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Genetic Mechanism of Food Allergies

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ABSTRACT

Food allergy (FA) is the culmination of different genetic and environmental factors. It is an increasingly concerning health problem affecting millions of people around the globe. Currently, there is research being done on the impact that genetics have on a person's likelihood of having a food allergy, as well as how genetics research can further help the prevention and treatment of food allergies. This paper aims to review current genetic studies, such as familial aggregation studies and candidate gene association studies, both of which provide evidence that certain genes make it more likely for people to have FA. Some genes including the HLA gene family linked to peanut and apple allergies, the CD14 gene linked to multiple FA studies, and SPINK5, a protease inhibitor protein, all make a person with any of these genes more likely to have FA. This paper also focuses on examining future treatments, specifically immunotherapy treatments like the OIT, and future diagnostic tests for FA, such as the BAT and CRD, all of which are now being tested in labs. The field of FA genetics is a new and promising area of study and has the potential to impact many lives in the future.

Introduction

Food allergy, commonly referred to as FA, is a growing health concern in the United States as well as around the world, affecting 32 million Americans, with around 6 million of those being children. It is an immunoglobulin-E-mediated hypersensitivity reaction to certain foods and is the most common cause of anaphylaxis (life-threatening allergic reaction) in children. If a person with FA consumes or comes in contact with the allergen, symptoms such as hives, hoarse throat, vomiting, anaphylaxis, dizziness, weak pulse, and shortness of breath will appear. A general consensus amongst scientists is that a food allergy is an effect of both environmental causes and a person's genetics. Concerningly, the Centers for Disease Control revealed that FA cases increased by 50% and peanut allergies in children tripled from 1997 to 2021. This is an incredibly alarming rate, especially when compared to other atopic conditions. Despite this, our understanding of the biological mechanisms of FA still lacks much-needed information. There are many reasons why more and more scientists are starting to study the genetics of food allergies. Some are investigating this topic to understand the current population distribution of FA and why there has been such a rise in affected individuals over the past few decades. Some are researching which genes are linked to a higher chance of developing FA with the goal of implementing preventative measures for those individuals. Another common reason is identifying genes that will help make treatments safer and more effective. So, the increasing prevalence of food allergies poses a significant health concern worldwide, necessitating a comprehensive understanding of the genetic and environmental factors influencing their development. This paper aims to elucidate the intricate relationship between genetics and FA, with a focus on key genetic studies and their implications for prevention and treatment strategies.

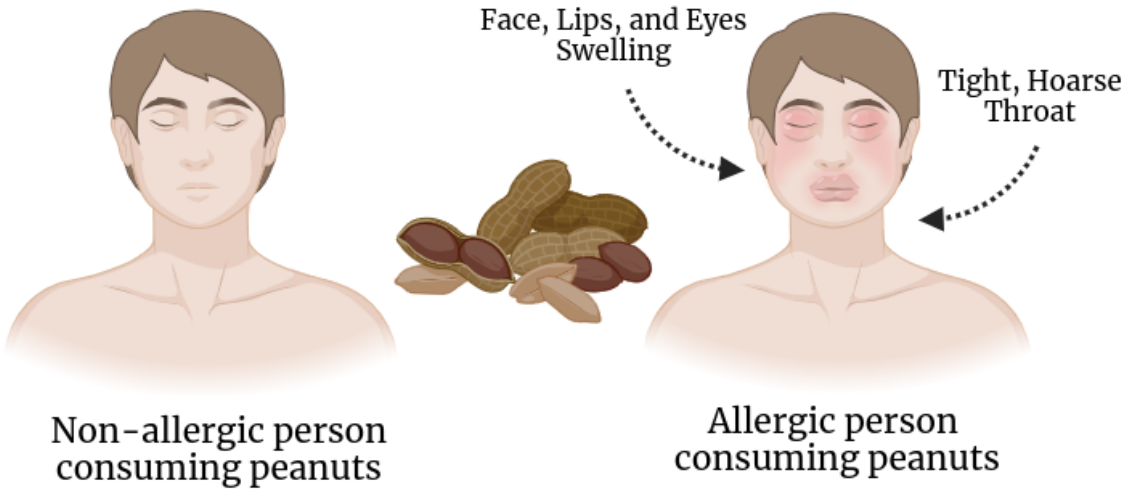

Figure 1. Visual representation of some allergic reactions that can be seen in affected individuals, Created and Copyrighted by Simran Goel using BioRender.

