

# Transgenerational Development of Food Allergies and Allergic Rhinitis

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## ABSTRACT

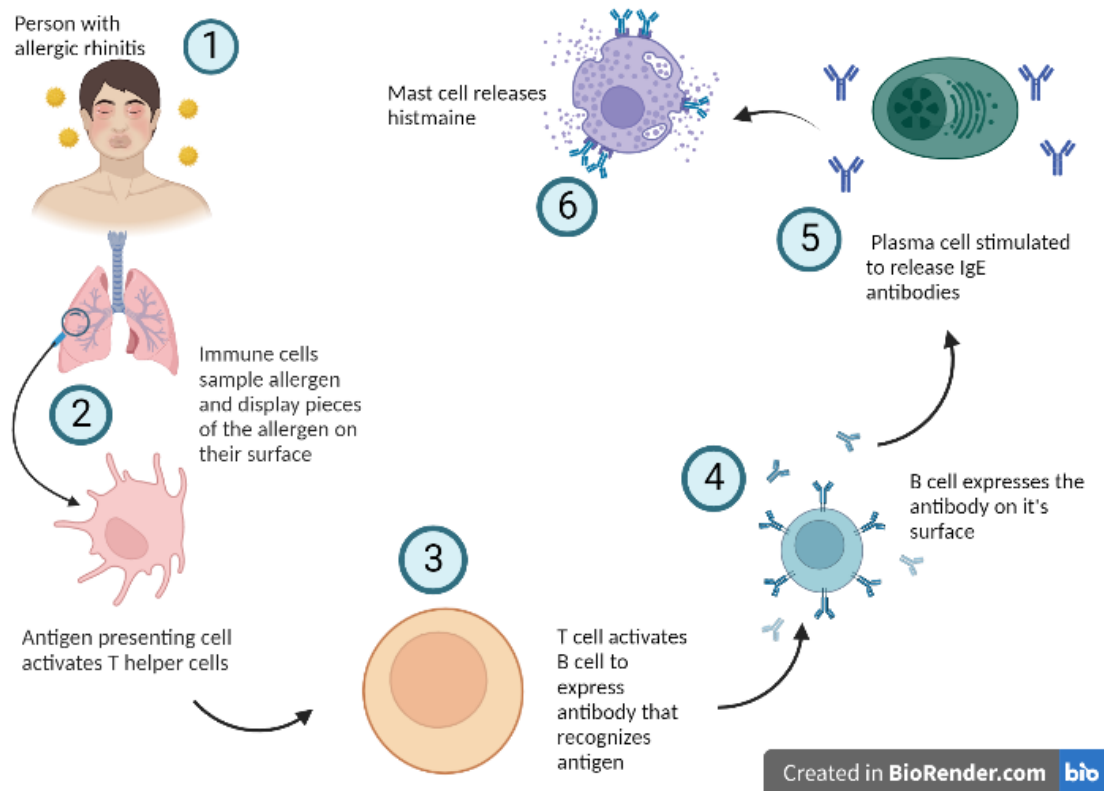
Both environmental and genetic factors play a role in allergies. Allergies are influenced by genes and how they control immune cell function. Several studies have examined the occurrence of allergic disease in children and its association with other risk factors, including allergic disease in parents. Specific toxins like CO<sub>2</sub> and other health conditions can be related to the diagnosis of allergic rhinitis. The response to food allergies was observed in many studies to conclude that heritability from parents to offspring is one of the leading risk factors for allergic diseases. Several studies have found a significant increase in the prevalence of allergic rhinitis in males than in females. Avoidance of a particular food was associated with an increased risk of developing an allergy to that food. At the molecular level, T cells are found to affect allergy outcomes through their part of the immune response. Food proteins such as milk, egg, and peanut - common food allergens - may cause an immune response in allergic individuals. Different therapies include Epicutaneous Immunotherapy (EPIT) and specific infant milk protein formulas. If this formula is taken from infancy, the allergic responses can be prevented/reduced. As with seasonal allergies, prevention can be mediated by avoiding different pollution environments that may cause additional irritation, temperature control in a given atmosphere/humidity, and therapies of Vitamin C for immunity. With many other seasonal allergy triggers, it is ubiquitous among populations and dependent on the area and season.

