

# Genetic Mechanisms and Heritable Risk Factors in Food Allergy Development

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## ABSTRACT

Food allergies are a growing public health issue both in the United States and worldwide. Immune responses to food allergies include the immune system producing antigen-specific IgE, which can lead to food sensitization. Reexposure of the allergen causes the allergen to bind to specific antibodies, causing the release of mediators, such as histamine. Histamine is what triggers reactions throughout the body. This is known as food allergic reactions. Essentially, when an allergen the body sees as an intruder or threat is consumed, the body produces IgE antibodies, which is specific for each allergen. These IgE antibodies bind to the allergen whenever consumed, causing the release of histamine, and therefore, an allergy reaction. Such reactivity can range from hives and rashes to anaphylactic means. A combination of genetic and environmental influences are known to affect food allergy development. It is difficult to separate genetic and environmental influences completely from one another to observe individually, as one's life is greatly influenced by both simultaneously. However, while the environmental effects are more obvious (early introductions versus late introductions, tolerance-building, food processing types, etc.), genetic influences are not as much. This review explores how specific genetic mutations can influence one's development of food allergies throughout their lifespan. Through the analysis of various candidate gene studies, it was found that such mutations, specifically polymorphisms, can have a critical role in food allergy development overtime, and in a population, can be considered heritable.

**Keywords:** Food allergy; IgE-binding; Gene; Mutation; Protein; Allergen

## INTRODUCTION

A food allergy can be defined as a condition in which the body mistakes the consumption of a specific food as a threat, causing an immune reaction (1), namely in the

release of histamine (2). This reaction can range from mild rashes and the development of hives on the skin, to anaphylactic, life-threatening responses (3).

The Dual Allergen Exposure Hypothesis states that low-dose skin exposure to food can possibly lead to sensitization and that early oral consumption of food might build tolerance (4). However, it is not a fool-proof method of ensuring allergy safety. The current recognized mechanism of food allergy development is known as the atopic march, which is the gradual progression of food allergies throughout the lifespan. The atopic march links together food allergies and eczema (atopic dermatitis) in

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childhood to an increased risk of other conditions (ex: asthma, hay fever) later in life (5). It also highlights the involvement of both skin barrier-related and immune-related genes.

There are a variety of challenges in current food allergy genetic studies (6). This includes the lack of environmental exposure data. Studies tend to leave out measuring in utero or early-life environmental exposures accurately. This can lead to failing to capture correct gene and environment interactions in the context of allergies together. This can reduce the ability to fully identify food allergy genetic determinants and causes. Additionally, small sample sizes pose a statistical problem in fairly evaluating these studies. Currently, the largest study focusing on food allergies and genetic connection includes around 11,000 samples, which, while substantial on its own, is much larger than most other studies on this topic. Meta-analysis study approaches, which involve drawing conclusions from various studies, prove a strong potential to improve experimentation and result accuracy, but study variability still poses a great challenge.

Definitions of food allergy outcomes differ widely, with different methods of data collection including health questionnaires, skin pricks, specific IgE biomarkers, double-blind placebo-controlled oral food challenges, etc. Additionally, in many experiments, control group definitions vary as well, with variables in atopic vs. nonatopic or unphenotyped population-based controls (6). Lastly, another large challenge in this type of specific study includes the distinction between a food allergy and a genetic food sensitization. The difference lies in the fact that food allergies trigger an immune response that can be life-threatening, while a food sensitivity causes typically milder digestive symptoms without involving the immune system. A difficulty arises in distinguishing genetic determinants of food allergies from food sensitivities (7). The heterogeneity in phenotype definitions also tends to add further complexity to meta-analyses.

Numerous genetic loci, a highly specific location on a chromosome where a gene or genetic marker is found, can be linked to food allergy development (8). Additionally, significant genetic overlap exists between food allergy loci and loci identified in genome-wide association studies for various related conditions, such as atopic dermatitis, asthma, hay fever. Overlapping between food allergies and atopic dermatitis genetic loci supports the atopic march mechanism for food allergy and related condition developments later in life (9).

Therefore, this review will mainly focus on candidate gene studies of food allergies. This is research found

specifically on how specific genes can be related to food allergy development and how it relates to the heritability of food allergies.

The Candidate Gene Association Studies on food allergies have focused on genes associated with asthma and atopic dermatitis.

