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Genetics of Food allergy

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Abstract

Purpose of the review—Food allergy (FA), a growing clinical and public health problem in the U.S. and worldwide, is likely determined by multiple environmental and genetic factors. The purpose of this review is to summarize recent advances in FA genetic research.

Recent findings—There is compelling evidence that genetic factors may play a role in FA. However, the specific genetic loci that may modulate individual risk of FA remain to be identified. To date, only a limited number of candidate gene association studies of FA have been reported. Polymorphism(s) in 9 genes have been associated with the incidence of FA or FA severity in at least one study. But most of these findings remain to be replicated in independent populations. In contrast, there are considerable advances in genetics of other allergic diseases such as asthma and atopic dermatitis. While asthma and atopic dermatitis often co-exist with FA, the relevance of their candidate genes to FA remains to be evaluated.

Summary—Genetics in FA is a promising research area but is still in its infancy. More studies are needed to dissect susceptible genes of FA. A genome-wide association approach may serve as a powerful tool to identify novel genes related to FA. Furthermore, the role of gene-environment interaction, gene-gene interaction, and epigenetics in FA remains largely unexplored. Given the complex nature of FA, future studies need to integrate environment, genomics and epigenomics in order to better understand the multi-facet etiology and biological mechanisms of FA.

Keywords

Food allergy; genetics; Allergic diseases

Introduction

Food allergy (FA), defined as an immunoglobulin (Ig) E-mediated hypersensitivity reaction to food, is emerging as a major clinical and public health problem worldwide [1,2]. It affects approximately 5-8% of children and 1-5% of adults [3-5]. Such prevalence has risen substantially over the past decade, in parallel to the rise in prevalence previously seen for other atopic conditions [1,2,6-10]. Despite this, our current understanding on the etiology and biological mechanisms of FA is still incomplete. It is generally believed that FA, like the other allergic diseases such as asthma and atopic dermatitis (AD), is determined by both environmental and genetic factors[11,12]. The use of genomic information, accelerated by the sequencing of the human genome and the advent of new tools and technologies, raised

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widespread hope that FA genetics can significantly contribute to the prediction, prevention, and treatment of FA. The main purpose of this review is to summarize current state in FA genetic research and to offer future perspectives.

Diagnosis of Food Allergy in the Research Setting

There is a lack of well-established methods to define FA in large population studies. Currently, various methods have been used, ranging from self-report to double-blind, placebo-controlled food challenge (DBPCFC) [13]. DBPCFC has been promoted as the gold standard for establishing the diagnosis of FA. However, the procedure is laborious, time-consuming, and associated with uncertain risks such as anaphylaxis, and is therefore not routinely performed in the large-scale studies [14]. Other tests such as prick skin tests (PST) and in vitro measurements of food-specific IgE, are more commonly used. These methods, however, do have limitations, with positive predictive value (PPV) of PST being only 50-60%. Some investigators have proposed clinical cut-offs which obviate the need for oral challenges for establishing the diagnosis. Those include proposed values for the wheal size of skin tests [15-17] and for food-specific IgE levels [18-21]. More recently, studies have attempted to combine clinical history, in vivo and/or in vitro testing to predict the likelihood of clinical reactivity [17,22-24]. To date, there is not a generally accepted definition of FA in large-scale genetic epidemiological research. In this review, we have included all the articles related to genetics of FA (regardless how it was defined) as well as the articles on the genetics of food-specific IgE or skin prick test (SPT).

Familial Aggregation in Food Allergy

Previous studies have documented that family history is a strong risk factor for FA development [25-28]. A survey of the 622 families with probands of peanut allergy in the UK noted an increased prevalence of peanut allergy in succeeding generations. A child has a 7-fold increase in the risk of peanut allergy if he or she has a parent or sibling with peanut allergy [26]. In another study carried out in the UK, the frequency of peanut allergy has been found to be significantly higher in relatives of peanut allergy patients than in the general populations (7% vs. 0.5%) [27]. In our ongoing study in a Chicago cohort, we demonstrated a strong familial aggregation of FA and food allergen sensitization among family members [28].

