HHS Public Access

Author manuscript

Curr Opin Allergy Clin Immunol. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Curr Opin Allergy Clin Immunol. 2016 June ; 16(3): 257–264. doi:10.1097/ACI.0000000000000268.

Are genetic tests informative in predicting food allergy?

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Abstract

Purpose of review—Food allergy is common among children and adults worldwide. Recent studies have improved our understanding of the genetic mechanism of food allergy and further studies may result in clinical application through genetic testing.

Recent findings—Genetic factors are important in the development of food allergy. An increasing number of genes have been associated with food allergy in recent years. These include mutations and variant in the Filaggrin (*FLG*) gene, the association of *HLA-DR* and *–DQ* regions with food allergy, CNVs impacting *CTNNA3* and *RBFOX1*, DNA methylation that partially mediates SNP association at the *HLA-DR* and *–DQ* loci as well as other genes. Several studies have implicated differences in gut microbiota composition in food allergy.

Summary—With the advance of high-throughput genotyping and sequencing techniques together with improved analytical methods, the contributions of genetic and environmental factors in development of food allergy are being clarified. Yet much remains to be explored and more studies with larger sample sizes, better phenotyping and improved quality control genomics methods are needed. The ultimate goal is the development of a panel of reliable markers for genetic testing in food allergy to improve overall patient care.

Keywords

food allergy; genetics; epigenetics

INTRODUTION

Food allergy is a type of adverse immune response where exposure to certain food(s) induces allergy rather than tolerance. The food allergens are diverse, with cow's milk, egg,

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Conflicts of interest

There are no conflicts of interest.

peanut, tree nut, soy, wheat, fish and shellfish being most common, especially in children. The overall prevalence of food allergy has been increasing and is around 8% in children and 5% in adults.[1] To date no known medication prevents food allergy and strict avoidance remains the main treatment.[2]

Genetic factors play an important role in the development of food allergy and are one of the major risk factors for its development. Family and twin studies show that family history is an important risk factor for food allergy, which imposes a 2–10 fold increased risk [3–6] or 15–80% higher incidence, depending on the study setting, population, method of measurement of allergy and food allergen. [5,7,8]

The genetic mechanism underlying development of food allergy and its interplay with environmental factors are a burning research topic. In this review, we will discuss recent discoveries from candidate gene studies, unbiased genome-wide approaches to findings from epigenetic and gut microbiome studies.

RESULTS FROM CANDIDATE GENE STUDIES

Most genetic studies of food allergy are candidate gene studies, testing only associations with specific variants, based on prior knowledge of the genes in which the variants reside. Here we briefly summarize the results of recent studies and advances made in the recent years. Table 1, includes studies where positive associations were found between commonly studied candidate genes and food allergy. It is important to be aware that many of these associations have not been extensively tested in other populations nor been replicated, and inconsistent results exist for some variants/genes, thus many associations remain inconclusive.

The Human leukocyte antigen (*HLA*) plays major roles in immune regulation. Therefore, it's not surprising that the *HLA* genetic locus has been highly significantly associated with multiple immune disorders, including allergic diseases[26–28]. The positive association between *HLA* and food allergy was first reported in 1997[9] and since then many *HLA* loci have been implicated[10,11,29]. A recent study in a relatively large Canadian pediatric cohort illustrated a significant association of HLA-DQB1*02 and DQB1*06:03P with peanut allergy.[12] However, the drawback of this study is the low genotyping call rate. [12,13]