## **REVIEW**

Notable Candidate Gene Association Studies-identified genes or loci include Filaggrin (FLG). FLG is located on chromosome 1q21.3 and plays a crucial role in the epithelial barrier function (10). The epithelial barrier lines the body both externally and internally, protecting it, particularly from allergy skin diseases like atopic dermatitis, asthma, and hay fever (11). FLG is also associated with food sensitivity and food-specific IgE increases. Food-specific IgE, when binded to allergens, is what causes reactivity. Mutated versions of this gene may lead to an impaired skin barrier. This triggers a pathway for food sensitivity and allergens through skin exposure.

## **SKIN BARRIER GENES**

Various studies have demonstrated the effects of such mutations on increased food allergy development across multiple ages. However, there is still some debate about whether FLG LOF mutations can directly lead to food allergy development or only food sensitivity. Nevertheless, FLG LOF mutations are found to affect multiple atopic conditions, with the strongest associations observed for atopic dermatitis, followed by food allergies and then asthma (12). FLG has also been confirmed to impact asthma development and possibly atopic dermatitis. Overall, FLG genes are among the strongest contenders and examples of genetic influence on food allergy development (12).

Multiple studies have shown that mutations in another gene, SPINK5, may give rise to food allergies. SPINK5 is another protein-coding gene whose main purpose is to provide programming instructions for the production of an inhibitor called LEKT1. LEKT1 helps control the breakdown and removal of cells in the outermost layer of the skin, known as the stratum corneum. LEKT1 is similar to FLG in dealing with skin barriers and how mutations in function can influence allergy development (13). When the skin barrier is damaged or partially dysfunctional due to a mutation in the SPINK5 gene, allergens and other irritants can penetrate directly into the skin, further leading to non-oral allergies (14). Defects in SPINK5 have

also been correlated with increased IgE levels, which can lead to heightened allergic reactivity (15).

### **ENZYMATIC DETOXIFICATION GENES**

Furthermore, NAT2 is another protein-encoding gene that codes for a specific enzyme critically involved in the detoxification of various drugs and carcinogens. Genetic variations in this gene can result in slow acetylator phenotypes (16). Acetylation is the enzymatic process of adding an acetyl group to a molecule, helping the body break down and eliminate potential toxins (17). Individuals with the slow acetylator phenotype have a reduced ability to metabolize certain substances, which may contribute to the development of food allergies. Researchers have found that individuals with the slow acetylation variant face nearly three times the risk of developing food allergies compared to those with normal metabolic rates. This finding reinforces the idea that acetylation genotypes can influence an individual's susceptibility to food allergies. Additionally, previous research has linked slow acetylation from NAT2 genetic variants to other allergic conditions, including asthma (18), elevated IgE levels, increased eosinophil counts in the blood and food allergies (19), further highlighting the association between acetylator speed and allergic risk. Overall, the study contributes to a growing body of evidence suggesting that the NAT2 slow acetylator phenotype may be an important genetic factor in allergic predisposition.

### **CYTOKINE AND IMMUNE REGULATION GENES**

While NAT2 highlights the role of metabolic enzymes in allergy development and risk, other genes prevalent in immune signaling also warrant attention. STAT6 is one such notable gene. It is widely regarded as critical in the assembly of IL-4 and IL-13 cytokines, which are protein messengers between cells, and their signaling pathways. Both cytokines play important roles in IgE class switching. This is when a B cell transitions from creating a non-IgE antibody to an IgE antibody (20). This process causes allergic reactivity. A specific study focused on how STAT6 is linked to tree nut allergies determined that it is correlated with both the development and severity of food allergies (21). Additionally, another group of researchers found that STAT6 was associated with higher IgE levels in the bloodstream, leading to greater reactivity and increased severity toward peanuts and cow milk (22). Overall, it can be concluded that the

STAT6 gene is associated with food allergy reactivity across various allergens, rather than a single specific type. Studies also suggest that the STAT6 gene can influence the severity of allergic reactions, not just the development of an allergy (21).

Expanding further, the gene IL-13 codes for the identically named protein and plays a significant role in immune regulation. In an Australian HealthNuts cohort study, IL-13 mutated variants were significantly associated with food allergies (23). They were notably less associated with food sensitization. IL-13 is strongly associated with increased IgE binding, highlighting its importance in allergic immune responses. IL-28B is another cytokine-encoding gene that may play a role in food allergy development. IL-28B codes for IFN- $\lambda$ 3, a cytokine protein that is known for its significant role in modulating immune reactions. A small study of Australian children found an association between IL-28B and increased IgE binding for food allergies (24). However, this finding has not been successfully replicated since, and the sample size of the initial study was relatively limited (24). This indicates that the evidence is insufficient and cannot, therefore, be deemed viable, although its role in food allergy development remains promising.

