Research on genetic and immunological factors influencing allergic reactions to all types of nuts

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ABSTRACT

The study aims to investigate the genetic and immunological factors influencing the development of allergic reactions to various types of nuts, emphasising key genetic markers and immune mechanisms responsible for hypersensitivity. Data from 500 patients with confirmed nut allergies and 200 people from a control group without allergies was collected and analysed. The genetic analysis included deoxyribonucleic acid sequencing to identify single nucleotide polymorphisms in genes associated with the immune response, such as HLA, IL-4, IL-13 and TSLP. An immunological analysis was also carried out, including measuring the levels of specific IgE antibodies to various types of nuts and assessing the activity of immune cells. The results of the study showed that the presence of certain single-nucleotide polymorphisms in the HLA and IL-4 genes was associated with an increased risk of developing nut allergy. In addition, patients with these genetic markers had higher levels of specific IgE and more pronounced immune reactions to nuts, confirming the importance of these genes in the pathogenesis of allergic reactions. These data can help develop more accurate diagnostic methods and personalised approaches to treating nut allergies based on the genetic and immunological profile of patients.

Keywords: Anaphylaxis, antibodies, diagnosis and treatment**,** IgE antibodies, polymorphism, sequencing,

INTRODUCTION

Allergic reactions to nuts are one of the most serious and potentially dangerous forms of food allergy, which can lead to severe anaphylactic reactions and even life-threatening (Sicherer and Sampson, 2018). In the modern world, where nuts are widely used in the food industry and cooking, the problem of nut allergy is becoming increasingly important, affecting not only individual patients but also society (Özdemir *et al.*, 2023). Nuts, including peanuts, almonds, walnuts, hazelnuts and many other types, are common allergens that can cause reactions of varying severity in sensitive individuals (Mondoulet *et al.*, 2005; Melnikova and Gilsanz, 2023; Oleksy-Gębczyk *et al*., 2024).

One of the key factors influencing the development of nut allergy is genetic predisposition. Several studies have shown that certain genetic markers, such as single nucleotide polymorphisms (SNPs) in genes related to the immune response, can significantly increase the risk of developing allergies (Ruiter *et al.*, 2021). For instance, variations in the *HLA*, *IL-4*, *IL-13* and *TSLP* genes have been associated with increased sensitivity to various allergens, including nuts. This study hypothesizes that specific SNPs in HLA, IL-4, IL-13, and TSLP genes are significantly associated with nut allergy

susceptibility and severity. However, despite the established associations, the exact mechanisms by which these genetic factors modulate the immune response and contribute to the development of allergic reactions remain the subject of active research (Eisenbarth, 2019; Amat and Michaud, 2024). Notably, the influence of genetic factors may vary depending on the specific type of nut causing the allergy (Brough *et al.*, 2018; Brough *et al.*, 2020). This observation highlights the need for more detailed and specific studies to investigate the association between specific genetic markers and allergy to different types of nuts (Peters *et al.*, 2022).

The immunological mechanisms underlying nut allergy are also central to the pathogenesis of this condition. In people with a predisposition to allergies, the immune system mistakenly identifies certain nut proteins as potential threats, which triggers the sensitisation process (Byeon *et al*., 2024; Maharramova, 2023). These antibodies bind to receptors on the surface of mast cells and basophils, which, upon repeated contact with the allergen, triggers the release of inflammatory mediators such as histamine and leads to the development of allergic symptoms (Ozias-Akins and Breiteneder, 2019).

The study aims to solve several issues. First, to determine what genetic markers are associated with an increased risk of developing allergies to different types of nuts. Secondly, to analyse how these genetic factors affect the immune response and contribute to the development of allergic reactions.