Diagnostic Tests for Food Allergies

Currently, various methods are being used to diagnose FA, though most cannot fully report whether or not a person has the condition. When IgE-mediated food allergy is suspected, there are two things that doctors recommend to determine the causative food. One common way is by measuring the total amount, as well as allergen-specific amounts, of serum IgE (sIgE) levels. Increased levels may suggest that one has a food allergy; sIgE thresholds with 95% positive predictive value have been linked to certain allergens. For example, in patients allergic to peanuts, the threshold sIgE level for peanut antigen is $14kU_A/L$ (U_A is an allergen-specific unit).

Another method employed for FA diagnosis involves skin prick tests (SPTs). In this procedure, a patient's skin is exposed to suspected allergy-causing substances and doctors then observe for signs indicating an allergic reaction. SPTs will cause allergen-mediated mast cell degranulation in a person's skin, which will lead to a wheal-and-flare response. Depending on the wheal size thresholds, the probability of FA is shown. Thresholds have been defined for some common allergies such as peanuts. If its SPT results in a wheal greater than or equal to 8 mm, then there is a 95% positive predictive value.

However, SPT and serum IgE levels only indicate that a person is sensitive to a certain allergen and can sometimes provide inaccurate results. The only definitive diagnostic test is the oral food challenge or OFC. In this test, patients ingest doses of certain allergens over fixed intervals until either the maximum dose is reached or an allergic reaction occurs. However, this is not commonly used because of the high risks to the patient and the amount of resources required for the test. So, most clinics stick to SPTs and testing sIgE levels until other options are made available. Towards this end, some diagnostic tests that are currently in development include component resolved diagnosis (CRD) and the basophil activation test (BAT). The CRD uses purified allergens to identify IgE and IgG4 allergen-specific antibodies that can separate various allergenic, non-allergenic, and cross-reactive molecules in standardized amounts. BATs use allergen proteins as stimulants, which increase the number of surface-level proteins such as CD63 and CD203c. Primarily, the BAT is used in research studies, though it produces highly accurate diagnoses of peanut and other food allergies. Hopefully, with further standardization and trials, these tests will become more accepted in clinical settings and will help doctors determine FA swiftly.

Heritability of Food Allergies

Familial aggregation, twin studies, and heritability estimates all indicate that there is a genetic link to food allergies. Family studies can discover whether a disease aggregates in families. This type of study typically compares the prevalence of the disease among relatives of people affected to the prevalence of the disease among unaffected controls or the general population. A higher risk among relatives of the subjects may indicate to scientists that the disease is familial, but it is not a sure sign that genetics are the cause. However, some family-based studies have produced relevant results. The most extensive familial aggregation study included 5,276 infants and was performed in the HealthNuts study cohort in Australia. They used oral food challenges to egg, peanut, or sesame allergies to determine FA. They reported that the risk of FA in children increased with larger numbers of atopic family members. It was also determined that if there was a maternal history of eczema and asthma, or a sibling had a history of AR, they could predict egg allergies in infants. A different cohort study has shown that a child with a parent or sibling who has a peanut allergy is at 7 times higher risk of having the condition in comparison to children with no family history of allergies. Additionally, birth order between siblings affects risk, with the youngest children having the most likelihood of having the allergy. The more siblings with FA one has, the more likely they are to also have the condition. Family-based studies prove that a person will be more likely to have a food allergy if a member or members of their family have the disease or other genetic indicators.

A more specific sub-branch of family studies is twin-based studies. These studies commonly compare the concordance rates of disease between fraternal/dizygotic (DZ) twins and identical/monozygotic (MZ) twins. In one such case, the concordance rate is 82% between MZ twins and 20% between DZ twins with peanut allergies. As twins typically have the same environmental influences, the higher concordance rate in MZ twins must reflect the impact of genes. Another study in a Chinese population included 826 pairs of twins and investigated food sensitization to 9 foods: milk, egg, wheat, peanut, soybean, sesame, walnut, shellfish, and fish. It confirmed that there was a higher concordance rate in sensitization for any of these foods in MZ versus DZ twins, with the rate being 52.1% compared to 39.2%. This all makes sense as MZ twins share 100% of their DNA whilst DZ twins only share 50% of their DNA. It goes to show that it is almost certain that MZ twins are more likely to have FA compared to DZ twins.

However, all these studies depict a wide variety of heritability estimates ranging from 39% to 81%. This is a wide range and while this may seem contradictory at first, it is not unexpected. FA is a condition strongly impacted by the environment of the person who has it. The different environmental conditions in various studies' samples can completely change the heritability estimate. For example, take a case in which one child is exposed versus where no child is exposed. Even if the subjects had the same genetics, the results would be completely different because of the drastically different exposure rates. Therefore, this collection of studies supports the idea that genetics and their interaction with the environment play a significant role in the likelihood of having a food allergy.

