which significantly limits the interpretation of the results [17].

In most cases, researchers used an increase in specific IgE levels (≥0.35 kU/L) and positive results of the skin prick tests with the most common food allergens (mean papule diameter

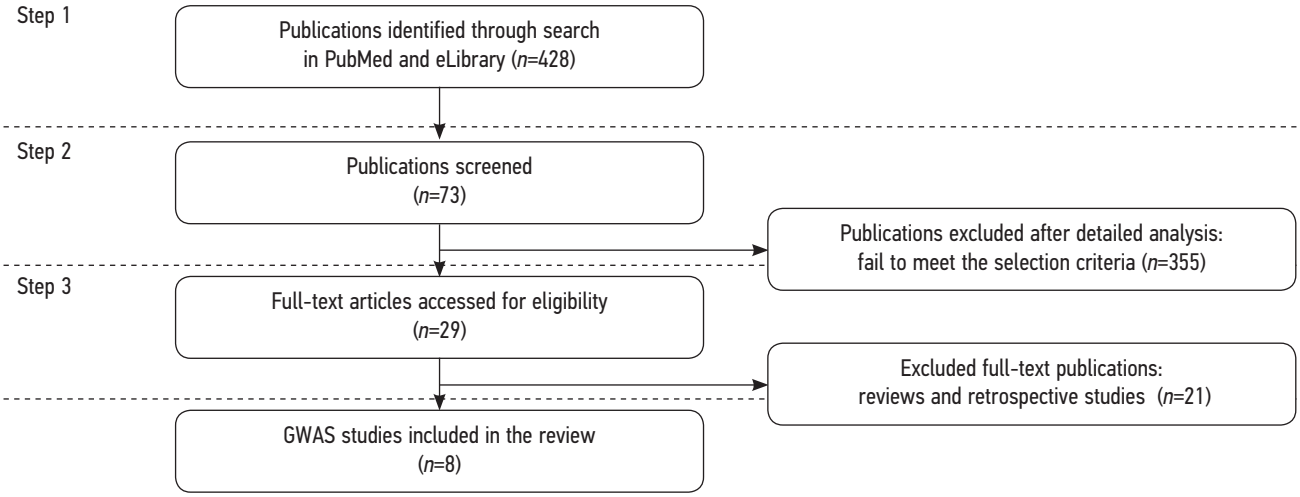

Fig. 1. Algorithm for the publication search.

⩾3 mm) in combination with clinical manifestations of FA as the main criteria for FA diagnosis [16, 19–23]. In some studies, oral provocation tests with food allergens, the gold standard of diagnostics, were used to confirm FA [20, 23].

Despite the wide geographical range of studies, authors mainly assessed sensitization to the most significant allergens such as milk, eggs, and peanuts [16, 19, 20, 22, 23]. Intolerance to products containing gliadin was also considered [18, 21]. In one of the studies, the analysis of food allergens took into account the dietary habits of a geographical region [17].

Whole-genome research technology

GWAS is a tool for investigating the genetic architecture of human multifactorial diseases and is used to identify genetic factors associated with developmental risk and clinical phenotypes. This method is based on determining the frequency of single nucleotide polymorphisms (SNP) distributed throughout the genome using microarrays or other technologies that allow simultaneous genotyping from several tens of thousands to several million SNPs in one sample. The ability to detect differences in the prevalence of SNPs between patients and controls has made GWAS a method widely used to analyze the genetic predisposition to complex diseases that are developed on a polygenic basis.