## **Introduction**

The immune system is a network of organs that defends an individual's body from outside invaders such as viruses and bacteria. The immune system also protects against exposure to foreign substances derived from environmental toxins and pollutants. The exaggerated reaction to a foreign substance by the immune system causes allergies. Some allergies are passed down genetically through generations, but most genetic causes are unknown. Children born into families with a history of allergies have a higher risk of developing an allergy themselves. Non-exposure to specific food proteins and foreign substances increases the likelihood of getting an allergy to them. The intensity of an allergic reaction is typically categorized into mild, moderate, and severe (anaphylactic shock). Smell/inhale and consumption of allergens trigger the immune system to identify a specific substance as a threat, sending a signal to stimulate the production of an Immunoglobulin E (IgE) antibody. IgEs are produced in response to the presence of allergens. Allergic rhinitis is a seasonal allergy, as "rhinitis" is when allergens in the air trigger histamine, which is then released into the body and creates an allergic reaction. Physical immune responses result in sneezing, itchy eyes, and a runny nose.

Allergic rhinitis can occur at any age and is considered one of the most common forms of chronic rhinitis. At the same time, food allergies are specific to a specific protein in the food that triggers the immune system. Food allergy is an immune system reaction triggered by consuming a food protein antigen (an antigen is any substance that makes an immune response against it). Immune system response is when activated. Its

response impacts the tolerance to allergens in T cells. Around 26 million U.S. adults and 5.6 million have food allergies (Allergy Facts). Many different types of atopic diseases indicate a higher risk of allergic diseases. Atopic diseases are allergic rhinitis, eczema, and asthma. Factors like environmental harm make an individual more susceptible to an allergy. A mild allergy occurs most commonly and naturally, as people who are not diagnosed try to avoid the allergic food or substance. The most common way of diagnosis is a skin prick test or bloodwork.



**Figure 1.** Process of Allergic Reaction

From the start of a person inhaling an allergen into their body, a foreign substance is then identified by the immune cells: the immune cells sample the allergen and display pieces on their surface. The antigen presented to the cell activates the T helper cells. The T cell activates the B cell to express an antibody that recognizes the antigen. That B cell expresses the antibody on its surface. The plasma cell stimulates the release of IgE antibodies, and the plasma cell is a type of immune cell that makes many antibodies. The mast cell is a type of white blood cell that releases histamine that works with nerves to create an allergic reaction in one's body. Example: itching, sneezing, hives.

## Sex-Based Heritability of Allergic Rhinitis

Allergic rhinitis (AR), also known as hay fever, is caused by certain substances in the air produced by the environment. Several studies have looked at the genetic heritability of AR in individuals from family histories, parents with allergies, and children. In Hungary, a study was conducted on children ages 6-12 years old randomly selected from primary schools to identify the prevalence of AR. Participants were asked to complete The International Study of Asthma and Allergies in Childhood questionnaire. The questionnaire tried to gauge a

