



# Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,  
Alergología y Asma Pediátrica

[www.all-imm.com](http://www.all-imm.com)



ORIGINAL ARTICLE

OPEN ACCESS 

## Analysis of *IL-13* gene polymorphisms in pediatric patients with food allergy

Maria-Teodora Coșoreanu<sup>a,b</sup>, Camelia-Elena Berghea<sup>a,b,\*</sup>, Felicia Galoș<sup>a,b</sup>, Luis-Ovidiu Popa<sup>c</sup>, Mara-Ioana Ionescu<sup>b,d</sup>, Andreea Ioan<sup>a,e</sup>, Ioana Țieranu<sup>b</sup>, Eliza-Elena Cintează<sup>a,b</sup>, Olivia-Mihaela Popa<sup>f</sup>

<sup>a</sup>Department of Pediatrics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

<sup>b</sup>Marie Curie Emergency Children's Hospital, Bucharest, Romania

<sup>c</sup>Grigore Antipa National Museum of Natural History, Bucharest, Romania

<sup>d</sup>Department of Physiology-Neurosciences, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

<sup>e</sup>Department of Clinical Immunology, National Institute for Mother and Child Health Alessandrescu-Rusescu, Bucharest, Romania

<sup>f</sup>Department of Pathophysiology and Immunology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Received 20 November 2025; Accepted 16 January 2026

Available online 6 February 2026

### KEYWORDS

IgE-mediated food allergies;  
*IL-13* gene;  
non-IgE-mediated food allergies;  
rs1800925;  
single-nucleotide polymorphisms

### Abstract

Food allergies represent immune-mediated adverse reactions to dietary proteins, with incompletely elucidated causes and etiopathogenic mechanisms, and have a significant negative impact on the quality of life of children and their families. The aim of the study was to assess the associations between *IL-13* gene single-nucleotide polymorphisms (SNPs) rs20541 and rs1800925 and the risk of developing IgE-mediated or non-IgE-mediated food allergies, as well as other patient characteristics. The study included 115 healthy controls and 165 children with food allergy, divided into two groups based on the presence of either IgE-mediated (N=85) or non-IgE-mediated (N=80) food allergy, all of Romanian origin. Genotyping of the two SNPs was performed using Real-Time PCR with TaqMan Allelic Discrimination Assays. OpenEpi and PLINK v1.07 were used for the statistical analysis. The frequency of carriers of the minor allele T of rs1800925 was significantly higher in patients with non-IgE-mediated food allergy (50% vs. 35.6%,  $p=0.04$ , OR=1.8). CT heterozygotes of rs1800925 were at high risk for non-IgE-mediated food allergy compared to CC and TT homozygotes ( $p=0.01$ , OR=2.13). No associations were found with IgE-mediated food allergy. The present study investigates for the first time *IL-13* gene SNPs in non-IgE-mediated food allergy. The results provide evidence that variation in the *IL-13* gene is involved in the pathogenesis of this disease. Further investigation is required to confirm these findings.

© 2026 Codon Publications. Published by Codon Publications.

\*Corresponding author: Camelia-Elena Berghea, Department of Pediatrics, Carol Davila University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021, Bucharest, Romania. Email address: [camelia.berghea@umfcd.ro](mailto:camelia.berghea@umfcd.ro)

<https://doi.org/10.15586/aei.v54iSP1.1637>

Copyright: Coșoreanu M-T, et al.

License: This open access article is licensed under Creative Commons Attribution 4.0 International (CC BY 4.0). <http://creativecommons.org/>

## Introduction

Food allergy represents an adverse reaction to dietary proteins involving immunological mechanisms and includes IgE-mediated food allergy, non-IgE-mediated food allergy, and mixed IgE- and non-IgE-mediated reactions.<sup>1</sup>

In patients with IgE-mediated food allergy, symptoms usually appear within minutes after ingestion of the culprit food and present a broad spectrum of severity, ranging from anaphylaxis to acute urticaria, vomiting, diarrhea, and rhinitis.<sup>2</sup> Non-IgE-mediated food allergy is characterized by clinical manifestations that usually develop between 6 and 72 hours after ingestion and include vomiting, diarrhea, hematochezia, constipation, food refusal, failure to thrive, chronic cough, and eczema.<sup>3,4</sup> A particular type of non-IgE-mediated food allergy is eosinophilic esophagitis (EoE), a chronic immune-mediated inflammatory disease that affects both children and adults.<sup>2,5</sup> In younger children, the clinical manifestations of this disease might be less specific, consisting in failure to thrive, vomiting, regurgitation, and feeding refusal, while adolescents usually present with food impaction and dysphagia.<sup>6,7</sup>

Although the prevalence of food allergy in children has shown a continuous increase over the last decades, many details regarding the exact etiology and pathophysiology still need to be elucidated.<sup>8-10</sup> One of the key immunological mechanisms involved in food allergy is the activation of T helper type 2 (Th2) pathways, characterized by elevated levels of proinflammatory cytokines, such as interleukin (IL)-13, IL-4, and IL-5.<sup>10,11</sup> Being the most studied cytokine involved in the pathogenesis of EoE, *IL-13* takes part in multiple pathways that lead to the development of this disease and other allergic diseases, such as atopic dermatitis, asthma, and allergic rhinitis.<sup>5,12,13</sup> *IL-13* is produced by T cells, natural killer cells, mast cells, basophils, and eosinophils and plays a central role in the regulation of IgE synthesis.<sup>13</sup> *IL-13* is able to determine the migration of eosinophils, T cells, and mast cells<sup>14</sup> and also generates disruptions of the epithelial barrier, alterations of smooth muscle contractility, and tissue remodeling by promoting collagen deposits and angiogenesis.<sup>5,12,14,15</sup> *IL-13* also plays a crucial role in the development of atopic dermatitis, a condition frequently encountered in patients with food allergies, the relationship between these two pathologies being characterized by complex, bilateral etiopathogenic and clinical interactions.<sup>16,17</sup> The clinical importance of exploring the implications of *IL-13* in allergic disease is also supported by the therapeutic benefits of monoclonal antibodies that interfere with *IL-4/IL-13* signaling in the management of EoE and atopic dermatitis.<sup>7,18,19</sup>