Another candidate locus for food allergy, now examined in multiple populations, is the Filaggrin (*FLG*) gene which interacts with keratin filaments. Filaggrin is important for the skin barrier and mutations in *FLG* have been found to be associated with severe eczema[30] and FLG loss-of-function (FLG-LOF) mutations have been associated with peanut allergy. [14,15] A recent longitudinal study in the UK examined the association between the total effect of FLG-LOF mutations and all-cause food allergy at different ages in 1150 children. Significant association was observed at ages 10 and 18 years.[17] Association of *FLG* mutations with food allergy has also been shown in populations of Netherlands and Denmark [16,18]. In addition to these LOF mutations, common variants in gene *FLG* have also been reported to be associated with food allergy. A Japanese study found a common

variant rs1933064 in *FLG* to be associated with food allergy sensitization. The variant might affect promoter activity and thus skin barrier function[19]. A separate study also showed that exposure to peanut antigen in household dust in early life increases the risk of developing peanut sensitization and allergy for children having FLG-LOF mutations[31]. Despite the large body of evidence for FLG association with food allergy, new study also suggests that FLG mutations are not significantly associated with food sensitization among adults without atopic dermatitis[32]. Thus the relationship between FLG mutations/variants, food allergy and potential confounding factor atopic dermatitis needs to be further evaluated.

Interleukins are a large class of genes that play crucial roles in immune responses and have been related to allergic disease. *IL10* has been mostly investigated for its potential association with food allergy. The cytokine IL10 is generated mainly from monocytes, but also lymphocytes, in response to commensal or pathogenic flora. IL10 plays pleiotropic regulatory roles such as suppressing the level of MHC class II antigens and Th1 cytokines, inhibiting NF-κB singling and promoting B cell proliferation and antibody production, which influences the balance between Th1 and Th2 responses[33,34]. Older studies have not presented convincing evidence supporting an association with food allergy, due to caveats in analytical methods, such as lacking of multiple testing adjustment [20,35,36]. A more recent study in Brazilian children examined several IL10 polymorphisms and a variant in the *TGFβ1* gene. The only significant association found was that of IL-10 polymorphism-1082G/A with cow's milk allergy [21].

The JAK-STAT signaling pathway serves many important functions in the immune system. STAT6 (Signal transducer and activator of transcription family member 6) is a key transcription factor in downstream response to cytokines such as IL2 and IL4. Upon phosphorylation by JAK tyrosine kinases STAT 6 forms homo- or hetero-dimers with other STAT family members and translocate to the nucleus. STAT6 is involved in immunoglobulin isotype switching and differentiation of Th2 cells via transcriptional regulation of genes. [37] Previous studies have demonstrated an association between polymorphisms in *STAT6* and nut allergy.[22] Furthermore, SNPs close to *STAT6* (within 20kb upstream/downstream of STAT6 transcript) have been associated with food allergen sensitization found as a secondary phenotype from a genome wide association study (GWAS).[23] In addition, the GG genotype of *STAT6* polymorphism rs324015 showed a nominally significant association with longer persistence of cow's milk allergy than the AA+AG genotype states. In that study variants of other candidate genes *CD14*, *IL10*, *IL13*, *SPINK5* and *TSLP* did not demonstrate such an association.[38]

Since T cells play key roles in food allergy responses, genes with functions in T cell maturation, activation and differentiation present candidate genes for food allergy. In this regards, *FOXP3* (Forkhead box P3) encodes a transcription factor of the forkhead/winged-helix family that is critical for the normal function of regulatory T cells. [39] Defects in *FOXP3* are associated with immune diseases such as immunodysregulation, polyendocrinopathy, enteropaty X-linked syndrome (IPEX) and an older study found an association between a deletion in the 5′ region of *FOXP3* and a subtype of IPEX patients showing multiple food allergies [24]. A more recent study found significantly lower levels of

FOXP3 mRNA expression among children with asthma and food allergy compared to healthy controls[40].

Taken together, while candidate gene studies have tried to explore the underlying genetic factors for food allergy for decades, very few firm associations have been established. Several reasons could explain why the studies yielded such inconsistent results. How the outcome variable, food allergy, is measured and defined is not consistent across studies. Many of the studies are underpowered due to limited sample size, suffered from diverse study populations and/or confounding issues due to population stratification. Also some studies did not adjust for multiple-testing. Furthermore, food allergy is highly subjected to environment impact and many of these candidate gene studies have different environmental exposure patterns that is not being controlled for.