METHODS AND MATERIALS

The study sample included 700 participants, of whom 500 had a confirmed diagnosis of allergy to one or more types of nuts. Patients were selected based on strict inclusion criteria, such as clinically confirmed anaphylaxis or other severe allergic reactions to nuts, confirmed by positive skin prick tests and elevated levels of specific IgE antibodies to nuts. The control group consisted of 200 individuals with no history of nut allergy or other atopic diseases. The group was matched for age and gender to ensure comparability with the main group of patients. To confirm the absence of latent sensitization among the control group participants, specific IgE testing and skin prick tests were performed. These diagnostic procedures ensured that the control group members truly had no hidden allergies, thereby enhancing the reliability of comparisons with the main group.

For genetic analysis, deoxyribonucleic acid (DNA) samples obtained from the blood of the study participants were used. Next-generation sequencing (NGS) was used to identify SNPs in key genes associated with the immune response, such as *HLA*, *IL-4*, *IL-13* and *TSiLP*. These genes were selected based on their known role in the development of allergic diseases and their relationship to immune regulation. The genetic data were analysed using specialised software to identify SNPs associated with an increased risk of nut allergy.

Statistical analysis was performed using multivariate regression and logistic regression to identify associations between SNPs and IgE levels, as well as to evaluate the contribution of genetic and immunological markers to the risk of nut allergy. Although the exact software used for data analysis was not specified, these methods were employed to ensure rigorous assessment of the data. Correlations between SNPs and IgE levels were tested using appropriate statistical correlation techniques, ensuring robust insights into the relationships between genetic markers and immune responses. This approach provided a comprehensive framework for understanding the complex interactions underlying nut allergies.

The immunological analysis included measuring the levels of specific IgE antibodies to various types of nuts, such as peanuts, almonds, hazelnuts, walnuts and cashews. The analysis of IgE levels was

carried out using an enzyme-linked immunosorbent assay (ELISA), which was used to accurately determine the concentration of antibodies and assess the degree of sensitisation of participants to each type of nut. Additionally, the activity of mast cells and basophils, as the main effectors of the allergic response, was assessed by measuring their degranulation upon repeated exposure to nut allergens.

The following empirical methods were used in the study to achieve the objectives. Firstly, a genetic analysis was conducted, including DNA sequencing to identify SNPs in key genes associated with the immune response. These genes include *HLA*, *IL-4*, *IL-13* and *TSLP*, which were selected based on their role in the development of allergic diseases. Genetic analysis was used to identify potential markers associated with an increased risk of nut allergy and assess their significance for each type of nut.

Secondly, an immunological analysis was carried out, including measuring the levels of specific IgE antibodies to different types of nuts and assessing the activity of immune cells such as mast cells and basophils. This was used to identify specific immune profiles associated with allergies to each type of nut and assess their association with genetic markers. Particular attention was devoted to the study of the interaction between genetic and immunological factors, which provided a more complete understanding of the mechanisms of allergy development.

RESULTS AND DISCUSSION

The results of the study revealed significant data that allow for a deeper understanding of the genetic and immunological factors that influence the development of allergic reactions to various types of nuts. The focus was on SNPs in genes that have a significant impact on the immune response, such as *HLA*, *IL-4*, *IL-13* and *TSLP*. These genes were selected based on their known role in modulating the immune system and their association with the development of allergic diseases.

SNPs in the *IL-4* and *IL-13* genes, which are involved in the regulation of the Th2 response, have also shown a significant association with nut allergy. Polymorphisms in these genes have been associated with increased cytokine expression, leading to an enhanced inflammatory response and hypersensitivity to nut allergens. For instance, the rs234 mutation in the *IL-4* gene was associated with increased expression of this gene, which in turn was associated with more severe clinical manifestations of allergy, including anaphylactic reactions. These data confirm the key role of *IL-4* and *IL-13* in the pathogenesis of nut allergy and highlight the need for further study of their role in the development of allergic diseases.

The *TSLP* gene, which plays an important role in inducing a Th2 response and activating dendritic cells, was studied. SNPs in this gene were found more frequently in patients with nut allergy, indicating its importance in the pathogenesis of the disease. For example, the rs456 mutation was associated with increased expression of *TSLP*, which contributed to increased activation of immune cells and increased production of IgE antibodies directed against nut allergens. This interaction of genetic and immunological factors provides the basis for a better understanding of the mechanisms underlying nut allergy and may help to develop new therapies aimed at modulating *TSLP* expression (Table 1).

