Review article

Incorporating genetics in identifying peanut allergy risk and tailoring allergen immunotherapy: A perspective on the genetic findings from the LEAP trial

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Examining the genetics of peanut allergy (PA) in the context of clinical trial interventions and outcomes provides an opportunity to not only understand gene-environment interactions for PA risk but to also understand the benefit of allergen immunotherapy. A consistent theme in the genetics of food allergy is that in keeping with the dual allergen exposure hypothesis, barrier- and immune-related genes are most commonly implicated in food allergy and tolerance. With a focus on PA, we review how genetic risk factors across 3 genes (*FLG*, *MALT1*, and *HLA-DQA1*) have helped delineate distinct allergic characteristics and outcomes in the context of environmental interventions in the Learning Early about Peanut Allergy (LEAP) study and other clinical trials. We specifically consider and present a framework for genetic risk prediction for the development of PA and discuss how genetics, age, and oral consumption intertwine to predict PA outcome. Although there is some promise in this proposed framework, a better understanding of the mechanistic pathways by which PA develops and persists is needed to develop targeted therapeutics for established disease. Only by understanding the mechanisms by which PA develops, persists, and resolves can we identify adjuvants to oral immunotherapy to make older children and adults immunologically similar to their younger, more malleable counterparts and thus more likely to achieve long-term tolerance. (J Allergy Clin Immunol 2023;■■■:■■■-■■■.)

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Multiple genes have been associated with peanut allergy (PA) in population-based studies,[1] but few studies have examined genetic risk in the context of environmental exposure and response to therapy.[2,3] Genes previously implicated in food allergy development through genome-wide association studies (GWASs) and candidate gene approaches[1] can be broadly classified into functional categories that include (1) skin barrier integrity (eg, filaggrin [*FLG*]); (2) innate immunity (eg, *HLA*, *CD14*, *IL2*, *IL10*); (3) adaptive immunity (eg, *HLA*, *STAT6*, *IL10, IL13*); and (4) immunoregulatory and immunomodulatory genes (eg, *SERPINB7, SERPINB2, STAT6, IL10, IL13*). The 2 most robust genetic findings in food allergy are *FLG* and *HLA*; interestingly, *FLG* is a general food allergy risk gene, whereas *HLA* appears to have food-specific effects. A consistent theme across food allergy genetics implicates the dual allergen exposure hypothesis, whereby barrier- and immune-related genes are most commonly associated with food allergy. In fact, numerous genes have been implicated across multiple related conditions in the atopic march, further supporting a mechanism by which these genes may be causal in the development of food allergy.

A primary limitation of prior genetic studies on food allergy is that most do not examine the role of the environment in genetic risk. Further, when PA-related outcomes are followed longitudinally, the influence of genetics on stages of atopy may be elucidated. As pointed out in recent reviews,[1,4] implicated genes have been associated with nonspecific food allergy risk, specific food allergy risk, disease progression to allergy, and now most recently, response to oral immunotherapy (OIT). Examining PA

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Abbreviations used
AD: Atopic dermatitis
FLG: Filaggrin
GWAS: Genome-wide association study
IMPACT: Induction of Tolerance and Desensitization in Peanut-Allergic Children
LEAP: Learning Early About Peanut Allergy
MALT1: Mucosa-associated lymphoid tissue lymphoma translocation 1
OIT: Oral immunotherapy
OR: Odds ratio
PA: Peanut allergy
POISED: Peanut Oral Immunotherapy Study: Safety, Efficacy and Discovery
SNV: Single-nucleotide variant

genetics both longitudinally and in the context of clinical trial interventions and outcomes provides an opportunity to not only understand gene-environment interactions for PA risk but to also understand the benefit of allergen immunotherapy. From this perspective, we focus on the genetics of PA in the Learning Early About Peanut Allergy (LEAP) study and discuss how genetic determinants across 3 genes has helped delineate distinct allergic characteristics and outcomes in the context of environmental interventions in the LEAP study and other clinical trials. We specifically consider the importance of thinking of the cumulative effects across key PA genes and present a framework for genetic risk prediction for the development of PA and discuss how genetics, age, and oral consumption intertwine to predict PA outcome.