Heritability of Food Allergy

In a small twin study (58 twin pairs) on peanut allergy, Sicherer et al reported that the concordance rate of peanut allergy (64.3%) among identical twins was significantly higher than that among dizygotic twins (6.8%) [29] and that the estimated heritability of peanut allergy was 81.6% [29]. This finding was similar to results concerning other allergic diseases, such as asthma (87%), atopic dermatitis (74%) and allergic rhinitis (74-82%). In our Chicago family-based cohort, the estimated heritability ranged from 0.15 to 0.35 for different food-specific IgE, all of which were statistically significant [28]. In our recent large twin study in a Chinese population [30], we demonstrated that sensitization to common food allergens were influenced by both genetic and environmental factors. The estimated heritability to peanut sensitization and to shellfish sensitization was 0.51 and 0.54, respectively [30].

Candidate-Gene Studies of Food Allergy

Positional cloning and candidate gene approaches are the two general approaches used to identify candidate genes of complex diseases. To our knowledge, there is no report on the positional cloning of FA. Several small-scale candidate-gene studies of FA have been reported, but with inconsistent results. The reported genes that were associated with FA or FA severity in at least one study were summarized below.

Major Histocompatibility Complex (HLA) Gene Family

Significant associations with peanut allergy were reported previously for the HLA class II DR beta 1(HLA-DRB1), DQ beta 1(HLA-DQB1) and DP beta 1(HLA-DPB1) gene polymorphisms [31]. Significant association with apple allergy were reported for HLA-DRB1*07 allele [32]. Hand et al also observed that the frequency of HLA-Beta*07 and HLA-DRB1*11 were increased in the nut-allergic patients compared to the atopic controls (12.20% vs 3.66%), and the frequency of HLA-DRB*13 and DQB1*06 were both increased in the nut allergy patients compared to both the atopic and blood donor controls. However, none of those increased frequencies were statistically significant after adjustment of multiple testing [33]. Shreffler et al showed that the genetic polymorphisms in the HLA class II gene family had no associations with peanut allergy in 73 children and 75 of their siblings [34].

CD14 Gene

Another gene of interest for FA is CD14 gene, which is the receptor for lipopolysaccharides. In a study comprised of 175 asthmatic and 77 food-allergic patients with varying ages, the C-159T polymorphism in the promoter of CD14 was found to be associated with non-atopic asthma and FA subjects, particularly in white subjects[35]. However, another study reported an inconsistent result, which found no association between two polymorphisms (C-159T and C-550T) in the promoter of *CD14* and FA [36].

FOXP3 Gene

The expression of Forkhead box P3 (FOXP3), a member of the forkhead/winged-helix family of transcriptional regulators, has been thought to be the best marker for naturally occurring regulatory T-cells. Torgerson et al reported that a 1300-base pair deletion in the non-coding region of the FOXP3 gene could lead to low FOXP3 mRNA expression levels and significantly decreased protein expression in peripheral blood lymphocytes [37]. They also observed that this gene variant could cause severe food allergy as a variant IPEX syndrome[37].

STAT6 Gene

Signal transducer and activator of transcription (STAT6) is a central molecule in the signal transduction pathway regulated by IL-4 and IL-13 in IgE isotype switching and production of TH2 cytokines[38,39]. Amoli et al reported that the G allele in the STAT6 G2964A polymorphism was significantly increased in nut-allergic patients compared with controls under a recessive model [40]. They also found that this polymorphism is associated with severity in nut-allergic patients[40]. However, Negoro et al found no association between this SNP and the severity of food allergy in 220 Japanese allergic children [41].

SPINK5 Gene

Serine protease inhibitor Kazal type 5 (SPINK5) is a protease inhibitor protein. It has been reported that SPINK5 can be expressed in the thymus and its defects have been suggested to cause abnormal maturation of T lymphocytes and leading to Th2 responses such as increased IgE level and eosinophilia [42]. A recent report in Japanese children with atopic dermatitis (AD) showed that patients with the SPINK5 1258AA or 1258GG genotype displayed a significantly higher prevalence of FA[43].

Interleukin 10 (IL10) Gene

IL10 down-regulates the expression of Th1 cytokines, MHC class II Ags, and costimulatory molecules on macrophages. Two SNPs in this gene, A-1082G and C-627A, lie on the putative

transcription factor-binding sites and are associated with the production of this cytokine [44, 45]. Negoro et al reported that *IL10* -627AA polymorphism was significantly associated with the severity of both FA and AD in 220 Japanese allergic children. Recently, in another study of atopic Japanese children, the authors observed no association between *IL10* -627AA and the prevalence of FA. However, they reported that Children carrying the *IL10* -1082AA genotype were significantly associated with 2.5 times higher risk of FA [46].