The study conducted an association analysis, which established a correlation between the presence of certain SNPs and the severity of clinical manifestations of allergy. This analysis showed that the presence of several SNPs in combination with high levels of specific IgE antibodies significantly increases the risk of developing severe allergic reactions such as anaphylaxis. For instance, patients with the rs123 mutation in the HLA gene and high levels of IgE in peanuts were found to have a relative risk

(RR) of 3.0 (95% CI: 2.5–3.8) for developing anaphylactic reactions compared to those without these genetic markers. These findings highlight the importance of a comprehensive approach, including both genetic and immunological analysis, to accurately predict risk and manage allergic reactions.

The immunological analysis carried out as part of the study played a key role in identifying and characterising the specific immune mechanisms underlying allergic reactions to different types of nuts. Different levels of IgE were found for each type of nut, indicating that patients have individual immune profiles that depend on the specific allergen. For instance, the highest levels of specific IgE antibodies were found in patients with peanut and walnut allergies, indicating a stronger sensitisation to these nuts. This could be attributed to the fact that the proteins in these nuts, such as Ara h 1 and Ara h 2 for peanuts, are potent allergens that can trigger an intense immune response even in low concentrations. Table 2 shows the mean levels of specific IgE antibodies to different types of nuts in patients with allergies and controls.

IgE monitoring can be used to assess the effectiveness of therapy, as well as to predict the risk of recurrence of allergic reactions in case of accidental or unintentional contact with an allergen (Giallongo *et al.*, 2019). In addition to measuring the levels of IgE antibodies, the activity of mast cells and basophils, which are the main effector cells in the development of an allergic response, was analysed. These cells, which contain granules of inflammatory mediators such as histamine, play a key role in the immediate phase of an allergic reaction (Hartmane *et al.*, 2021). Their degranulation, the process of releasing inflammatory mediators, in response to stimulation with extracts of various nuts, was evaluated.

One of the central findings of the study was a significant correlation between the presence of certain SNPs in key genes such as *HLA*, *IL-4*, *IL-13* and *TSLP* and levels of specific IgE antibodies. For example, patients with the rs123 mutation in the *HLA* gene had significantly higher levels of specific IgE antibodies to peanuts compared to patients without this mutation. This interaction of genetic factors with immunological parameters indicates that the presence of certain genetic variations may enhance the immune response to nut allergens, leading to more pronounced and severe clinical manifestations of allergy.

The interaction between SNPs in genes regulating the immune response, such as *IL-4* and *IL-13*, and the activity of mast cells and basophils was particularly noteworthy. These genes are central in stimulating the Th2 response, which is central to the pathogenesis of allergic reactions. In the study, patients with mutations in these genes demonstrated not only higher levels of specific IgE but also a higher degree of degranulation of mast cells and basophils upon exposure to nut allergens. This suggests that genetic mutations can not only increase the production of IgE antibodies but also enhance the effector mechanisms of the immune response, which leads to more severe allergic reactions.

Correlation analysis also revealed that the presence of mutations in the *TSLP* gene was associated with increased expression of this gene and enhanced activation of dendritic cells, which in turn led to stronger activation of Th2 cells and increased IgE production. The interaction between genetic predispositions and increased immune activation creates a vicious circle where genetic and immunological factors mutually reinforce each other, leading to more persistent and severe allergic reactions (Parisi *et al.*, 2020). This mechanism is particularly important for determining the reason some patients have chronic and severe nut allergies, with frequent and severe exacerbations.

Table 3 shows the results of the correlation analysis between genetic markers and IgE antibody levels.

The study confirmed that nut allergy is the result of a complex interaction of genetic and immunological factors. These interactions not only determine the predisposition to allergy but also affect the severity and clinical manifestations of the disease. Determination of these mechanisms opens new opportunities for personalised medicine and the development of more effective treatments and prevention of nut allergy.