Food allergies are characterized by a strong but only partially described genetic etiology, with first-degree relatives of patients being at an increased risk of developing the disease compared to the general population.<sup>6,20</sup>

The *IL-13* gene is located on chromosome 5, in the region 5q31, and is part of the type 2 cytokine cluster along with *IL-4* and *IL-5* genes.<sup>17</sup> Several studies have found significant associations between *IL-13* gene polymorphisms and atopic dermatitis risk, severity, and other characteristics of the disease.<sup>16,17,21</sup> Polymorphisms in the *IL-13* gene were also explored in studies that found associations with IgE-mediated food allergy,<sup>22,23</sup> food sensitization,<sup>24-26</sup>

asthma,<sup>27-31</sup> respiratory allergies,<sup>32</sup> allergic rhinitis,<sup>33-36</sup> high levels of total serum IgE,<sup>24,25,31,37-40</sup> and elevated cord blood IgE levels.<sup>41-44</sup>

In this study, we aimed to assess the association between two *IL-13* single-nucleotide polymorphisms (SNPs), rs20541 and rs1800925, and both IgE-mediated and non-IgE-mediated food allergy. The *IL-13* rs20541 SNP is a functional variant in the coding region of the *IL-13* gene (within the fourth exon) and determines an exchange of arginine with glutamine at codon 144.<sup>25,45</sup> The *IL-13* rs1800925 SNP represents a regulatory functional polymorphism that is able to enhance the *IL-13* promoter activity in Th2 human lymphocytes.<sup>46</sup>

Given the reduced specificity of symptoms and the lack of accurate diagnostic tools in the case of food allergies, diagnosis remains challenging, leading to an increased risk of both underdiagnosing and overdiagnosing these diseases.<sup>2</sup> The cornerstone in the management of food allergy consists in strict adherence to the elimination diet,<sup>2</sup> with a considerable impact on the quality of life of children and their families and a possible risk of nutritional inadequacies. All of the aspects mentioned above point to the need to identify new risk factors and diagnostic tools that could help reach a faster, more accurate diagnosis and eventually develop more efficient preventive and therapeutic strategies.

## Materials and Methods

### Study population

We performed a study that included two groups of pediatric patients, one with non-IgE-mediated food allergy (NFA, N=80) and one with IgE-mediated food allergy (FA, N=85), in the evidence of Marie Curie Emergency Children's Hospital in Bucharest. All patients were unrelated Caucasians of Romanian origin. In 74 cases, the diagnosis of non-IgE-mediated food allergy was made based on the presence of suggestive symptoms (chronic diarrhea, hematochezia, vomiting, failure to thrive, chronic abdominal pain, anemia, etc.), a positive response to the elimination diet, and the exclusion of other diagnoses. Six of the patients were diagnosed with EoE after performing upper gastrointestinal endoscopy with biopsies that revealed a peak eosinophil count of at least 15 eosinophils/high power field. For the group of patients with IgE-mediated food allergies, the diagnosis was made based on a relevant patient history of specific symptoms developed shortly after ingestion of the culprit foods and elevated levels of specific serum IgE. The control group included 115 unrelated healthy Romanian subjects with no history of allergic diseases.

The study obtained approval from the Ethics Committee of Marie Curie Emergency Children's Hospital. All parents of patients and all controls provided consent for inclusion in the study after being informed about the tests to be performed.

### Genotyping and statistical analysis

Peripheral venous blood samples were collected from all patients and controls for DNA extraction. The QIAamp DNA

Blood Mini Kit (Qiagen, Hilden, Germany) was used according to the manufacturer's protocol to obtain genomic DNA. Two SNPs in the *IL-13* gene were selected for analysis: rs1800925 and rs20541. Genotyping of these polymorphisms was performed using real-time polymerase chain reaction with TaqMan Allelic Discrimination Assays C\_8932051\_10 and C\_2259921\_20 (Real-time PCR System, Applied Biosystems by Thermo Fisher Scientific, Foster City, CA, USA).

OpenEpi software and PLINK v1.07 were used to assess the statistical significance of the associations. A two-sided *p*-value of 0.05 was considered significant. The groups of patients were described based on general and demographic characteristics, which were reported as absolute and relative frequencies for categorical variables and medians and interquartile ranges (IQR) for non-normally distributed continuous variables. Normality was assessed using Kolmogorov-Smirnov tests. The Hardy-Weinberg equilibrium (HWE) was assessed for both SNPs using the chi-squared test. Mid-*P* exact tests were performed in order to compare the frequencies of genotypes and alleles between NFA, FA, and the control group. Moreover, the NFA group of patients was further divided based on the presence of atopic dermatitis, a positive family history of atopy, and elevated total IgE levels, and differences in genotype and allele distribution were evaluated separately for each case. The odds ratio was calculated, and a 95% confidence interval (CI) was used. Haplotype frequencies were also analyzed, and association tests were performed.

## Results

Demographic characteristics for patients are presented in Table 1. We noticed a significant difference in sex ratio between the two patient groups: NFA (38.7% males) and FA (64.7% males,  $p=9 \times 10^{-4}$ , OR 0.34, 95% CI = 0.18-0.64).

For the NFA group, data were available on the presence of atopic dermatitis (28.7%), a positive family history of allergic diseases (40%), and elevated total IgE levels (32.5%).

Patient and control groups were in Hardy-Weinberg equilibrium for both investigated SNPs. The genotyping success rate was 100% for rs1800925 and 99.2% for rs20541.

**Table 1** Demographic data for patients with food allergy.

	NFA patients (N=80)	FA patients (N=85)
Gender distribution		
Male	31 (38.7%)	55 (64.7%)
Female	49 (61.2%)	30 (35.2%)
Age (median [IQR])	5 [0, 11.75]	2 [0, 5.5]
Background		
Rural	19 (23.7%)	15 (17.6%)
Urban	61 (76.2%)	70 (82.3%)

\*NFA=non-IgE mediated food allergy, FA=IgE mediated food allergy.

Single-marker analysis revealed that the genotype distribution for *IL-13* rs1800925 was significantly different between controls and NFA patients (Table 2). Considering the largely used dominant model, we found that carriers of the minor allele were more frequent in the NFA group compared to controls (50% vs. 35.6%,  $p=0.04$ , OR 1.80). Based on the over-dominant model that assumes the heterozygote has the strongest impact, we observed that subjects with the CT genotype presented a higher risk for the disease compared to CC and TT homozygotes ( $p=0.01$ , OR 2.13). The minor allele T for this polymorphism was more frequent in patients, but the difference was not statistically significant. No association with the risk of NFA was observed for rs20541.