pattern in individuals with AR in certain months. Results from the study highlight a seasonal way in months between July and September. Additional data support that individuals with AR associate it with sleep disturbance due to nasal symptoms. Likewise, in Taiwan's study, seasons correlated to AR in children and adolescents were 4.4% in autumn and winter. When looking at the sex of the child, there was a higher prevalence of AR in boys than in girls (39.7% vs. 35.8%). In fact, a pattern in sex in this study was identified, with boys having a significantly higher chance of developing AR symptoms than girls. With additional information, eczema diagnosis relates to an increased risk of AR (Sultész, 2020). Furthermore, analyzing atopic dermatitis (AD) with a correlation with AR. Of 66,446 patients diagnosed with atopic dermatitis, 49.8% had AR. A correlation to the Hungarian study with a relation between AR and eczema (Chang, 2010). With individuals who have AR, a study looked at autoimmune disorders in parents and the risk of allergic disease in their children. In one study, 10,575 households and 9,904 children were included in the analysis. There was a significant link between parental autoimmune disorders, and the risk of their children developing the allergic disease with the offspring of parents with allergies was 39.4% for seasonal allergies out of the sample. Additionally when the parents' allergies had the most significant impact on the likelihood of their oldest child developing the allergic disease. Males, in general, were shown to have increased chances of being diagnosed with allergic diseases that followed the pattern from the previous studies (Maas, 2014). A similar study analyzed the trends of parental allergy to the sex of the child. Maternal allergies did not affect the child in its prevalence of getting AR in any age range. However, paternal rhinitis is significant at all ages except 18. There was no specific gender relation to parental rhinitis, but from the father, the risk is higher for the child. This is interesting because of the pattern found with a prevalence of AR in boys. Children between the ages of 4-17 were more likely to have allergies if their father also had AR (Arshad, 2012). Data from additional studies consisted of the same pattern of related genetic risk, with almost every child who was said to have the allergic disease also having a family history of it. This study identified 16% with one allergic parent, 25% when both parents contain the allergy, and 28% with more than two in the family history. When examining the data on the mother and father's significance of passing down AR, a slightly higher risk of the mother's effect was shown. Despite the pattern in results, a study on the risk factors of AR in Peruvian populations showed that AR is more common in females than males (27.1%- 25.1%). This contradicts findings from the previous studies. One thousand four hundred forty-one children aged 13-15 years were diagnosed with AR based on a written questionnaire, spirometry (breathing test), exhaled nitric oxide, allergy skin testing, and blood samples. Offspring with AR are more likely to have a father with rhinitis. The potential risk factors of AR were determined and categorized into percentages. Of the 1441 offspring with AR, 25% had high exhaled nitric oxide, 22% had household aeroallergens, 22% had paternal rhinitis, 10% were obese, and 7% had elevated total serum IgE. (Baumann, 2014) This study had opposite results; however, with a similar parental history of AR, they were said to have three times the odds of having the disease than those born to parents without AR. Concluding a pattern of prevalence in boys has a higher risk of developing AR. A strong link between parenthood and offspring and a correlated chance of passing down AR.

While looking at households in its effect on individuals of toxins in the air. It was found that homes without cigarette smokers had a 36% chance of developing AR compared to families with smokers with a 27% chance of catching AR (Dold, 1992). When examining aeroallergens and toxins, a study on 1511 high school students in Iran was concluded. With individuals taking a questionnaire to determine results, it was found that 19.3% of high school students in the Iranian model were found to have AR. Dust was the most common cause of AR. There were no significant differences between the male and female sex with different prevalences. AR was determined to depend highly on smoking and opium drugs (Amizadeh, 2013). Furthermore, a similar study found findings with 306 participants who underwent multivariate analysis tests. The most common triggering factor was house dust. As well as statistics from the individuals' family history identified, participants with allergic parents were much more likely to have AR, supporting the Hungary study findings.

## Immune Response & Genetic Basis of Food Protein Allergies

Allergies can be caused by specific food proteins when the body's immune system mistakes food protein as an invader. T cells are part of the immune system, a type of white blood cell that focuses on specific foreign particles. Since T cells work with the immune system to react and attack the foreign substance, it is vital to processing the immune response to food proteins. Epigenetics is the study of how cells control gene activity in the DNA sequence with having a role in the immune system of regulating immune system-related genes—a study examining allergy-mediated epigenetic changes to the immune system evaluated infants whose food allergies persisted throughout childhood. The study took blood from infants with allergies and measured the T cell activation at 1, 2, and 4 years. It was found that T cell activation-induced changes in the epigenetic and transcriptional landscape were related to a food allergy. The transcriptional landscape refers to an area with an identified pattern of control signals and types of different transcripts produced. T cell activity in food-allergic children portrayed attenuated proliferative response capacity. Attenuated proliferative response capacity is to hold back the immune system against the increase of the production of more T cells. It was found that food allergy was associated with the loss of 89% of methylation (chemical reaction produced by the body) 11% in samples. Therefore, a cumulative epigenetic disturbance was associated with a poor T cell rapid increase compared to children who resolved an egg allergy (Martino, 2018).