COMMON VARIANTS AND CNVS DISCOVERED BY UNBIASED GENOME WIDE APPROCHES

As an unbiased approach to detect susceptibility loci for complex diseases, GWAS have undergone rapid development and yielded numerous successful discoveries that replicate consistently even across different ethnic groups. In GWAS, the association between the genotype of common variants (minor allele frequency > 1%) and disease status are examined across the genome. So far, only one published study focuses specifically on food allergy [13], in this study Hong et al. reported that *HLA-DR* and *–DQ* regions at locus 6p21.32 are significantly associated with peanut allergy (top SNPs: rs7192, $P=5.5\times10^{-8}$; rs9275596, $P=6.8\times10^{-10}$) in a cohort of 2197 US subjects of European ancestry (Table 1). The association was replicated in an independent cohort of 62 peanut allergy cases and 69 controls of European ancestry. The results are in line with previous studies suggesting the important role of *HLA* in allergic diseases and suggestive associations from previous candidate gene studies of food allergy.[13]

Copy number variation (CNV) is another type of genetic variants associated with susceptibility for multiple diseases, especially psychiatric diseases[41,42]. To date, only a single, very recent study has examined the association of CNV with food allergy[25]. In this study, a significant association was found between food allergy and CNVs in gene *CTNNA3* using genome-wide SNP array analysis in both a pediatric discovery cohort (357 cases, 3980 controls) and a replication cohort (167 children with food allergy, 1573 controls) (Table 1). Additional significant association was found in gene *RBFOX1* in the subset of participants of European ancestry (Table 1). In addition, more prominent expression upregulation of CD63 and CD203c following PMA stimulation was observed in mononuclear cells treated with CTNNA3 siRNA compared to controls, implicating that CTNNA3 is involved in sensitization to allergen. [25]

RARE VARIANTS IDENTIFICATION WITH SEQUENCING TECHNOLOGY

Apart from common variant association with complex diseases, rare variants could also contribute to the etiology of complex diseases including allergic diseases and in some cases may have a large effect. DeWan and colleagues reported co-segregation of rare coding

variants in the genes *PDE4DIP*, *CBLB* and *KALRN* with an asthma phenotype. This was a family based study using whole-exome sequencing, however functional studies are lacking to evaluate the roles of these variants in disease etiology[43]. Another study of sequencing candidate genes found an association with asthma and rare variants in or at the flanking regions of *DPP10*, *IL12RB1*, *IKBKAP* and *AGT* in either European Americans or African Americans[44]. There has been no report of rare variants associated with food allergy via targeted sequencing, whole exome sequencing or whole genome sequencing. However, with the advance of sequencing technology, analytical tools and reduced cost, we anticipate that this will change soon, especially for identification of underlying variants in severe and familial cases.

FINDINGS FROM EPIGENETIC STUDIES

Similar to other complex diseases, the development of FA is shaped by host factors, environmental factors and the interactions between those. Differential DNA methylation is an epigenetics mechanism that reflects environmental effects upon the human genome. It has been shown that during T cell differentiation, epigenetic modification plays a critical role, highlighting its relevance to the development of food allergy.[45,46] A few studies have attempted to assess the role of DNA methylation in food allergy.

By using an epigenome-wide association analysis, Martino et al. compared the DNA methylation profile of CD4+ T cells between 12 children with IgE-mediated food allergy and 12 healthy controls at birth and 12 months of age. A group of 92 probes were identified as differentially methylated from case-control analyses at both time points, and to be non-SNP associated. Pathway enrichment analysis of the genes that these probes are mapped to yielded the nominally significant association of MAPK (mitogen-activated protein kinases) signaling pathway (P=0.042) and food allergy. Four genes in this pathway contain differentially methylated probes. Fifteen probes at 3 genes were further validated by Mass spectrometry, and the expression level of some genes was correlated with differential methylation.[47] In a study examining the effect of oral immunotherapy on peanut allergy, Syed and colleagues observed the correlation of low methylation level of *FOXP3* CpG sites with immune tolerant status[48]. When comparing overall promoter methylation level of cytokine genes *IL4*, *IL5*, *IL10*, *INF-γ*, Canani and colleagues observed that the methylation level of these genes were significantly different between children with active IgE mediated cow's milk allergy (CMA), those who outgrew CMA and healthy controls. Methylation levels were lowest within the active CMA group and the highest amongst healthy controls for both *IL4* and *IL5*, with the opposite pattern being seen for *IL10* and *INF-γ*. The expression level of these genes correlates with their methylation levels.[49] In the GWAS study of food allergy by Hong and colleagues, the authors also examined the potential epigenetic contribution. They demonstrated a significant correlation between the two top associated SNPs and CpG sites methylation levels in the genes *HLA-DQB1* and *HLA-DRB1*, and furthermore, showed that the SNP association with the phenotype is partially mediated by the differential methylation[13].