Interleukin 13 (IL13) Gene

IL13 is an important immunoregulatory cytokine produced primarily by activated Th2 cells. *IL13* gene polymorphisms have been linked to asthma by more than 25 studies [47]. A recent study in unrelated German children drawn from the multicenter atopic study also showed that the C-1055T polymorphism in the *IL13* gene is associated with increased risk of food sensitization [48].

Candidate-Gene Studies of Other Allergic Diseases

FA is strongly associated with certain allergic diseases such as asthma and atopic dermatitis (AD) [49-51]. Our studies in Chinese twin cohorts have shown that allergen sensitizations (including both food allergens and aero-allergens) might be contributed by some common genetic factors, suggesting some common genes shared by FA and the other allergic phenotypes [30]. Among all of the allergic phenotypes, asthma is one of the most studied allergic phenotype in genetic research. Some excellent reviews have summarized current advances in asthma genetics [47,52]. Briefly, more than 100 genes have been linked to asthma or asthma-related phenotypes in at least one population and 33 genes have been validated in more than five independent populations [47].

To our knowledge, most of the asthma candidate genes are involved in IgE synthesis, innate immunity, allergic inflammation, and/or hyperreactivity of the cells and organs, which are the common pathways shared by multiple allergic diseases including asthma, AD and FA. The current findings have supported that these genes may be also associated with some other allergic phenotypes. For example, five genes, including the mast cell chymase 1 gene (*CMA1*), *IL13*, the interleukin 4 receptor gene(*IL4R*), *SPINK5*, and the filaggrin gene(*FLG*), are not only among the most validated genes for asthma, but also have been linked to AD in at least two or more independent studies[53]. Meanwhile, the membrane-spanning 4-domains, subfamily A, member 2 gene (*MS4A2*) variants were significantly associated with asthma[54,55], total IgE [54,56,57], specific IgE to grass pollen allergen [54], nasal allergy [57] and atopy [58]. Additionally, *IL18* genetic variants were significantly associated with asthma[59], AD[60], total IgE [61], specific sensitization to common allergens, and seasonal allergic rhinitis[61]. N-acetyltransferase 2 (*NAT2*) genetic variants were significantly associated with asthma[62], total serum IgE[62], blood eosinophil counts[62], and allergy (defined as inhalational, food or mixed allergy)[63]. The cytotoxic T-lymphocyte antigen 4 gene (*CTLA4*) variants were significantly associated with asthma[64], total IgE[64], allergy[64], AD[65], and cord blood IgE[66]. Conceivably, asthma candidate genes, especially those validated in multiple populations, may also serve as candidate genes for food allergy. However, the relevance of these candidate genes to FA remains to be evaluated.

Genome-Wide Associations (GWA) of Allergic Diseases

GWA studies rely on searching for common genetic variants in dense sets of SNPs across the genome that are risk factors for diseases of interest [67]. As compared to candidate gene approach, the main strength of GWA studies lies in their ability to discover truly novel disease candidate genes (not relying on previous knowledge), especially those associated with moderate disease risks. [68]. Although no published GWA studies of FA are currently

available, some progress has been made for other allergic phenotypes. Moffatt et al genotyped more than 317,000 SNPs in 994 patients with childhood asthma and 1243 subjects without asthma and identified that genetic variants regulating *ORMDL3* expression are determinants of childhood asthma[69]. In a GWA study of 403 asthma families, Murphy et al identified two significant SNPs in chromosomes 1 (rs10863712) and 14 (rs1294497) for childhood asthma [70]. Esparza-Gordillo et al reported the first GWAs study of AD in 939 cases and 975 controls as well as 270 complete nuclear families [71]. Their study identified that subjects carrying AA genotypes in the rs7927894 had a 1.47 times higher risk of developing AD, comparing to those noncarriers[71]. Also, two large-scale GWA studies on allergic-related quantitative traits have been reported. One was conducted using 9,392 Icelanders using Illumina 317K SNP, in which 5 SNPs (including rs1420101, rs12619285, rs4857855, rs4143832 and rs3184504) were significantly associated with blood eosinophil counts[72]. The other was conducted in 1,530 population-based individuals testing 353,569 SNPs, which identified *FCER1A* as the novel susceptibility locus for total serum IgE levels. These GWA studies not only shed light on the further genetic studies of FA, but also underscore the promise of GWAS in dissecting genetics of FA.