Candidate Gene Association Studies in Food Allergies

Candidate gene association studies for FA have mainly focused on figuring out the genetic determinants of food allergies. Most genes scientists have connected with FA are involved in immune responses or skin/epithelial barrier function. Among the most studied genes are filaggrin and genes in the human leukocyte antigen complex. A brief description of each gene that is mentioned in one or more studies will be given to summarize what developments have been made.

HLA Gene Family

The HLA gene family has many associations to FA. HLA class II DR beta, DQ beta 1, and DP beta 1 are all gene polymorphisms that have been linked to patients with peanut allergies. Additionally, the HLA-DRB1*07 allele has been associated with apple allergy. Scientists have also observed that the frequency of HLA-Beta*07 and HLA-DRB1*11 was increased in the nut-allergic patients compared to the control patients, with the rate being 12.2% compared to 3.66%.

CDI4 Gene

The CD14 gene plays a crucial role in the human body as a part of the protein complex in the immune system. Several studies have looked into CD14 as a candidate gene for FA. In a study containing 175 asthmatic and 77 food-allergic subjects, the C-159T polymorphism in the CD14 gene was found to be linked to FA subjects. Both patients with FA and those with nonatopic asthma had an increased number of T alleles relative to control subjects, with FA patients having 1.7 times the amount and nonatopic asthmatic patients having 2 times the amount. In another study, it was shown that though the CD14 gene could be linked to some patients, the CD14-159 and -550 polymorphisms have no association with Japanese children who have FA.

Filaggrin

Filaggrin (FLG) plays a crucial role in epithelial barrier function in skin disease and has been well-associated with many allergic disorders. The filaggrin gene maintains skin barrier integrity, and if this barrier is disrupted in early life, a person will be more likely to have food sensitivity, most commonly to peanuts. The HealthNuts cohort confirmed that FLG has a substantial impact on FA (OR=2.9, 95%CI=1.0-8.6) and FS (OR=3.0, 95%CI=1.0-8.7).

STAT6

Several studies have connected the STAT6 gene with food allergies. In one such study containing subjects of European ancestry, the genotype was shown to be linked with general nut allergies, and this claim was proved later on by many other studies. In a family study done with 369 trios, 262 of which had FA, the STAT6 SNPs rs324015 and rs1059513 were found to be associated with challenge-proven FA and peanut allergies. These SNPs were also linked to more severe symptoms of food allergy. But the evidence for the STAT6 gene goes beyond just nut allergies. A study focusing on Dutch children with FA figured out that STAT6 is connected to peanuts as well as cow milk allergies, and it causes more severe allergic reactions for those two foods. All of these studies demonstrate that STAT6 is not only a factor in causing FA, but it also impacts the severity of allergic reactions.

SPINK5

Serine protease inhibitor Karzal type 5 (SPINK 5) is a protease inhibitor protein. It causes defects in the thymus, which leads to the T lymphocytes maturing abnormally fast, resulting in IgE levels increasing. A recent report done by HealthNuts study found associations between a polymorphism in IL-13 (rs1295686) and SPINK5 genetic variants with challenge-proven FA in infants. Another study, done on Japanese children, showed that subjects with the SPINK5 1258AA or 1258GG genotype are more susceptible to having food allergies.

IL10 and IL13

Interleukin-10 (IL10) is an anti-inflammatory cytokine that is known for repressing allergen-specific IgE production. The association between FA and polymorphisms of IL10 was investigated in a study done on a group of Brazilian children. It was shown that among the 5 polymorphisms studied, homozygous for the G allele was notably higher in subjects compared to the controls. It was particularly noticeable in the patients allergic to cow milk. Interleukin-13 is an immunoregulatory cytokine that is well-connected to atopic diseases like asthma. But, the C-1055T polymorphism of the gene has also been linked to food sensitivity. As shown above, scientists have made many developments in figuring out what genes in the human body are causing FA.