For IgE-mediated food allergy (FA) patients, the minor allele frequencies for the two SNPs were also higher compared with controls, but not significantly. No significant differences in the allele or genotype distributions were obtained when the NFA group of patients was compared with the FA group.

A low level of linkage disequilibrium was obtained for the two polymorphisms of the *IL-13* gene ( $r^2=0.2$ ). The analysis of haplotypes showed that all four haplotype combinations had frequencies over 5% (Table 3). Although we observed several differences in haplotype frequencies between patient groups and controls, none were statistically significant.

The analysis of the two *IL-13* gene polymorphisms in relation to clinical characteristics of the patients (Tables 4, 5) revealed that in the case of children with NFA who associated AD, the minor allele T of rs1800925 was more frequent compared to children without AD (32.6% vs. 24.5%), but the difference was not statistically significant ( $p=0.3$ ).

Children with NFA and a positive family history of atopic disease were more frequently carriers of the minor allele T of rs20541 (41.9% vs. 34%), and the minor allele T was more frequent in this subgroup of patients (27.4% vs. 19.1%), but statistical significance was not reached ( $p=0.49$  and  $p=0.23$ , respectively).

The minor allele T of rs20541 showed a higher frequency in children with elevated total serum IgE levels (30.7% vs. 18.2%), but the difference was not statistically significant ( $p=0.08$ ). Moreover, the TT and CT genotypes were more frequent in these patients (50.0% vs. 30.7%), but the difference did not reach statistical significance ( $p=0.1$ ).

## Discussions

The present study investigates, for the first time, *IL-13* gene variability in non-IgE-mediated food allergy (NFA). Despite extensive research, we could not identify in the literature any association study specifically regarding *IL-13* gene polymorphisms and the broad category of non-IgE-mediated food allergies. The only partially related finding was a phenotype-wide association study that identified a cluster of associations between the *IL-5-IL-13* region and eosinophilic esophagitis (EoE), a particular type of NFA.<sup>47</sup>

We found a significant association between *IL-13* rs1800925 and the risk of NFA. Carriers of the minor allele were at high risk for the disease. We also found that the heterozygote genotype is a risk factor for NFA compared

**Table 2** Results of the study of association of *IL-13* gene polymorphisms and non-IgE mediated food allergy and IgE mediated food allergy.

<i>IL-13</i> gene SNP	Controls (N=115) N (%)	NFA (N=80) N (%)	Statistics	FA (N=85) N (%)	Statistics
<b>rs20541</b>					
Minor allele					
T	47 (20.4%)	35 (22.4%)	OR=1.12 95% CI=0.68-1.84 p=0.63	40 (23.5%)	OR=1.19 95% CI=0.74-1.93 p=0.46
Genotypes					
TT+CT	7+33 (34.7%)	6+23 (37.1%)	OR=1.11 95% CI=0.61-2.01 p=0.73	6+28 (40.0%)	OR=1.25 95% CI=0.70-2.23 p=0.45
CC	75 (65.2%)	49 (62.8%)	OR=1.03 95% CI=0.55-1.95 p=0.90	51 (60.0%)	OR=1.22 95% CI=0.66-2.23 p=0.52
CT	33 (28.6%)	23 (29.4%)		28 (32.9%)	
TT+CC	82 (71.3%)	55 (70.5%)		57 (67.0%)	
<b>rs1800925</b>					
Minor allele					
T	49 (21.3%)	43 (26.8%)	OR=1.35 95% CI=0.84-2.17 p=0.20	39 (22.9%)	OR=1.1 95% CI=0.68-1.77 p=0.69
Genotypes					
TT+CT	8+33 (35.6%)	3+37 (50.0%)	OR=1.80 95% CI=1.00-3.22 p=0.04	4+31 (41.1%)	OR=1.26 95% CI=0.71-2.24 p=0.43
CC	74 (64.3%)	40 (50.0%)	OR=2.13 95% CI=1.17-3.88 p=0.01	50 (58.8%)	OR=1.42 95% CI=0.78-2.59 p=0.24
CT	33 (28.6%)	37 (46.2%)		31 (36.4%)	
TT+CC	82 (71.3%)	43 (53.7%)		54 (63.5%)	

\*NFA=non-IgE mediated food allergy, FA=IgE mediated food allergy, OR=odds ratio, 95% CI=95% confidence interval; level of statistical significance  $p < 0.05$  (significant values are indicated in bold).

**Table 3** Distribution of the haplotype combinations in the studied groups.

rs1800925/rs20541 haplotype	Controls (N=115)	NFA (N=80)	p	FA (N=85)	p
TT	11.06%	11.93%	0.70	13.84%	0.43
CT	9.37%	10.50%	0.81	9.68%	0.86
TC	10.24%	13.71%	0.35	9.09%	0.75
CC	69.32%	63.86%	0.29	67.37%	0.64

\*NFA=non-IgE mediated food allergy, FA=IgE mediated food allergy; level of statistical significance  $p < 0.05$ .

to homozygote genotypes. The single-nucleotide polymorphism rs1800925 (-1112C/T, also known as -1055 or -1111) located in the promoter of the *IL-13* gene is a functional SNP that affects the level of gene expression.<sup>46</sup> The 1112\*T allele, which, according to comparative analysis of the *IL-13* promoter, is the ancestral allele, increases gene transcription depending on various factors such as cell type, cell differentiation, and surrounding polymorphisms.<sup>46</sup> High levels of mRNA for *IL-13* and *IL-4* and low levels of mRNA for *IL-5* and *IL-10* were found in children with NFA compared with healthy children.<sup>48</sup> Another study addressing cytokine gene expression reported significantly higher levels

of mRNA for *IL-4*, *IL-10*, and *IL-13* in the rectum compared to the duodenum in NFA children.<sup>49</sup> All these data suggest a dysregulation of gene expression involving the Th2 cluster in non-IgE-mediated food allergy that requires more research efforts.