Similarly, an additional study chose 19 children with peanut allergies (randomly chosen) to examine the genetic cause of allergies. Subjects underwent a skin pricking test, to which all responded within the first two hours to confirm their allergy. The most common peanut allergy symptom was distress, followed by throat tightness. Using linear mixed-effects models (statistical model) to measure the interactions of peanut exposure on gene expression in relation to time. Observed were three significant differences in cell types. False Discovery Rate (FDR) was used to test multiple hypotheses for comparison in this study of placebo and peanut. The authors then examined three significant gene expression pattern changes in CD4+ T cells, macrophages, and neutrophils pre and post-peanut exposure. Macrophages (FDR=0.016), neutrophils (FDR=0.016), and naive CD4+ T cells (FDR=0.018). Macrophages and neutrophils continuously increased over time during the study, but not in the placebo. A reduction in naive CD4+ T cells was found between four hours (Watson,2017). Likewise, a study observed CD4+T cells in allergic food groups. This study consisted of children who developed food allergies primarily to hen's egg, cow's milk, or peanut. After an hour or two, food allergy was defined only by immediate reaction symptoms. Analysis of the pathway of methylated genes identified several signaling molecules. It was concluded that CD4+ T-cell populations were associated with food allergies with a role in epigenetic disruption in allergic diseases. (Martino,2014) Similarly, a study examined the differences in T-cell gene expression in samples collected at birth and one year of age in children. A low-level soluble (anti-CD3 stimulus) activated the T-cell receptor. The authors concluded that through the pathway of T-cell activation, signals through a complex could affect T-cell phenotypes (Martino, 2011). This study examined why peanut allergy in children has grown increasingly. Ninety-eight participants had positive test results for peanut allergy—35.3% of the sample which tested positively avoided peanuts, while 10.6% consumed peanuts. Early introduction of peanuts significantly decreased the possible development of peanut allergy in children and mediated individuals' immune systems to peanuts. (Du Toit, 2015) A lack of immune response to ingested antigens characterizes oral tolerance—phenotypes (observable characteristics)for oral tolerance to ovalbumin, a protein found in egg white. A study found through studying mice tolerance that they have twenty times less IgE level and diminished mast cell numbers compared to mice with oral tolerance. There also was a high susceptibility to allergic inflammation and anaphylactic shock. An individual's IgE levels can be reflected by having an egg white allergy (da Silva, 2006).

Lastly, an additional study found a relationship between polymorphism and atopic food allergies. Polymorphisms in 9 genes have been associated with the development of food allergies and their severity (Hong, 2009). Furthermore, it was shown that interaction between different polymorphisms in helper T cells (Th2)

influences the genetic control of serum IgE levels and the development of atopic diseases. Th2 play a role in the activation/recruitment of IgE antibodies (Kabesch,2006). T cells, CD4+ T cells, macrophages, neutrophils, and polymorphisms are common trends found in cells of food protein allergy; there is a strong correlation.

## **Prevention (Environment Impact/Therapeutic Solutions)**

Prevention of allergies may involve therapy or environmental changes. Multiple studies have shown that certain living conditions can increase the risk of allergies. One study compared allergy rates in 4,545 elementary students across three different categories: one school had no evidence of pollutants, three with traffic-related pollutants, and three with traffic-related and other industrial contaminants. This study found a link between AR and sulfur dioxide in vastly polluted areas. (Kim, 2013) Sulfur dioxide is a gas that comes from burning fossil fuels, especially traffic-related pollutants. A similar study in Korea discussed how the long-term effects of environmental factors affect individuals. The International Study of Asthma and Allergies in Childhood distributed a survey to determine the prevalence of allergic diseases and ecological risk factors. It concluded that indoor pollution is linked to AR and atopic dermatitis. (Lee, 2020) Exposure to indoor chemicals is also linked to allergic conjunctivitis. While AR is associated with nose issues, allergic conjunctivitis is an issue of allergic reactions involving the eyes and the nose. A separate study examined the association between AR in children and air pollution. During the investigation, skin prick tests of 24 specific antigens were done to test on the children. It also measured the concentrations of sulfur dioxide (SO<sub>2</sub>), nitrogen dioxide (NO<sub>2</sub>), ozone (O<sub>3</sub>), and carbon monoxide (CO) in the atmosphere. The study found a high risk of AR from living in a particular house built in the past year because of the toxins. Higher concentrations of SO<sub>2</sub> were also related to the prevalence of AR. Based on these studies, it is clear that air pollution can contribute to the majority of allergic diseases.