Since the first GWAS in 2002 [24], which analyzed the genetic predisposition to myocardial infarction, the progress of these studies in identifying genetic variants remains limited. This is mainly due to the study of phenotypes (phenotypes depend not only on genetic factors but also on the significant contribution of the environmental component), population characteristics, and difficulties in forming groups of patients and controls. The GWAS performed by Klein et al. in 2005 [25] is considered the most successful among GWAS. That study identified a variant in the complement factor H (CFH) gene that affects the development of age-related macular degeneration, the most common form of blindness in the Western world. Later, similar advances were made for other diseases, for example, an association between Crohn's disease and the rs11209026 variant in the interleukin 23 receptor (*IL23R*) gene was found, which was later confirmed in replication studies [26, 27]. Significant GWAS signals regarding allergic diseases have been registered for genes, and their products are predominantly involved in immune responses, including *HLA-DQ, C11orf30, IL1R1*, and other genes, particularly *FLG*, whose product maintains the skin barrier function [28]. Some associations are exclusively phenotype-specific, for example, the rs4915551 variant in *DENND1B* (1q31) was associated with asthma in patients with high body mass index [29]. Currently, the potential of GWAS for discovering the causative genes of multifactorial diseases is still high.

FLG. Filaggrin is a protein critical to the structure and function of the stratum corneum. This protein plays a significant role in the development of atopic dermatitis [30]. Its precursor prophyllagrin is encoded by *FLG* on chromosome 1q23.3 [31]. Scientists have found that loss-of-function mutation in *FLG* is strongly associated with the development of atopic dermatitis [32]. This mutation in the epidermal barrier gene increases the risk of sensitization to peanuts and, subsequently, the risk of FA to peanuts, probably due to increased penetration of the allergen through the defective skin barrier [33].

In a null mutation, the activity of a certain product associated with a gene completely disappears, or a product that does not function properly appears. For example, null *FLG* mutations have been associated with the development of allergic conditions throughout life [31]. In the European population, the rs12123821 variant, located in the 1q21.3 region and in linkage disequilibrium with a null *FLG* mutation, significantly affected the FA development associated with the ingestion of products such as peanuts, milk, and eggs; moreover, FA development is more likely with this mutation regardless of whether the patient has atopic dermatitis [20]. This indicates that *FLG* mutations contribute greatly to

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Table 1. Results of studies on genome-wide associations performed from 2012 to 2021

Author, year country	Ethnicity	Total sample size	Sampling criteria	Food allergy phenotype	Allergens	Genetic aspects			Validity
						Locus	Chromosome	SNP	
Marenholz et al., 2017, Germany [20]	European population	Case group (*n*=523); control group (*n*=2682)	Clinical symptoms of FA, and/or specific IgE levels in the blood serum ≥0.35 kU/L, and/or food provocation tests	Children with IgE-mediated FA without AD symptoms	-	-	1q21.3	rs12123821	OR 2.55; $p=8.4\times10^{-10}$
					-	-	5q31.1	rs11949166	OR 0.60; $p=1.2\times10^{-13}$
					-	*FLG*	1q21.3	rs12123821	OR 1.77; 95% CI 1.15–2.74; $p=0.0094$
					Chicken egg	*FLG*	1q21.3	rs12123821	OR 2.67; $p=7.0\times10^{-8}$
					Milk	*FLG*	1q21.3	rs12123821	OR 3.59; $p=2.4\times10^{-9}$
					Peanut	*FLG*	1q21.3	rs12123821	OR 2.35; $p=1.5\times10^{-4}$
				Children with IgE-mediated FA without AD symptoms	-	*IL5/RAD50* and *IL4/KIF3A*	5q31.1	rs11949166	OR 1.61; 95% CI 1.27–2.04; $p=8.9\times10^{-5}$
				Children with IgE-mediated FA and AD	-				OR 1.69; 95% CI 1.50–1.91; $p=2.4\times10^{-17}$
				Children with IgE-mediated FA without AD symptoms	-	*C11orf30/ LRRC32*	11q13.5	rs2212434	OR 1.14; 95% CI 0.90–1.44; $p=0.29$
				Children with IgE-mediated FA and AD	-				OR 1.40; 95% CI 1.25–1.58; $p=1.9\times10^{-8}$
				Children with IgE-mediated FA	-	*SERPINB7*	18q21.3	rs12964116	$p=1.8\times10^{-8}$
					Peanut			rs12964116	$p=1.9\times10^{-10}$
					Chicken egg	*SERPINB7/B2*	18q21.3	rs1243064	$p=4.2\times10^{-8}$
					Peanut	*HLA-DQB1*	6p21	rs9273440	$p=6.6\times10^{-7}$
Fukunaga et al., 2021, Japan [21]	Asian population	Case group (*n*=107); control group (*n*=1359)	Clinical symptoms of FA, and/or specific IgE level in the blood serum ≥0.35 kU/L	IgE-mediated FA induced by exercise after ingestion of wheat products	Gliadin	*HLA-DPB1*02: 01:02*	6	rs9277630	OR 4.51; 95% CI 2.66–7.63; $p=2.28\times10^{-9}$
Liu et al., 2018, China [19]	European population	*n*=588	Clinical symptoms of PA, and/or specific IgE level in the blood serum ≥0.35 kU/L, and/or skin test wheal diameter >3 mm	IgE-mediated FA	-	*LOC101927947*	4	rs4235235	$p=4.82\times10^{-8}$
					Egg	*ZNF652*	17	rs1343795	$p=4.47\times10^{-7}$
					Egg	*ZNF652*	17	rs4572450	
					Peanut	*ADGB*	6	rs4896888	OR 0.15; 95% CI 0.07–0.31; $p=2.66\times10^{-7}$
					-	*IQCE*	7	rs1036504	OR 2.95; 95% CI 1.84–4.75; $p=8.29\times10^{-6}$