Regarding IgE-mediated food allergy, we did not find any associations for rs20541 or rs1800925 SNPs with the risk of the disease. Data on this pathology and the *IL-13* gene are also sparse, but they have been reported in a couple of studies presented below.

An Australian study demonstrated an association between *IL-13* gene polymorphism rs1295686 (found in

**Table 4** Genotype distribution of rs1800925 for a series of characteristics of the NFA group.

rs1800925	Minor allele		Genotypes		Statistics
	T	Statistics	TT+CT	CC	
<b>Atopic dermatitis</b>					
No (N=57)	28 (24.5%)	OR=1.48	28 (49.1%)	29 (50.8%)	OR=1.13
Yes (N=23)	15 (32.6%)	95% CI=0.70-3.14 p=0.30	12 (52.1%)	11 (47.8%)	95% CI=0.42-2.97 p=0.81
<b>Allergy family history</b>					
Negative (N=48)	25 (26.0%)	OR=1.11	25 (52.0%)	23 (47.9%)	OR=0.81
Positive (N=32)	18 (28.1%)	95% CI=0.54-2.26 p=0.77	15 (46.8%)	17 (53.1%)	95% CI=0.33-1.98 p=0.65
<b>Total IgE levels</b>					
Normal (N=54)	29 (26.8%)	OR=1.00	28 (51.8%)	26 (48.1%)	OR=0.79
High (N=26)	14 (26.9%)	95% CI=0.47-2.11 p=0.98	12 (46.1%)	14 (53.8%)	95% CI=0.31-2.03 p=0.64

\*OR=odds ratio, 95% CI=95% confidence interval; level of statistical significance  $p < 0.05$ .

**Table 5** Genotype distribution of rs20541 for a series of characteristics of the NFA group.

rs20541	Minor allele		Genotypes		Statistics
	T	Statistics	TT+CT	CC	
<b>Atopic dermatitis</b>					
No (N=57)	24 (21.0%)	OR=1.33	21 (36.8%)	36 (63.1%)	OR=1.05
Yes (N=23)	11 (26.1%)	95% CI=0.58-3.02 p=0.49	8 (38.0%)	13 (61.9%)	95% CI=0.37-2.96 p=0.91
<b>Allergy family history</b>					
Negative (N=48)	18 (19.1%)	OR=1.59	16 (34.0%)	31 (65.9%)	OR=1.39
Positive (N=32)	17 (27.4%)	95% CI=0.74-3.40 p=0.23	13 (41.9%)	18 (58.0%)	95% CI=0.54-3.56 p=0.49
<b>Total IgE levels</b>					
Normal (N=54)	19 (18.2%)	OR=1.98	16 (30.7%)	36 (69.2%)	OR=2.25
High (N=26)	16 (30.7%)	95% CI=0.91-4.29 p=0.08	13 (50.0%)	13 (50.0%)	95% CI=0.85-5.92 p=0.10

\*OR=odds ratio, 95% CI=95% confidence interval; level of statistical significance  $p < 0.05$ .

complete linkage disequilibrium with the functional variant rs20541) and challenge-proven IgE-mediated food allergy, while no association was found in the case of the other eight assessed polymorphisms, including rs1800925.<sup>22</sup> In the same study, rs1295686 and rs1800925 were found to be associated with increased total IgE levels.<sup>22</sup> These two SNPs (rs1295686 and rs20541) were reported to be significantly associated with total IgE concentrations in a genome-wide association study on the Framingham Heart Study cohort.<sup>50</sup>

Another study that described the association of rs20541 and rs1800925 SNPs with food allergy included Indian patients with challenge-proven shrimp allergy, one of the most frequent food allergies and a common cause of food-induced anaphylaxis.<sup>23</sup> Significant associations were found between the homozygous genotypes *IL-13* rs20541 AA (OR=3.60, 95% CI=1.30-9.95,  $p=0.01$ ) and *IL-13* rs1800925 TT (OR=5.48, 95% CI=1.16-26.01,  $p=0.03$ ) and the presence of challenge-proven shrimp allergy.<sup>23</sup> Moreover, these genotypes were associated with higher levels of shrimp-specific

IgE and a higher risk of shrimp allergy in younger people compared to older people.<sup>23</sup> In the haplotype analysis, the combination of rs1800925 T and rs20541 A alleles was associated with both challenge-proven shrimp allergy and shrimp sensitivity.<sup>23</sup>

The two *IL-13* polymorphisms selected for our research were also investigated in four studies, including European children with food sensitization. In German children, Liu et al. found that the *IL-13* rs1800925 SNP was associated with a higher risk of food sensitization in the pediatric population (children with increased levels of specific IgE antibodies to hen's egg, cow's milk, soy, and wheat, OR=3.49, 95% CI=1.52-8.02), while no association was found for rs20541.<sup>26</sup> In a previous study performed by the same author and including the same study population, both rs20541 and rs1800925 were associated with elevated total serum IgE levels ( $p < 0.0001$  and  $p = 0.0002$ , respectively).<sup>37</sup> Bottema et al. found that the rs1800925 SNP was associated with egg sensitization at the ages of 1 and 2 years old

in a study including three Dutch birth cohorts; furthermore, *IL-13* rs20541 and rs1800925 SNPs were associated with increased total serum IgE levels.<sup>24</sup> The association between rs1800925 and egg sensitization was confirmed by a study conducted by Zitnik et al. that included children with atopic dermatitis ( $p=0.0001$ ).<sup>25</sup> Moreover, they found associations between rs20541 and higher IgE levels ( $p=0.013$ ), sensitization against egg ( $p=0.0001$ ), milk ( $p=0.0006$ ), and peanut (0.04).<sup>25</sup> An interesting finding of this research is that IgE levels did not differ significantly between individuals with TT and CC genotypes for rs1800925, but heterozygotes presented slightly higher levels of total IgE.<sup>25</sup>

In the literature, there are multiple reports of associations between *IL-13* gene SNPs rs20541 and rs1800925 and atopic dermatitis, elevated levels of total serum IgE, or asthma, while there are also studies with contradictory results.