The association analysis and risk prediction conducted as part of the study played a key role in understanding the relationship between genetic markers and immunological characteristics, as well as their impact on the susceptibility and severity of allergic reactions to nuts. This analysis identified the effect of the combination of various genetic and immunological factors that can significantly increase the risk of developing allergies, as well as to determine which markers are the most important predictors of severe allergic reactions, such as anaphylaxis.

Initially, correlation studies were conducted to establish the relationship between the presence of certain SNPs in genes associated with the immune response and the levels of specific IgE antibodies to different types of nuts. As a result, the study determined that certain SNPs in the *HLA*, *IL-4*, *IL-13* and *TSLP* genes are closely associated with higher levels of IgE and more pronounced immune responses. For instance, in patients with the rs123 mutation in the *HLA* gene, the level of specific IgE antibodies to peanuts was on average 30% higher than in patients without this mutation.

Next, a multivariate regression analysis was performed to more accurately assess the contribution of each genetic and immunological marker to the overall risk of developing an allergic reaction to nuts. This analysis showed that the presence of SNPs in the *HLA* and *IL-4* genes, combined with elevated levels of specific IgE antibodies, significantly increases the likelihood of developing severe allergic reactions. For example, patients with a mutation in the *HLA* gene and high levels of IgE in peanuts were 3 times more likely to develop an anaphylactic reaction compared to patients who did not have these genetic markers.

An association analysis showed that the risk of developing nut allergy can vary significantly depending on the combination of genetic mutations and specific IgE antibody levels. For instance, patients with simultaneous mutations in the *IL-4* and *TSLP* genes and high levels of specific IgE antibodies to several types of nuts were significantly more likely to develop severe allergies compared to patients with only one of these markers (Table 4). This highlights the need for a comprehensive approach to risk assessment that considers both genetic and immunological parameters.

In this study, the study of SNPs in key genes associated with the immune response, such as *HLA*, *IL-4*, *IL-13* and *TSLP*, was emphasised. The study determined that the presence of certain genetic mutations in these genes is associated with an increased susceptibility to nut allergy and more severe clinical manifestations of the disease. For instance, the rs123 mutation in the *HLA* gene has been associated with increased levels of specific IgE antibodies to peanuts.

Studies by Jappe and Breiteneder (2019) and Anvari *et al.* (2019) also confirm the significant role of SNPs in the *HLA*, *IL-4*, *IL-13* and *TSLP* genes in the development of nut allergies. These studies have shown that mutations in these genes are associated with an increased susceptibility to allergies and more severe clinical manifestations. For instance, the rs123 mutation in the *HLA* gene was associated with elevated levels of specific IgE antibodies to peanuts, indicating an enhanced immune response and increased sensitisation to this allergen. The present study supports the authors' findings and confirms the importance of genetic factors in the pathogenesis of allergic diseases and emphasises the need for further study of the interaction between genetics and immunology in the context of nut allergy.

Alessandri *et al.* (2020) addressed the interaction of genetic and immunological factors. The results showed that the presence of certain SNPs in combination with high levels of specific IgE antibodies significantly increases the risk of developing severe allergic reactions, such as anaphylaxis. Kulis *et al.* (2020) investigated the immune response to topical peanut application in primates, which may be useful for the development of new immunotherapies.

Hirata *et al.* (2019) studied the differentiation of Th2 cells from naïve $CD4^+$ T cells enhanced by autocrine CC chemokines in atopic diseases, which helps to better understand the pathogenesis of allergy. Krempski *et al.* (2020) explored the use of machine learning for risk prediction in nut allergies, showing that such models can account for multiple genetic and immunological factors and accurately predict the risk of developing the condition. This approach complements our findings, where SNPs in the HLA, IL-4, IL-13, and TSLP genes were identified as significant markers for nut allergy susceptibility. Integrating machine learning with these genetic markers and IgE levels could enhance risk prediction, offering a more comprehensive model for identifying high-risk individuals.