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Table 1. Ending

Author, year country	Ethnicity	Total sample size	Sampling criteria	Food allergy phenotype	Allergens	Genetic aspects			Validity
						Locus	Chromosome	SNP	
Martino et al., 2016, Australia [23]	European population	Case group (*n*=73); control group (*n*=148)	Clinical symptoms of PA, and/or specific IgE level in blood serum ⩾0.35 kU/L, food provocation tests, and/or skin test wheal diameter >3 mm	IgE-mediated FA	Peanut	*SLC2A9*	4	rs10018666	OR 5.9; $p=4\times10^{-8}$
Hong et al., 2015, USA [16]	European population	*n*=2197	Clinical symptoms of FA, and/or specific IgE level in blood serum ⩾0.35 kU/L, and/or skin test wheal diameter >3 mm	IgE-mediated FA	Peanut	Intergenic region *HLA-DQB1-HLA-DQA2*	6p21.32	rs7192-T	OR 1.7; 95% CI 1.4–2.1; $p=5.5\times10^{-8}$
								rs9275596-C	OR 1.7; 95% CI 1.4–2.1; $p=6.8\times10^{-10}$
	Non-European population (Mexicans, Indians, Chinese, etc.)	*n*=497		IgE-mediated FA	Peanut	*HLA-DR* and -DQ	6p21.32	rs7192-T	OR 1.2; 95% CI 0.8–1.8; $p=0.198$
								rs9275596-C	OR 1.2; 95% CI 0.8–1.8; $p=0.327$
Asai et al., 2017, Canada [22]	European population	Case group (*n*=850); control group (*n*=926)	Clinical symptoms of FA, and/or skin test wheal diameter >3 mm	IgE-mediated FA	Peanut	*ITGA6*	2	rs115218289	$p=1.80\times10^{-8}$
Rubicz et al., 2014, USA [18]	Mexican-American population	*n*=1367	IgG	Cell mediated FA	Gliadin	*HLA-DRA* and *BTNL2*	6	rs3135350	$p=8.6\times10^{-8}$
Khor et al., 2017, Japan [17]	Asian population	*n*=11379	Questionnaire	IgE-mediated FA	Peach	*HLA-DR/ HLA-DQ*	6	rs28359884	OR 1.68; $p=1.15\times10^{-7}$
					Shrimp			rs74995702	OR 1.91; $p=6.30\times10^{-17}$

Note: AD, atopic dermatitis; FA, food allergy.

sensitization to various allergens, facilitating the development of not only atopic dermatitis but also other allergic diseases (specifically, it is a significant risk factor for FA development).