IL-10 is another cytokine that suppresses the production of IgE antibodies, which generally cause allergen-specific reactivity when bound to an allergen (25). A study on Brazilian children found that mutations in IL-10 led to an overall increase in food allergy development, specifically to cow milk, as the suppression of IgE antibody production decreased (26). Another study on a Japanese population found similar results, with IL-10 mutations leading to greater food allergies (27). In all, the associations between IL-10 mutations and the increased development of food allergies appear to be consistent across varying populations. These studies' findings suggest that polymorphisms, which are variations in DNA sequences common in a population, in IL-10 may contribute to the risk of developing food allergies.

### **INNATE IMMUNITY AND INFLAMMATORY PATHWAY GENES**

In addition to cytokine-related genes like IL-10, genes involved in innate immune recognition also play an important role. These include CD14, which encodes a specific receptor that binds to lipopolysaccharides (LPS). LPS stimulates antigen-presenting cells and promotes the release of proinflammatory cytokines, which are widely known for their role in asthma and the regulation

of responses in the immune system (28). While various studies have linked CD14 defects to possible allergic responses, discrepancies in findings still remain. In a study with a predominately white-based population, a previously asthma-linked genetic variation in CD14 was associated with food allergy development (29). However, no such association between allergy development and that specific mutation in CD14 was found in a Japanese population (30). This could be an example of how different populations and their environments can affect genetic associations with food allergy developmental outcomes.

Another case with a study population of mainly European descent found associations of CD14 variants with specifically peanut-specific IgE (29). Therefore, there may be underlying differences in environmental factors causing specific groups to have different reactivity when faced with genetic variations in CD14. Such variations likely still do have a substantial effect on food allergy development in certain populations.

Beyond CD14, other genes involved in inflammatory signaling may also contribute to food allergy development. The NLRP3 gene, which encodes the pyrin protein, plays a vital role in regulating caspase-1, an enzyme involved in protein cleavage with a significant role in inflammation (31). This inflammatory process is crucial for immune defense and has been associated with several autoinflammatory conditions (31). When it comes to food allergy development, a study conducted in Japan (32) explored how NLRP3 mutations might relate to food allergies, with a specific focus on anaphylactic responses. Although the study did not find a direct link between NLRP3 and food allergies, it revealed a positive correlation between food allergies and anaphylaxis, a reaction often seen triggered by severe food allergies.

On a similar note, C-Rel is another gene involved in immune regulation. C-Rel encodes a subunit of the NF- $\kappa$ B transcription factor, which contributes to inflammatory and immune-related pathways (33). This function is similar to that of NLRP3, as stated earlier. A separate study involving children with cow milk allergies identified a connection between single-nucleotide polymorphisms in the C-Rel gene and increased allergy susceptibility (34). These findings suggest that C-Rel may influence the risk of developing cow milk allergies. The roles of NLRP3 and C-Rel highlight how genetic factors shape food allergy risk and severity. While NLRP3 may heighten inflammatory responses that lead to anaphylaxis, C-Rel appears to play a more direct role in allergy susceptibility, particularly in cow milk allergy (34). Ultimately, both genes highlight the importance of inflammation-related genetic pathways

in determining allergic outcomes and clarify the immune system's role in food allergy development.

## OVERVIEW

Mutations in various genes can significantly affect immunological responses, specifically in the development of allergies. Mutations in cells are relatively common, as the copying and replication of one's DNA leaves a margin for error. Still, most of these mutations are fixed or do not cause an observable difference in the body (35). However, of the various mutations discussed earlier, many are considered polymorphisms. Polymorphisms are variations in the DNA sequence of a gene that can occur in at least 1% of a population, making them fairly common (36). However, for any mutation to be inherited by the next generation, it must be present in the germline DNA, or gamete cells, of one or both parents (37).

For the aforementioned mutations to be heritable in a population, they must be present in the reproductive cells of one of the parents. Given the prevalence of polymorphisms, these mutations may occur in gamete cells more frequently than other mutation types, which could contribute to a higher heritability level; however, further empirical evidence and specific research is required to confirm this. Therefore, genetics most likely play a significant factor in the heritability of food allergies through the transfer of inherited gene mutations. Understanding the role genetics can play in the development of food allergies can assist in the development of improved diagnostic mechanisms and further personalized treatment strategies. This can ultimately enhance both the treatment and prevention of food allergies for many individuals.

## CONFLICT OF INTEREST

There are no conflicts of interest regarding the publication of this article.

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