Contributions from the Environment in FA

Over the last half-century, there has been a significant rise in FA cases around the globe. This is more likely due to environmental causes and not genetic causes, as the environment around people greatly influences their chances of having a food allergy. Such environmental causes include dietary habits, amount of vitamin D, pollution, and hygiene-related factors such as pets. Ecological factors can even modify the risk of FA in a person genetically likely to have the disease. It is believed that Gene-Environment (GE) Interactions are crucial to understanding the risk of FA. One such example is the case of shellfish allergies. House dust mite exposure contributes to the difference in the prevalence of shellfish allergies. Primary sensitization to dust mite allergens causes allergic reactions to shellfish through cross-reactive tropomyosin allergens. The Manchester Asthma and Allergy Study looked into the effects of early exposure to peanut protein in household dust and whether or not this would impact peanut allergy development in children. An increase in exposure to infants raises the chances of peanut allergy by 3.3 fold and peanut sensitivity by 6 fold. Another study found that the GSTP1Ile105Val polymorphism modifies the effect that air pollution has on allergic sensitization to inhalant and food allergens. One more environmental influence on FA is parental nativity. A study showed that children who immigrated to the US in early childhood rather than being born in the US had a greater risk of sensitization to milk, eggs, and peanuts. Another environmental factor that impacts the risk of FA is vitamin D insufficiency. A study was done with over 5000 infants and it was shown that those without enough vitamin D were 3 times more likely to have egg and/or peanut allergies. Additionally, young children with a lack of vitamin D insufficiency have a greater chance of having 2 or more allergies rather than just a single allergy. A person's surrounding environment as well as their genetics play a prominent role in the way that food allergies impact them. The two causes go hand in hand to form parts of the complex disease.

Prevention and Treatments

Each day, more research is being done into FA, with much of it focusing on reducing risk factors and making life easier for those with the disease. Prevention for FA aims to avoid developing allergies, while treatment focuses on managing existing allergies. For example, whereas in the past, avoidance of common allergens during pregnancy was recommended, things are now changing as scientists discover more about the mechanisms of FA. Many recent studies now suggest that exposing a child to potential allergies early on will make them less likely to develop the allergy in the future. A landmark study indicates that if 4 to 11-month-old babies eat peanuts, they will be at a decreased risk of developing the allergy. Another trial conducted by the Enquiring About Tolerance study group, containing more than 1300 infants, found that introducing 6 common allergens to breastfeeding babies can be accomplished without interfering with breastfeeding. The study also revealed that this practice will reduce risks of FA and FS. Another similar idea explored by studies is that mothers consuming common food allergens during their pregnancy may decrease the risk of that allergy in infants. These studies indicate that introducing food allergens early on is a promising prevention tactic. However, many questions still remain such as the size and frequency of the doses and the effect of different allergens. Although a

definitive process hasn't yet been determined, current guidelines recommend that mothers maintain a regular diet during pregnancy and begin introducing allergens once their children are 4 to 6 months of age.

Currently, there is no real treatment for FA that will cure those affected by the disease. Most with FA just avoid the allergen(s) and any allergic reactions are treated with adrenaline. Adrenaline can reverse the effects of many symptoms such as edema, urticaria, bronchospasm, hypotension, and gastrointestinal symptoms. Although, it will be much more effective as long as it is treated within 6 minutes after exposure. Early response is crucial in preventing death by anaphylaxis. Pharmaceuticals, such as antihistamines, or more specifically, H1 receptor blockers like cetirizine, are also used to treat localized symptoms caused by FA. However, all pharmaceuticals that are currently available only deal with the symptoms of FA and aren't able to deal with the underlying cause. As a result, scientists are currently looking into immunotherapy as a different option to treat FA. New immunotherapies are being developed that aim to mimic the way desensitization to food protein antigens naturally happens in the human body. Desensitizing immunotherapy is typically delivered to the patient orally or through the skin. One such therapy is called OIT, an encouraging new proposal that allowed most of the children it was tested on to be desensitized to considerable amounts of whatever food they are allergic to. In OIT, the patient ingests a small amount of the allergen daily, and over time, the dose will slowly increase in size. As a result of the larger doses used in this therapy, patients are often desensitized to enough of the allergen that they no longer have to be concerned about life-threatening reactions. Sometimes patients are even able to consume small amounts of the allergen without any harm coming to them. The OIT was tested with patients who had an egg allergy and the results were promising with 75% of patients being desensitized to eggs and 28% sustained unresponsiveness. Though most are still just under clinical trials, immunotherapy seems like it has the potential to help many people who are affected by food allergies.

Conclusion

Food allergies are most likely the effect of a person's genetics and environment. FA genetics research has the potential to affect millions of lives by helping scientists figure out the genes linked to the condition and by allowing them to develop new treatments and early detection options to help make it less severe on affected people. This is all being achieved through familial aggregation studies, candidate gene association studies, and immunotherapy treatments. Hopefully, in the future, research will continue in this field and it is anticipated that it will help us better understand the various molecular processes involved in FA that will lead to more effective treatment and prevention of FA.

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