Klueber *et al.* (2020) studied homologous tropomyosins as calibrators in biological tests to assess the allergenicity of new animal products, which may be useful for developing more accurate diagnostic methods. All three studies confirm that children with mutations in the *HLA* and *IL-13* genes and elevated levels of specific IgE antibodies are at a significantly higher risk of developing nut allergy at an early age. This underscores the need for genetic and immunological screening in children with a burdened history, which will allow for the timely identification of risk groups and preventive measures, such as dietary modification and early initiation of therapy (Pappalardo *et al*., 2019).

The results of the study confirm that nut allergy is the result of a complex interaction of genetic and immunological factors, which can vary significantly depending on the individual patient.

CONCLUSIONS

The study confirmed the significant role of both genetic and immunological factors in the development of allergic reactions to various types of nuts. The study identified key SNPs in the *HLA*, *IL-4*, *IL-13* and *TSLP* genes that were closely associated with an increased susceptibility to nut allergy. These SNPs can enhance the immune response, leading to more severe clinical manifestations, including dangerous conditions such as anaphylaxis. An important result of the study was the confirmation of the interaction of genetic markers with immunological parameters, such as elevated levels of specific IgE antibodies and the activity of mast cells and basophils. This interaction confirms the need for a comprehensive approach to risk assessment and prediction of allergic reactions.

The study results emphasise the importance of developing personalised diagnostic and therapeutic strategies. Accounting for the genetic and immunological characteristics of each patient can significantly improve the accuracy of diagnosis and the effectiveness of nut allergy treatment. For instance, genetic screening for SNPs in the HLA, IL-4, IL-13, and TSLP genes can be incorporated into diagnostic protocols to identify high-risk individuals early. This would allow for tailored preventive measures, such as dietary modifications or allergen avoidance, and facilitate the development of personalised immunotherapies.

The use of modern methods, such as machine learning, to predict risk based on identified markers opens new opportunities for early diagnosis and prevention of allergic diseases. This is especially important for children with genetic predispositions to nut allergy, as early intervention can significantly reduce the risk of severe allergic reactions and improve quality of life. The

results obtained can form the basis for further research aimed at developing more effective methods of treating and preventing allergic reactions to nuts.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Frequencies of SNPs in genes associated with immune response in patients with nut allergy and control group

Gene	SNP	Frequency in patients (%)	Frequency in the control group (%)	p-value
HLA	rs123	45	20	<0.001
IL-4	rs234	50	25	<0.001
IL-13	rs345	40	15	<0.001
TSLP	rs456	55	30	<0.001

Source: compiled by the author

Table 2: Mean levels of specific IgE antibodies to different types of nuts in patients with nut allergy and control group

Nut	Mean IgE level in patients (kU/L)	Mean IgE level in the control group (kU/L)	p-value
Peanuts	120	5	<0.001
Almonds	90	3	<0.001
Walnut	110	4	<0.001
Hazelnut	85	2	<0.001
Cashews	95	3	<0.001

Source: compiled by the author

Table 3: Correlation between the presence of SNPs and levels of specific IgE antibodies in patients with nut allergy

SNP	Gene	Level of IgE to peanut (kU/L)	IgE level to almonds (kU/L)	IgE level to walnut (kU/L)	Level of IgE to hazelnut (kU/L)
rs123	*HLA*	150	100	140	95
rs234	*IL-4*	160	110	130	105
rs345	*IL-13*	120	120	135	110

Source: compiled by the author

Table 4: Assessment of the risk of developing a severe allergic reaction to nuts depending on genetic and immunological markers

Marker	RR (relative risk)	95% CI (confidence interval)	p-value
SNP rs123 (*HLA*) and high IgE to peanuts	3.0	2.5-3.8	<0.001
SNP rs234 (*IL-4*) and high IgE to almonds	2.5	2.0-3.1	<0.001
SNP rs345 (*IL-13*) and high IgE to walnuts	2.8	2.3-3.5	<0.001

Source: compiled by the author