UNDERSTADNING OF THE GUT MICROBIOTA

In addition to the genetic makeup of the host, the gut microbiota composition likely plays an important role, based on epidemiology studies of allergic diseases and mouse models [50]. Two large cross-sectional studies of more than 14,000 and 79,000 children previously showed and recently confirmed that farm exposure is associated with reduced prevalence of allergic disease and atopy[51,52]. Multiple other studies, including those directly assessing the gut microbiota composition using 16S rDNA analysis, have demonstrated the inverse correlation between gut microbiota diversity and the risk of developing allergic diseases [53–55]. Several studies using mouse models have shown that alterations in gut microbiota constitution affect allergen sensitization [56–58]. The underlying mechanisms include impact on intestinal barrier function through IL-22 signaling and toll-like receptors[57,59–61].

Very few studies have specifically explored the association between intestinal microbiota and food allergy. Recently, Ling and colleagues revealed that the proportion of several important gut bacterial phylotypes showed significant changes among food allergy patients compared to healthy controls by targeted parallel pyrosequencing of the 16S rRNA gene. Furthermore, differences also exist between IgE-mediated food allergy and non IgE mediated food allergy. Ling Z. et al also demonstrated a negative correlation between host IL10 level and food allergy-enriched phylotypes. This study was conducted among Chinese subjects.[62] A new Canadian study examined the abundance and diversity of gut microbiota by illumina 16S rRNA sequencing and found the risk of developing food allergen sensitization to be inversely correlated with microbiota richness and positively associated with the ratio of Enterobacteriacaea/Bacteroidaceae [63]. The inverse correlation between food sensitization and diversity of gut microbiota was similarly observed in a study in Taiwan [64]. However, these studies are of small sample sizes and lack of replication, and therefore the results need to be interpreted with caution. The gut microbiota composition is affected by various environmental factors, like diet, exposure to pets [65,66]. Further studies need to assess how host genetic factors interact with gut microbiota and environmental factors, which is an important yet complicated aspect in predicting the risk of developing food allergy and in establishing reliable genetic testing for food allergy.

FUTURE GENETIC TESTING

Genetic testing evaluates for underlying mutations/variants that are causal or relevant to the diseases in question. The general purpose of genetic testing includes several aspects, such as disease diagnosis, identifying causal mutations, predicting disease progression and prognosis, predicting responses to medication/treatment, and identification of populations at risk for early prevention. Genetic testing is now applied in the clinic for many diseases, for example, to test for mutations in *BRCA1* and *BRCA2* for breast and ovarian cancers, checking for *CFTR* mutations for cystic fibrosis and checking the hemoglobin A gene for sickle cell mutations. A reliable genetic test should provide reliable and relevant information regarding development of the disease in question. As discussed above, though underlying genetic mechanism for food allergy are starting to unravel, a panel of reliable markers for genetic testing in food allergy is still lacking. The future possibilities of such testing lies in

further research dissecting the complex interplay between genetic components and diverse environmental factors, including the microbiota, in the pathogenesis and expression of food allergy. In the near future, we anticipate to establish a panel of biomarkers to identify high-risk populations where preventive measures can reduce severe food allergy emergencies, facilitate accurate identification of allergen sources and to predict effective treatment options and thus improve overall patient care.