A meta-analysis and systematic review of candidate gene associations in atopic dermatitis analyzed the *IL-13* gene SNP rs1800925. The authors found a significant association between this polymorphism and the risk of developing atopic dermatitis in patients with European ancestry (based on four studies including 931 patients), but no significant associations with atopic dermatitis in patients with Asian ancestry (two studies,  $N=1803$ ).<sup>17</sup> One of the studies included in this meta-analysis also found associations between the rs1800925 SNP and increased IgE levels and asthma in the Polish population, while no associations were found with allergic rhinitis and early onset of atopic dermatitis.<sup>21</sup> Lesiak et al. described no correlation between *IL-13* levels and a specific genotype of the rs1800925 SNP.<sup>51</sup> In a previous study by the same author, no associations were found between any of the analyzed polymorphisms in the *IL-13*, *IL-4*, and *IL-10* genes and the severity of atopic dermatitis, clinical manifestations, or early onset of asthma.<sup>52</sup> On the other hand, in a whole-population birth cohort from 1989 from the Isle of Wight ( $N=1456$ ), no significant associations were found between *IL-13* rs20541 and rs1800925 genotypes and the prevalence of eczema, the disease being assessed at different ages from birth to 10 years old.<sup>55</sup>

Associations between the rs20541 SNP and higher total IgE levels were reported by several studies in both Caucasian and Asian populations.<sup>31,38-40</sup> A study that included fine mapping of the *IL-13* rs20541 SNP also identified significant associations with atopic dermatitis and increased IgE levels.<sup>54</sup> However, in a Polish study assessing the *IL-13* rs20541 SNP, no significant associations were found with atopic dermatitis, asthma, allergic rhinoconjunctivitis, and total IgE levels; the only significant correlation for the rs20541 SNP was with positive results of skin prick tests for aeroallergens.<sup>55</sup> No significant association between the *IL-13* rs20541 SNP and elevated levels of total IgE was also found in a study involving two Caucasian prospective cohorts.<sup>56</sup>

An interesting finding from a birth cohort study is the interaction between the *IL-13* polymorphisms and birth order, as only in the case of firstborn children was there a significant association between rs1800925 and rs20541 and increased levels of total IgE, positive skin prick tests, and positive levels of serum inhalant-specific IgE.<sup>57</sup>

With regard to gene-gene interactions, it was demonstrated that the interaction between *IL-13* (rs20541) and

*STAT6* (rs1059513) led to an increased risk of developing eczema.<sup>58</sup> Interactions were also described between the *IL-13* rs20541 SNP and the type of birth and prenatal antibiotic exposure with respect to the increased risk of atopic dermatitis.<sup>59</sup> Children with certain *IL-13* rs20541 SNP genotypes also presented a higher risk of developing early-persistent atopic dermatitis after receiving antibiotic treatment.<sup>60</sup>

Children with food allergies present an increased risk of developing asthma,<sup>61</sup> another allergic disease in which the implications of the *IL-13* rs20541 SNP and rs1800925 SNP have been largely evaluated. A meta-analysis that included 45 studies on rs20541 and 31 studies on rs1800925 concluded that both polymorphisms are significantly associated with the risk of developing asthma in both European and Asian populations.<sup>29</sup> The same conclusion was drawn by Cui et al. in another meta-analysis that assessed both polymorphisms.<sup>30</sup> Another study demonstrated the association between rs1800925 and elevated levels of total serum IgE in patients with asthma.<sup>62</sup>

In a large study on a longitudinal birth cohort ( $N=2918$ ) from 1946, *IL-13* rs20541 and rs1800925 were significantly associated with a self-reported positive history of asthma and allergy, while no confounding factor was identified regarding any of the assessed environmental factors (breastfeeding duration, region of birth, parental smoking, atmosphere pollution during childhood, most recent occupation, etc.).<sup>63</sup> However, in models that evaluated the association of both polymorphisms together, the rs20541 SNP reduced the association of the rs1800925 SNP with asthma, as well as with allergy, to the extent that there was no longer a statistically significant independent effect on the outcome for rs1800925.<sup>63</sup>

The interplay between genetic and environmental factors in the development of atopic diseases begins in the prenatal stage, the risk of allergy later in life being correlated with the level of cord blood IgE levels.<sup>42</sup> Both *IL-13* polymorphisms, rs1800925 and rs20541, were associated with elevated levels of IgE in cord blood samples, and interactions with SNPs found in other genes and environmental factors, such as maternal atopy or exposure to smoking, were also described.<sup>41-44</sup>

Considering the fact that associations between *IL-13* gene SNPs and diverse allergic pathologies were demonstrated in several studies, but some of these associations were not found to be statistically significant in other studies, more research in this area is still necessary. The main limitation of the present study is the reduced number of patients available for each type of food allergy. Additionally, the results need confirmation in cohorts from other populations.

## Conclusion

The main finding of our study was the significant association between *IL-13* rs1800925 and the risk of non-IgE-mediated food allergy. Individuals carrying the minor allele T, as well as CT heterozygotes, presented an increased risk of the disease. No associations were found for rs20541 or in the case of children with IgE-mediated food allergy. Additionally, in patients with non-IgE-mediated food

allergy, rs1800925 and rs20541 were not associated with the risk of presenting atopic dermatitis, a positive family history of allergy, or elevated total IgE levels. These findings could represent a step toward identifying the potential of *IL-13* to be part of the future generation of diagnostic tools used in food allergy, but validation is needed in larger groups of patients.

## Author Contributions

The conceptualization and design of the study were realized by MTC, CEB, and OMP. MTC, CEB, FG, MII, AI, and IT contributed to methodology and data collection. Data analysis was performed by OMP, LOP, and MTC. OMP, EEC, and FG were responsible for study supervision and project administration. The initial manuscript was written by MTC and OMP. All of the authors checked, provided feedback, and approved the final version of the manuscript.

## Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

## Funding

The publication of this article was supported by Carol Davila University of Medicine and Pharmacy.