Gene-Environment (G×E) and Gene-Gene (G×G) Interactions

Gene-environment (G×E) interactions, which reflect the complex interplay between environmental exposure and genetic predisposition, have received increasing attention. Studies in mice showed that G×E interactions explain a proportion of the phenotypic variance that may be higher than the main effect explained by either genetic or environmental effects considered separately[73]. Currently, research of G×E interactions on allergic diseases is limited, mainly focusing on three environmental factors, including smoking, air pollution and microbial exposures. Specifically, the *GSTP1* Ile105Val polymorphism would modify the effect of air pollution on allergic sensitization to inhalant and/or food allergens[74]. The influence of the C-159T polymorphism on the *CD14* gene seems to depend on environmental sources of microbial simulation[75-79]. Additionally, subjects carrying the *CD14* TT genotype of the C-159T polymorphism was noted to increase the protective effect of dog exposure on AD [75] and to modify the effect of farm exposures on atopy[76].

Gene-gene interactions, which are the functional interplay between genetic variants, are also likely to contribute to the complexity of human diseases[47]. Current evidence in the genetics of allergic phenotypes and/or food allergy has strongly suggested significant G×G interactions among genes involving the Th2-cell differentiation and signaling pathways. For example, a large study in German children showed that combining polymorphisms in *IL4*, *IL13*, *IL4RA*, and *STAT6* genes leads to a 10.8 fold increase in the risk for high serum IgE levels and a 16.8 fold increase in the risk for development of asthma, compared with the effect of any single SNP[80]. Liu et al reported that, among unrelated German children from a multicenter atopy study, the effect of *IL13*-1112TT genotype on food sensitization was modified by polymorphisms in the *IL4RA* gene[48]. Currently, the roles of G×G and G×E interactions in FA development remain largely unexplored, and represent a promising area of research.

Epigenetics

Epigenetics is broadly defined as changes in gene expression patterns that can be inherited and are independent of changes in DNA sequences. Epigenetic alterations are believed to occur not only prenatally or shortly after birth, but also during later developmental periods, influencing gene expression differentially throughout the lifespan. As such, epigenetic regulation provides an attractive mechanistic explanation for some molecular events linking early exposure to later disease development [81]. Particularly, DNA methylation and chromatin modifications are the two major mechanisms that are most studied in epigenetic research.

Previous data has suggested that epigenetics plays an important role in Th cell differentiation and cytokine gene expression[82-86], leading to the conclusion that both are important biological pathways of FA. For example, Jones et al reported that methylation on the -53 CpG site in the IFN- γ promoter suppressed IFN- γ transcription by inhibiting cAMP response element binding protein (CREB), and thus, was associated with Th2 polarization [84]. By using an animal model, Liu et al found that altering methylation of IL-4 and IFN- γ promoter regions by inhaling environmental exposures was significantly correlated with changes in IgE levels [85]. In addition, Su et al found that inhibition of endogenous histone deacetylase (HDAC) activity shifted Th1:Th2 ratios by 3-fold to 8-fold, skewing recall responses toward a more Th2-like phenotype[86]. We anticipate that further studies on how epigenetic alternation affects the risk of FA and how these epigenetic alternations induced by environmental exposure hold great promise to clarify the mechanisms concerning how early exposure affects the development of FA and to identify early biomarkers to effectively predict and prevent the incidence of FA.

Conclusion

FA is likely the results of complex interplay of a large number of genetic and environmental factors. Given our limited understanding of the complex biological pathways and mediators involved in FA, GWA studies with adequate design and power to detect G $\times$ E and G $\times$ G interactions may represent the best available approach to discover a novel set of genes related to FA. One challenge but promising area in FA research is how to integrate environment, genomics and epigenomics to better understand the complex etiology and biological mechanisms of FA (Figure 1). Such study would require ascertainment of phenotypic, environmental, genomic, and epigenomic data in a same study population with sufficient sample size. It would also require strong interdisciplinary collaboration and adequate funding support. It is anticipated that the advances in FA genetics and epigenetics will help us better understand the molecular processes involved in various pathways of FA and, ultimately, lead to more effective prevention and treatment of FA.

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Figure 1.
Interplay of environment, genetics and epigenetics in the development of food allergy