HLA. *HLA* encodes families of cell surface proteins that function as key determinants of antigen recognition by the immune system. This area is associated with several immune, infectious, and allergic diseases [34]. Several studies have shown the high significance of *HLA* in FA development [20]. Researchers from Germany found that the *HLA-DQB1* locus, located on chromosome 6p21, significantly contributed to the development of peanut allergy; specifically, an association with the rs9273440 variant (p=6.6×10^{-7}) was found. Children with allergy to milk and eggs did not have this association, which indicates the specificity of the *HLA-DQB1* locus to peanut allergy [20].

A Chicago study also established an association between FA and peanuts with *HLA-DQB1* (rs7192-T) and *HLA-DQA2* (rs9275596-C) [16], regardless of the level of specific IgE in peanuts. However, the data obtained are representative only of the European population: in the study of variants rs7192 and rs9275596 in patients with peanut FA, no associations were found in the population of non-European origin [16]. No evidence has linked these SNPs (rs7192 and rs9275596) with egg and milk allergy [16].

A questionnaire-based study including 11,379 people of Asian origin found an association between *HLA-DR* and *HLA-DQ* and region-specific allergens such as peach and shrimp [17]. A significant association was found between the rs28359884 variant (*HLA-DQA1, HLA-DRB5,* and *HLA-DRB1*) and peach consumption and between the rs74995702 variant (*HLA-DQA1, HLA-DRB5, HLA-DRB1, HLA-DQB1, HLA-DQA2,* and *HLA-DRA*) and shrimp consumption. These SNPs were nominally associated in individuals with allergic reactions to apples and crabs [17].

Moreover, several studies have established a link between *HLA* and allergy to food agents containing gliadin: specifically, a link was found for the rs3135350 polymorphic variant located in the intergenic region (*HLA-DRA/BTNL2*) [18]. Significant signals were obtained at the *HLA-DPB1*02:01:02* (rs9277630) locus for IgE-mediated exercise-induced FA after consumption of wheat products [21]. This polymorphism may be a potential marker of exercise-induced anaphylaxis with wheat ingestion.

These studies once again confirm the importance of *HLA* in the development of allergic diseases, specifically in FA. However, *HLA* involvement in FA development is not highly specific.

Locus C11orf30/LRRC32. The *C11orf30/LRRC32* region, located on chromosome 11, plays an important role in the development of allergic diseases: generally, this region apparently determines the development of atopic march [35, 36]. *C11orf30* encodes the EMSY protein, which is associated with atopy and a predisposition to polysensitization [37, 38]. *LRRC32* encodes a membrane protein of the same name containing leucine-rich repeats (LRRC32 protein) [39].

A GWAS performed on the European population (Germany) showed that the nucleotide substitution (rs2212434) in this locus was associated with FA development [20]. The results indicated that the *C11orf30/LRRC32* region contributes to FA development regardless of whether an individual has atopic dermatitis or not (Table 1) [20]. This indicates the possibility of using this SNP as a potential FA marker.

SERPINB7. *SERPINB7* is located on chromosome 18 and encodes a protein of the same name, which is a class B serpin peptidase inhibitor, type 7 [40]. Two nucleotide substitutions associated with FA were identified in this locus, one of which, rs12964116, showed a significant association with FA and peanut allergy [20]. The rs12964116 variant is low polymorphic globally [41]. The second nucleotide substitution, rs1243064, is associated with chicken egg allergy [20] and, unlike rs12964116, is widespread in both Europeans and other populations.

In addition to the pronounced effect on the development of allergic diseases, the rs12964116 polymorphic variant is associated with kidney diseases and oncological diseases [42–46], whereas the rs1243064 variant is significantly associated with attention-deficit hyperactivity disorder. Characteristic mutations of *SERPINB7* are detected in patients with palmoplantar keratoderma (Nagashima type) [40]. There are reports on keratosis comorbidity with allergic pathology and atopic dermatitis [47].