## References

- Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. *Nutrients*. 2020;12(7):2086. <https://doi.org/10.3390/nu12072086>
- Vandenplas Y, Broekaert I, Domellöf M, Indrio F, Lapillonne A, Pienar C, et al. An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413. <https://doi.org/10.1097/MPG.0000000000003897>
- Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy - a UK primary care practical guide. *Clin Transl Allergy*. 2013;3(1):23. <https://doi.org/10.1186/2045-7022-3-23>
- Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol*. 2015;135(5):1114-1124. <https://doi.org/10.1016/j.jaci.2015.03.025>
- O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, Rothenberg ME. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology*. 2018;154(2):333-345. <https://doi.org/10.1053/j.gastro.2017.06.065>
- Muir A, Falk GW. Eosinophilic Esophagitis: A Review. *JAMA*. 2021;326(13):1310-1318. <https://doi.org/10.1001/jama.2021.14920>
- Dellon ES, Muir AB, Katzka DA, Shah SC, Sauer BG, Aceves SS, Furuta GT, Gonsalves N, Hirano I. ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis. *Am J Gastroenterol*. 2025;120(1):31-59. <https://doi.org/10.14309/ajg.0000000000003194>
- Spolidoro GCI, Amera YT, Ali MM, Nyassi S, Lisik D, Ioannidou A, et al. Frequency of food allergy in Europe: An updated systematic review and meta-analysis. *Allergy*. 2023;78(2):351-368. <https://doi.org/10.1111/all.15560>
- Bartha I, Almulhem N, Santos AF. Feast for thought: A comprehensive review of food allergy 2021-2023. *J Allergy Clin Immunol*. 2024;153(3):576-594. <https://doi.org/10.1016/j.jaci.2023.11.918>
- Zhang S, Sicherer S, Berin MC, Agyemang A. Pathophysiology of Non-IgE-Mediated Food Allergy. *ImmunoTargets Ther*. 2021;10:431-446. <https://doi.org/10.2147/ITT.S284821>
- Morita H, Nomura I, Orihara K, Yoshida K, Akasawa A, Tachimoto H, et al. Antigen-specific T-cell responses in patients with non-IgE-mediated gastrointestinal food allergy are predominantly skewed to TH2. *J Allergy Clin Immunol*. 2013;131(2):590-592.e6. <https://doi.org/10.1016/j.jaci.2012.10.052>
- Patel RV, Hirano I, Gonsalves N. Eosinophilic Esophagitis: Etiology and Therapy. *Annu Rev Med*. 2021;72(1):183-197. <https://doi.org/10.1146/annurev-med-042020-112441>
- Rael EL, Lockey RF. Interleukin-13 Signaling and Its Role in Asthma. *World Allergy Organ J*. 2011;4(3):54-64. <https://doi.org/10.1097/WOX.0b013e3182118c68>
- Davis BP. Pathophysiology of Eosinophilic Esophagitis. *Clin Rev Allergy Immunol*. 2018;55(1):19-42. <https://doi.org/10.1007/s12016-017-8665-9>
- Rothenberg ME. Molecular, Genetic, and Cellular Bases for Treating Eosinophilic Esophagitis. *Gastroenterology*. 2015;148(6):1143-1157. <https://doi.org/10.1053/j.gastro.2015.02.002>
- Brandt EE. Th2 Cytokines and Atopic Dermatitis. *J Clin Cell Immunol*. 2011;02(03). Available from: <https://www.omicsonline.org/th2-cytokines-and-atopic-dermatitis-2155-9899.1000110.php?aid=1712>
- Pontikas A, Antonatos C, Evangelou E, Vasilopoulos Y. Candidate Gene Association Studies in Atopic Dermatitis in Participants of European and Asian Ancestry: A Systematic Review and Meta-Analysis. *Genes*. 2023;14(7):1456. <https://doi.org/10.3390/genes14071456>
- Hirano I, Collins MH, Assouline-Dayana Y, Evans L, Gupta S, Schoepfer AM, et al. RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis. *Gastroenterology*. 2019;156(3):592-603.e10. <https://doi.org/10.1053/j.gastro.2018.10.051>
- Wang M, Gao XH, Zhang L. A Review of Dupilumab in the Treatment of Atopic Dermatitis in Infants and Children. *Drug Des Devel Ther*. 2024;18:941-951. <https://doi.org/10.2147/DDDT.S457761>
- Marenholz I, Grosche S, Rüschemdorf F, Kalb B, Blumchen K, Schlags R, et al. Evaluation of food allergy candidate loci in the Genetics of Food Allergy study. *J Allergy Clin Immunol*. 2018;142(4):1368-1370.e2. <https://doi.org/10.1016/j.jaci.2018.07.012>
- Trzeciak M, Gleń J, Rębata K, Bandurski T, Sikorska M, Nowicki R. Coexistence of 2282del4 FLG gene mutation and IL-18 -137G/C gene polymorphism enhances the risk of atopic dermatitis. *Adv Dermatol Allergol*. 2016;33(1):57-62. <https://doi.org/10.5114/pdia.2015.48050>
- Ashley SE, Tan HTT, Peters R, Allen KJ, Vuillermin P, Dharmage SC, Tang MLK, Koplin J, Lowe A, Ponsonby AL, Molloy J, Matheson MC, Saffery R, Ellis JA, Martino D; HealthNuts team. Genetic variation at the Th2 immune gene *IL13* is associated with IgE-mediated paediatric food allergy. *Clin Exp Allergy*. 2017;47(8):1032-1037. <https://doi.org/10.1111/cea.12942>