CONCLUSION

The development of food allergy is shaped by both genetic components and environmental factors. Through candidate gene studies, GWAS, and CNV studies, we have begun to dissect the genetic mechanisms underlying food allergy. However, due to the limitation of sample sizes, population differences and phenotype heterogeneity, many results are inconsistent and more studies are needed to validate the discoveries, as well as to identify contributions from additional genetic variants, such as rare variants. The interactions between genetic components and environmental factors constitute another important aspect to explore. Important topics in this regard include, but are not limited to, epigenetic effects and gut microbiota. Gaining a better understanding of the genetic and environmental impact of food allergy will allow us to develop a clinically-applicable biomarker panel for genetic testing, which will be of benefit in diagnosis, therapeutics and even prevention of food allergy – a prototype precision medicine focus.

Acknowledgments

None

Financial support and sponsorship

This work was supported by a gift from the Kubert Estate family, an Institutional Development Fund to the Center for Applied Genomics and grant from the NIH's Electronic Medical Records and Genomics (eMERGE) program.

Abbreviations

CNV	Copy number variation
FLG	Filaggrin
FOXP3	Forkhead box P3
GWAS	genome wide association study
HLA	Human leukocyte antigen
IPEX	enteropaty X-linked syndrome
STAT6	Signal transducer and activator of transcription family member 6

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• of special interest

•• of outstanding interest

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Key points

1. Results from candidate gene studies suggest that genetic variants in several genes, including the *HLA* locus, *IL10*, *STAT6*, *FOXP3* and *FLG*, are associated with food allergy, however, inconsistent results were found in different populations.
2. The only GWAS of food allergy identified genome wide significant association at the *HLA-DR* and *–DQ* regions, and demonstrated that this association is partially mediated by differential DNA methylation.
3. The only CNV study of food allergy using genome-wide SNP array identified association of CNVs impacting the *CTNNA3* and *RBFOX1* genes in subjects with food allergy.
4. Epigenetic studies implicate DNA methylation effects impacting genes in the MAPK pathway, as well as *IL4*, *IL5*, *IL10*, *INF-γ* all of which are associated with food allergy. Recent studies also revealed the differences in the gut microbiota between food allergy patients and healthy controls.
5. Further research dissecting the genetic underpinnings and the interplay between genetic components and diverse environmental factors will hopefully lead to the development of a panel of reliable biomarkers for the genetic testing of food allergy.

Table 1

Association studies addressing food allergy, including candidate gene analysis and more recent genome wide approaches.

Gene (Variants)	Population	FA phenotype	Cases	Controls	Main finding of association	Reference	Approach
HLA-DQ7	Italian	cow milk protein allergy	37	35	RR=4.42, P<0.05	[9]	candidate gene study
HLA-DRB1 (HLA-DRB1*08)	United Kingdom	peanut allergy	50	293	P=0.0021;Pc=0.027	[10]	candidate gene study
HLA-DRB1 (HLA-DRB1*08/12)	United Kingdom	peanut allergy	50	293	P=0.0023; Pc=0.029	[10]	candidate gene study
HLA-DQB1 (HLA-DQB1*04)	United Kingdom	peanut allergy	50	293	P=0.00042; Pc=0.0029	[10]	candidate gene study
HLA-DRB1 (DR4)	eastern France	birch pollen and food allergy	42	42	Pc=0.018	[11]	candidate gene study
HLA-DRB1 (DR7)	eastern France	birch pollen and food allergy	42	42	Pc=0.0037	[11]	candidate gene study
HLA-DQB1 (DQB1*02)	Canada	peanut allergy	311	226	OR=0.09, P=1.1×10−8	[12]	candidate gene study
HLA-DQB1 (DQB1*06:03P)	Canada	peanut allergy	311	226	OR=2.82, P=2.1×10−2	[12]	candidate gene study
HLA-DR region (rs7192)	US	food allergy	316	144 controls and 1737 controls of uncertain phenotype	Allele T vs. G OR=1.7, P= 5.5×10−8	[13]	GWAS
HLA-DQ region (rs9275596)	US	food allergy	316	145 controls and 1737 controls of uncertain phenotype	Allele C vs. T OR=1.7, P= 6.8×10−10	[13]	GWAS
FLG (R501X, 2282del4, R2447X, and S3247X)	English, Dutch, and Irish, Canadian	peanut allergy	Dis cohort: 71; Rep cohort: 390	Dis cohort:1000; Rep cohort: 891	Dis cohort: FLG-LOF P=3.0×10−6; OR=5.3; Rep cohort: P=5.4×10−5, OR=1.9	[14]	candidate gene study
FLG (R501X, 2282del4, R2447X, and S3248X)	Canada	peanut allergy	663	889 Ontario controls; 267 Quebec controls	FLG-LOF OR=1.96, P=5.12×10−7 with the combined controls	[15]	candidate gene study
FLG (R501X, 2282del4)	Denmark	Self-reported allergy to eggs, milk, fish and wheat	3471 Caucasian participants were surveyed and genomic DNA were collected from 3366 of them		FLG-LOF for having food allergy to at least one type of allergens surveyed OR=2.13, P<0.001	[16]	candidate gene study
FLG (R501X, 2282del4, and S3247X)	United Kingdom	food allergy	1150 children in a birth cohort followed up for 18 years		10 years old, FLG-LOF OR=31.46, P=0.005; 18years old: OR=4.25, P=0.005	[17]	candidate gene study
FLG (R501X, R2447X, 2282del4, and S3247X)	Netherlands	Clinical reactivity to foods	102	53	FLG-LOF OF=4.9, P=0.005	[18]	candidate gene study
FLG (rs1933064)	Japan	food sensitization	116 infants tested for food specific IgEs		Allele G showed negative association with the number	[19]	candidate gene study