ZNF652. A study in China that evaluated the effect of allergic diseases in parents on FA development in offspring found that rs4572450 and rs16948048, localized in *ZNF652*, are associated with the development of allergic symptoms to chicken eggs [19]. Interestingly, atopic dermatitis in mothers was associated with a high risk of developing FA to eggs in their children, whereas such data have not been shown for peanuts [19]. *ZNF652* located on chromosome 17 encodes "zinc finger" 652 family protein. Both FA-associated variants rs4572450 and rs16948048 affect the binding sites of transcription factors and are functionally significant to different diseases. Previously, rs16948048 was found to be also associated with the development of dermatitis in both European and Asian populations [48]. In addition to the relationship between FA and dermatitis, both polymorphic variants are associated with circulatory system diseases (such as arterial hypertension and coronary heart disease) [49–52]. The pleiotropic associations of the rs4572450 variant are related to nervous system disorders such as Parkinson's disease and metabolism-associated diseases such as osteoporosis [53–56].

ADGB and IQCE. *ADGB* encodes the androglobin protein and is located on chromosome 6. *IQCE* encodes the IQ protein, a region containing protein E, which is part of the protein complex of the plasma membrane [19]. A research team from China found an association between peanut consumption and the rs4896888 variant located in the androglobin gene. In *IQCE*, an association between FA, and two genome-wide variants, rs1036504, and rs2917750, was first discovered [19]. Interestingly, all three nucleotide substitutions occurred only in boys. Both genes (*ADGB* and *IQCE*) are not specific imprinted

genes [19]. Variants localized in the region of these genes are associated with infectious diseases, for example, rs4896888 is associated with leprosy, and rs1036504 is associated with human immunodeficiency virus infection [57, 58]. The association with other allergic diseases is still unknown.

SLC2A9. *SLC2A9* is located on the short arm of chromosome 4 and encodes the protein facilitated glucose transporter 9 (GLUT9). In humans, GLUT9 has two splicing variants with different expression patterns: GLUT9a is expressed in many tissues, whereas GLUT9b (also called GLUT9ΔN) is expressed predominantly in the kidney and to a lesser extent in the liver [59]. Basolateral GLUT9 is the main renal transporter involved in urate reabsorption [61]. An association between peanut allergy and the rs10018666 variant of *SLC2A9* was found for the first time in an Australian group of children with confirmed IgE-mediated FA [23]. However, this association is not specific to FA because several studies have established a link between the rs10018666 variant and the development of urinary system diseases (such as hyperuricemia, nephrolithiasis, and gout), cardiovascular system diseases (such as coronary heart disease and myocardial infarction), and other metabolism-related disorders (such as type 2 diabetes mellitus and obesity) [60–71], which indicates a pronounced pleiotropy of *SLC2A9*.

ITGA6. *ITGA6* is located on chromosome 2 and encodes a part of the integrin alpha chain protein family. Integrins are heteromeric integral membrane proteins consisting of alpha and beta chains that are involved in adhesion and signaling on the cell surface [22]. A Canadian GWAS found an association between the rs115218289 variant and peanut allergy [22]. Literature data revealed that *ITGA6* is related to epidermolysis bullosa, a rare hereditary disease characterized by severe damage to the skin and mucosa of the gastrointestinal tract [72, 73].

CONCLUSIONS

The rapid development of personalized medicine technologies dictates the need for population studies using molecular epidemiology approaches. In the analysis of published genetic studies in patients with food allergies, GWAS was employed as an informative tool for studying the genetic architecture of multifactorial diseases. Although this review included studies of different power and homogeneity, it systematically presented the sets of loci, genes, and nucleotide sequences associated with FA development. The most valuable results were obtained in large-scale multicenter studies, including large biological collections.

The result of the literature analysis revealed that some loci are associated not only with FA development but also with atopic dermatitis, asthma, and allergic rhinitis. For some allergens, specific loci associated with the common development of sensitization to a particular food allergen have been identified, for example, the *HLA-DQB1* locus was found to be associated with FA development to peanuts.

This study highlights the importance of investigating genetic characteristics, particularly considering the differences between ethnic groups in various geographical regions, such as China, USA, and Europe. Currently, no molecular epidemiological data on the association between FA and various genes in the Russian population have been published. Thus, large-scale epidemiological studies of the risk of FA development in the Russian population using the results of GWAS to identify associated loci are relevant.

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