23. Laha A, Ghosh A, Moitra S, Biswas H, Saha NC, Bhattacharya S, et al. Association of HLA-DQ and IL13 gene variants with challenge-proven shrimp allergy in West Bengal, India. *Immunogenetics*. 2020;72(9-10):489-498. <https://doi.org/10.1007/s00251-020-01182-5>
24. Bottema RWB, Reijmerink NE, Kerkhof M, Koppelman GH, Stelma FF, Gerritsen J, et al. Interleukin 13, CD14, pet and tobacco smoke influence atopy in three Dutch cohorts: the allergenic study. *Eur Respir J*. 2008;32(3):593-602. <https://doi.org/10.1183/09031936.00086707>
25. Zitnik SE, Rüschenhoff F, Müller S, Sengler C, Lee Y, Griffioen RW, et al. IL13 variants are associated with total serum IgE and early sensitization to food allergens in children with atopic dermatitis. *Pediatr Allergy Immunol*. 2009;20(6):551-555. <https://doi.org/10.1111/j.1399-3038.2009.00832.x>
26. Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: The German Multicenter Atopy Study. *J Allergy Clin Immunol*. 2004;113(3):489-495. <https://doi.org/10.1016/j.jaci.2003.12.460>
27. Howard TD, Whittaker PA, Zaiman AL, Koppelman GH, Xu J, Hanley MT, et al. Identification and Association of Polymorphisms in the Interleukin-13 Gene with Asthma and Atopy in a Dutch Population. *Am J Respir Cell Mol Biol*. 2001;25(3):377-384. <https://doi.org/10.1165/ajrcmb.25.3.4289>
28. Van Der Pouw Kraan T, Van Veen A, Boeijs L, Van Tuyl S, De Groot E, Stapel S, et al. An IL-13 promoter polymorphism associated with increased risk of allergic asthma. *Genes Immun*. 1999;1(1):61-65. <https://doi.org/10.1038/sj.gene.6362858>
29. Omraninava M, Eslami MM, Aslani S, Razi B, Imani D, Feyzinia S. Interleukin 13 gene polymorphism and susceptibility to asthma: a meta-regression and meta-analysis. *Eur Ann Allergy Clin Immunol*. 2022;54(4):150-167. <https://doi.org/10.23822/EurAnnACI.1764-1489.180>
30. Cui L, Jia J, Ma CF, Li SY, Wang YP, Guo XM, et al. IL-13 polymorphisms contribute to the risk of asthma: a meta-analysis. *Clin Biochem*. 2012;45(4-5):285-288. <https://doi.org/10.1016/j.clinbiochem.2011.10.029>
31. Heinzmann A. Genetic variants of IL-13 signalling and human asthma and atopy. *Hum Mol Genet*. 2000;9(4):549-559. <https://doi.org/10.1093/hmg/9.4.549>
32. Hummelshoj T, Bodtger U, Datta P, Malling HJ, Oturai A, Poulsen LK, et al. Association between an interleukin-13 promoter polymorphism and atopy. *Eur J Immunogenet*. 2003; 30(5):355-359. <https://doi.org/10.1046/j.1365-2370.2003.00479.x>
33. Xiang F, Zeng Z, Wang L, Yang YP, Zhang QX. Polymorphisms and AR: A Systematic Review and Meta-Analyses. *Front Genet*. 2022;13:899923. <https://doi.org/10.3389/fgene.2022.899923>
34. Tang L, Chen Y, Xiang Q, Xiang J, Tang Y, Li J. The association between IL18, FOXP3 and IL13 genes polymorphisms and risk of allergic rhinitis: a meta-analysis. *Inflamm Res*. 2020;69(9):911-923. <https://doi.org/10.1007/s00011-020-01376-z>
35. Chen ML, Zhao H, Huang QP, Xie ZF. Single nucleotide polymorphisms of IL-13 and CD14 genes in allergic rhinitis: a meta-analysis. *Eur Arch Oto-Rhino-Laryngol*. 2018;275(6):1491-1500. <https://doi.org/10.1007/s00405-018-4973-3>
36. Bunyavanich S, Shargorodsky J, Celedón JC. A meta-analysis of Th2 pathway genetic variants and risk for allergic rhinitis. *Pediatr Allergy Immunol*. 2011;22(4):378-387. <https://doi.org/10.1111/j.1399-3038.2010.01128.x>
37. Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German children: The German Multicenter Atopy Study. *J Allergy Clin Immunol*. 2003;112(2):382-388. <https://doi.org/10.1067/mai.2003.67>
38. Graves PE, Kabesch M, Halonen M, Holberg CJ, Baldini M, Fritzsche C, et al. A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children. *J Allergy Clin Immunol*. 2000;105(3):506-513. <https://doi.org/10.1067/mai.2000.109318>
39. Wang M, Xing ZM, Lu C, Ma YX, Yu DL, Yan Z, et al. A common IL-13 Arg130Gln single nucleotide polymorphism among Chinese atopy patients with allergic rhinitis. *Hum Genet*. 2003;113(5):387-390. <https://doi.org/10.1007/s00439-003-0973-8>
40. Hoffjan S, Ostrovnaia I, Nicolae D, Newman DL, Nicolae R, Gangnon R, et al. Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. *J Allergy Clin Immunol*. 2004;113(3):511-518. <https://doi.org/10.1016/j.jaci.2003.11.069>
41. Hua KD, Chang JC, Chuang H, Liang HM, Kuo HC, Lee YS, et al. Gene-gene and gene-environment interactions on IgE production in prenatal stage. *Allergy*. 2010;65(6):731-739. <https://doi.org/10.1111/j.1398-9995.2009.02295.x>
42. Hua L, Liu Q, Li J, Zuo X, Chen Q, Li J, et al. Gene-gene and gene-environment interactions on cord blood total IgE in Chinese Han children. *Allergy Asthma Clin Immunol*. 2021;17(1):69. <https://doi.org/10.1186/s13223-021-00578-9>
43. Chen CH, Lee YL, Wu MH, Chen PJ, Wei TS, Chen PC, et al. Sex-moderated interactions between IL4/IL13 pathway genes and prenatal environment on cord blood IgE levels. *Clin Exp Allergy*. 2019;49(8):1128-1138. <https://doi.org/10.1111/cea.13404>
44. Hong X, Tsai HJ, Liu X, Arguelles L, Kumar R, Wang G, et al. Does genetic regulation of IgE begin in utero? Evidence from T(H)1/T(H)2 gene polymorphisms and cord blood total IgE. *J Allergy Clin Immunol*. 2010;126(5):1059-1067.e1. <https://doi.org/10.1016/j.jaci.2010.08.048>
45. rs20541 RefSNP Report. dbSNP. NCBI [Internet]. [cited 2025 Nov 3]. Available from: [https://www.ncbi.nlm.nih.gov/snp/rs20541#variant\\_details](https://www.ncbi.nlm.nih.gov/snp/rs20541#variant_details)
46. Cameron L, Webster RB, Stempel JM, Kiesler P, Kabesch M, Ramachandran H, et al. Th2 Cell-Selective Enhancement of Human IL13 Transcription by IL13 -1112C>T, a Polymorphism Associated with Allergic Inflammation. *J Immunol*. 2006;177(12):8633-8642. <https://doi.org/10.4049/jimmunol.177.12.8633>
47. Namjou B, Marsolo K, Carroll RJ, Denny JC, Ritchie MD, Verma SS, et al. Phenome-wide association study (PheWAS) in EMR-linked pediatric cohorts, genetically links PCLL1 to speech language development and IL5-IL13 to Eosinophilic Esophagitis. *Front Genet* [Internet]. 2014 Nov 18 [cited 2025 Sept 1];5. Available from: <http://journal.frontiersin.org/article/10.3389/fgene.2014.00401/abstract>
48. Savino F, Giuliani F, Giraudi S, Galliano I, Montanari P, Daprà V, et al. Analysis of Serum Th2 Cytokines in Infants with Non-IgE Mediated Food Allergy Compared to Healthy Infants. *Nutrients*. 2022;14(8):1565. <https://doi.org/10.3390/nu14081565>
49. Toro-Monjaraz EM, Fonseca-Camarillo G, Zárate-Mondragón F, Montijo-Barríos E, Cadena-León J, Avelar-Rodríguez D, et al. Differential Cytokine Expression in the Duodenum and Rectum of Children with Non-Immunoglobulin E-Mediated Cow's Milk Protein Allergy. *Dig Dis Sci*. 2021;66(11):3769-3775. <https://doi.org/10.1007/s10620-021-07074-0>
50. Granada M, Wilk JB, Tuzova M, Strachan DP, Weidinger S, Albrecht E, Gieger C, Heinrich J, Himes BE, Hunninghake GM, Celedón JC, Weiss ST, Cruikshank WW, Farrer LA, Center DM, O'Connor GT. A genome-wide association study of plasma