Gene (Variants)	Population	FA phenotype	Cases	Controls	Main finding of association	Reference	Approach
					of positive food specific IgEs, P=0.0055		
IL-10 (A-1082G)	Japan	food allergy	111	atopic control 115	A allele OR=2.4, P=0.04, adjusted for age and sex	[20]	candidate gene study
IL-10 (A-1082G)	Brazil	Persistent IgE-mediated cow milk allergy	34	217	Genotype GG vs. AA: OR=6.15, P=0.001, Pc=0.002	[21]	candidate gene study
STAT6 (G2964A in the 3′ UTR)	United Kingdom	nut allergy	71	184	G allele OR=2.9, P< 0.0001	[22]	candidate gene study
STAT6 (rs703817 at 3′ UTR of *STAT6*)	Mexico City	food allergen sensitization	162 trios with a food-sensitized child		P=0.0076	[23]	candidate gene study
STAT6 (rs4759044 in gene *LRP1*, nearby of *STAT6*)	Mexico City	food allergen sensitization	162 trios with a food-sensitized child		P=0.0056	[23]	candidate gene study
STAT6 (rs4759044 in gene *LRP1*, nearby of *STAT6*)	Mexico City	food allergen sensitization	162 trios with a food-sensitized child		P=0.0077	[23]	candidate gene study
FOXP3 (del-6247_-4859)	France	IPEX syndrome severe food allergy	A four-generation kindred including 4 IPEX patients		The deletion variant cosegregates with the disease phenotype in males	[24]	candidate gene study
CTNNA3 (CNV)	United States	food allergy	Dis cohort 357; Rep cohort 167	Dis cohort 3980; Rep cohort 1573	Deletion variants PCA corrected meta-analysis P=1.24×10−3	[25]	CNV study based on genome-wide SNP array
RBFOX1 (CNV)	United States	food allergy	Dis cohort Caucasians: 222; Rep cohort Caucasians: 106	Dis cohort Caucasians:2002; Rep cohort Caucasians:1414	Deletion variants Meta-analysis P=7.35×10−5 in Caucasians	[25]	CNV study based on genome-wide SNP array

RR=relative risk; P=P-value; OR=odds ratio; LOF=loss of function; Pc=multiple-comparison corrected P-value; GWAS=genome-wide association study; IPEX=Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PCA= principal component analysis; Dis=Discovery; Rep=Replication; SNP=single nucleotide polymorphism