However, many significant risk factors come from genetics and family history. A study on additional therapies for AR focused on a treatment involving intravenous vitamin C. A connection was found to ADPH oxidase proteins through pollen in allergic airway inflammation. Overall, a 93.8% improvement was observed in all patients who took vitamin C. (Vollbracht, 2018). Another therapy resulting in improvement is the EPIT treatment (Epicutaneous Immunotherapy) used for peanut allergies. This double-blind study included 75 participants in the treatment group, and 25 were in the placebo group. The authors found that children under 11 significantly responded to treatment. Doses of VP100 and VP250 (Viaskin Peanut dosage) resulted in 79.8% mild reactions and increased IgG4 levels in peanut-treated patients. It determined the effectiveness of EPIT therapy for the improvement of allergies. (Jones, 2017) A similar study on the prevention of allergy to milk looked at infants at risk for getting allergies from family history and the prevention of this. Infants were randomly assigned to receive a particular cow milk formula to understand if this would be beneficial to preventing allergies in infants. This study concluded that early feeding of a protein hydrolysate formula to young children/infants has long-term prevention of eczema and specific allergic diseases other than asthma. (Mallet, 1992) Comparably, newborns in Japan that ingested at least 10 mL of cow milk formula daily prevented cow milk allergy development compared to the control group. (Sakihara, 2020) A study was conducted on the oral immunity of cow milk to individuals who have an allergy to it. Through immunotherapy for two weeks, followed by an increase of cow's milk to 100 mL for a year, then up to a year. Both groups underwent an OFC (Oral food challenge test) with 100 mL of cow's milk at one year. It was found that the treatment group had higher rates of negative OFC. It was then determined that the effect of immunotherapy was 50% (Maeda, 2021). This study analyzed the trends in families of multiple children. If one child has a peanut allergy, it is more likely for the rest of the family and the other sibling to be unexposed to peanuts. This resulted in a lack of immunity to the peanut protein in individuals' bodies. The data estimated that more than 10% who live with someone with a peanut allergy would avoid peanuts. A recommended therapeutic solution would be for siblings and nonallergic ones to consume protein to prevent a lack of immunity (Lavine, 2014). Likewise, a study examining infants found that exposure to allergenic foods from 3 months to 36 months is beneficial. The intervention groups had

a lower food allergy prevalence than the no-food intervention group. Supporting the early introduction of common allergenic foods is a therapeutic strategy to prevent food allergies (Skjerven, 2022).

## Conclusion

Overall, AR was more common in males than females. Parents with AR are also more likely to pass it to their offspring, as family history is a vital link. This showed an essential link between parental rhinitis AR and children. Exposure to many toxins can result in the development of AR or further progression of the intensity of this allergic disease. While looking at the genetic basis of food proteins and their effect on the body, it was found that a common theme of T cells and CD4+ T cells has changed. An early introduction of peanuts also significantly decreased the possible development of peanut allergy in children and mediated individuals' immune systems to the allergic protein. Polymorphism has a role in the genetic sequence that influences the Ige levels and T helper cells when trying to create an antibody. More study on the genetic basis of cells and their reaction to allergies can lead to further explanation around the field and better understanding. With environmental impact and therapeutic solution, it was found that pollution does have a substantial cause in getting AR. Chemicals like sulfur dioxide and indoor chemicals cause increased chances of AR. The presence of sulfur dioxide in the vicinity of an air-polluting factory increases the risk of AR. Therapeutic ways involve EPIT treatments, early introduction to allergic foods, ingestion of cow milk formula, intravenous vitamin C, protein hydrolysate formula, and food protein exposure. Most significant is the therapeutic way of milk formulas for hen's milk allergy prevention for younger individuals. An increase in direction since childhood in moderate levels tends to help any food protein allergy. With preventions considered, it can make individuals reasonable their allergies to foods before further adulthood to avoid severe allergies and lack of protein foods. There are many unanswered questions about allergies, such as why the body mistakes a threat, even though it is a very complex system. However, specific interventions, such as many available therapies by age group, to reduce the risk of getting an allergy by early exposure and observing patterns in cells and genes can further expand knowledge on this subject.

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