- total IgE concentrations in the Framingham Heart Study. *J Allergy Clin Immunol.* 2012;129(3):840-845.e21. <https://doi.org/10.1016/j.jaci.2011.09.029>
51. Lesiak A, Zakrzewski M, Przybyłowska K, Rogowski-Tylman M, Wozniacka A, Narbutt J. Atopic dermatitis patients carrying G allele in -1082 G/A IL-10 polymorphism are predisposed to higher serum concentration of IL-10. *Arch Med Sci.* 2014;6:1239-1243
  52. Lesiak A, Kuna P, Zakrzewski M, Van Geel M, Bladergroen RS, Przybyłowska K, et al. Combined occurrence of filaggrin mutations and IL-10 or IL-13 polymorphisms predisposes to atopic dermatitis: Filaggrin mutations and IL-10 or IL-13 polymorphisms. *Exp Dermatol.* 2011;20(6):491-495. <https://doi.org/10.1111/j.1600-0625.2011.01305.x>
  53. Arshad SH, Karmaus W, Kurukulaaratchy R, Sadeghnejad A, Huebner M, Ewart S. Polymorphisms in the interleukin 13 and GATA binding protein 3 genes and the development of eczema during childhood. *Br J Dermatol.* 2008;158(6):1315-1322. <https://doi.org/10.1111/j.1365-2133.2008.08789.x>
  54. Lee E, Kim JH, Lee SY, Kang MJ, Park YM, Park MJ, et al. Association of IL13 genetic polymorphisms with atopic dermatitis: Fine mapping and haplotype analysis. *Ann Allergy Asthma Immunol.* 2020;125(3):287-293. <https://doi.org/10.1016/j.anai.2020.04.023>.
  55. Narożna B, Hoffmann A, Sobkowiak P, Schoneich N, Bręborowicz A, Szczepankiewicz A. Polymorphisms in the interleukin 4, interleukin 4 receptor and interleukin 13 genes and allergic phenotype: A case control study. *Adv Med Sci.* 2016;61(1):40-45. <https://doi.org/10.1016/j.advms.2015.12.002>
  56. Imboden M, Nieters A, Bircher A, Brutsche M, Becker N, Wjst M, et al. Cytokine gene polymorphisms and atopic disease in two European cohorts (ECRHS-Basel and SAPALDIA). *Clin Mol Allergy.* 2006;4:9. <https://doi.org/10.1186/1476-7961-4-9>
  57. Ogbuanu IU, Karmaus WJ, Zhang H, Sabo-Attwood T, Ewart S, Roberts G, et al. Birth order modifies the effect of IL13 gene polymorphisms on serum IgE at age 10 and skin prick test at ages 4, 10 and 18: a prospective birth cohort study. *Allergy Asthma Clin Immunol.* 2010;6(1):6. <https://doi.org/10.1186/1710-1492-6-6>
  58. AH, Davies GA, Ewart S, Hopkin JM, Schauburger EM, Wills-Karp M, et al. Interactive effect of STAT6 and IL13 gene polymorphisms on eczema status: results from a longitudinal and a cross-sectional study. *BMC Med Genet.* 2013;14:67. <https://doi.org/10.1186/1471-2350-14-67>
  59. Lee SY, Yu J, Ahn KM, Kim KW, Shin YH, Lee K-shin, et al. Additive Effect between IL-13 Polymorphism and Cesarean Section Delivery/Prenatal Antibiotics Use on Atopic Dermatitis: A Birth Cohort Study (COCOA). *PLoS ONE.* 2014;9(5):e96603. <https://doi.org/10.1371/journal.pone.0096603>.
  60. Park MJ, Lee SY, Lee SH, Kang MJ, Song KB, Jung S, et al. Effect of early-life antibiotic exposure and IL-13 polymorphism on atopic dermatitis phenotype. *Pediatr Allergy Immunol.* 2021;32(7):1445-1454. <https://doi.org/10.1111/pai.13497>
  61. Cunico D, Gianni G, Scavone S, Buono EV, Caffarelli C. The Relationship Between Asthma and Food Allergies in Children. *Children.* 2024;11(11):1295. <https://doi.org/10.3390/children1111295>
  62. Li J, Lin LH, Wang J, Peng X, Dai HR, Xiao H, et al. Interleukin-4 and interleukin-13 pathway genetics affect disease susceptibility, serum immunoglobulin E levels, and gene expression in asthma. *Ann Allergy Asthma Immunol.* 2014;113(2):173-179. e1. <https://doi.org/10.1016/j.anai.2014.05.002>
  63. Black S, Teixeira AS, Loh AXW, Vinall L, Holloway JW, Hardy R, et al. Contribution of functional variation in the IL13 gene to allergy, hay fever and asthma in the NSHD longitudinal 1946 birth cohort. *Allergy.* 2009;64(8):1172-1178. <https://doi.org/10.1111/j.1398-9995.2009.01988.x>