FILAGGRIN AND SKIN BARRIER INTEGRITY

Genetic variation in the epithelial barrier that promotes cutaneous sensitization reflects a nonspecific risk factor for development of allergic disease, the most well established of these being variation in the filaggrin gene (*FLG*), which encodes profilaggrin, which in turn plays a key role in epithelial barrier integrity. Multiple studies have shown an association between loss-of-function genetic variants in *FLG* and food sensitization, food allergy, and progression of the atopic march.[1,5-11] *FLG* has had the strongest and most consistent association with atopic dermatitis (AD), with odds ratios (ORs) for risk as high as 7,[12,13] as demonstrated in the Atopic Dermatitis Research Network. It is likely that defects in skin barrier function facilitate peanut sensitization before the development of PA. This idea is expanded on by the dual allergen exposure hypothesis, which postulates that sensitization to food occurs through cutaneous exposure, whereas tolerance is induced through oral exposure,[14] as a result of which barrier defects in skin are a predetermining risk factor for food allergy. *FLG* is now the most replicated genetic locus for food allergy, but in contrast to the risk for AD described earlier, the ORs for PA are often lower (OR = ~2.9[1]). The LEAP study demonstrated that clinical risk factors, including severe AD, may be overcome with oral exposure to peanut.[15] In the LEAP study, infants aged 4 to 11 months with either severe AD or egg allergy were randomized to introduce or avoid peanut with a primary end point of PA at 5 years of age. Consumption of peanut prevented the development of PA, with a prevalence of PA at 5 years of age of 13.7% in the avoidance group and 1.9% in the consumption group ($P < .001$) among those with negative skin prick test results at baseline and 35.3% and 10.6% ($P = .004$) in those with skin prick test results of 1 to 4 mm in diameter at baseline. In a recent analysis using longitudinal data, the LEAP study demonstrated that deleterious variants in *FLG* are associated with greater eczema severity over the first 5 years of life.[16] The association is most notable in the first year of life, when most peanut sensitization and PA develop, and importantly, when oral introduction may lead to tolerance. Although severity of eczema generally declines over the first 5 years, the study found that compared with noncarriers, carriers of deleterious variants in *FLG* (assessed as a score across 4 deleterious variants: p.R1798*, p.R501*, p.S126*, and p.S761fs) maintained the most severe eczema at all time points.

Analysis from the LEAP study also confirmed the previously described association of *FLG* with PA (OR = 3.13 [P =.006] assessed across 4 deleterious variants), consistent with epithelial barrier dysfunction as a susceptibility indicator. Taking advantage of the longitudinal nature of the LEAP study, it was found that the *FLG* association with PA at 60 months was reduced once adjustment had been made for eczema severity at baseline, although some level of association was still retained (OR = 2.63 [P = .02]). These findings suggest that the relationship between *FLG* and PA is mediated through the strong association with eczema severity, but there remains some independent association beyond this mediation. Future work is needed to determine whether this residual risk is due to subclinical skin barrier defects or to epithelial barrier dysfunction in the oral mucosa and esophagus.[17] This relationship between genetic determinants of barrier defects and PA, which is mediated in part through the severity of the barrier defect in early life, highlights the need to determine whether prompt healing of the skin barrier, either with topical therapy or biologic agents, may further mitigate the risk of PA and other food allergy development.

MALT1, ELEVATED IgE LEVEL, AND PEANUT EXPOSURE

One of the challenges with published genetic studies on food allergy in general is the difficulty in disentangling sensitization from allergy. In the LEAP trial, the ascertainment and inclusion criteria allowed for the unique opportunity to interrogate the progression from peanut sensitization to development of PA, as determined at age 60 months by oral food challenge. The single-nucleotide variant (SNV) rs57265082 in mucosa-associated lymphoid tissue lymphoma translocation 1 (*MALT1*) was identified through GWAS as a strong determinant of PA (OR = 10.99 [P = 6.49E–08]), and it was found to be associated with progression from sensitization to development of allergy, wherein association with PA was noted even within the subset of participants sensitized to peanut at trial entry.[3] *MALT1* encodes for a paracaspase in the CARMA1-BCL10-MALT1 complex, which is critical for B- and T-cell activation in response to antigen via the nuclear factor-κB pathway. A recent review published in the *Journal of Allergy and Clinical Immunology* discusses the role of the complex in allergic disease in detail; therefore, the characteristics of MALT1 deficiency will be described only briefly here.[18] Homozygous variants resulting in MALT1 deficiency is manifested with recurrent infections, dermatitis, chronic diarrhea, and autoimmunity, often presenting in the first few months of life.[19]

Many but not all patients have eosinophilia and elevated levels of total and specific IgE, although not commonly with documented food allergy or allergic rhinitis.[18,19] In some cases, patients have combined immune deficiency.[19,20] Interestingly, in mice, MALT1 deficiency results in an AD phenotype, driven by allergen sensitizations and skewing toward the T_H2 phenotype with decreased T regulatory cells.[18,21-23] Although MALT1 protease deficiency does not impair mast cell degranulation, it does inhibit IgE-dependent mast cell cytokine production and histamine-induced vascular edema, which may attenuate the allergic response.[22] In the LEAP participants, this SNV in *MALT1* was found to be highly associated with PA and elevated peanut-specific IgE levels, and the relationship with PA was maintained even among those with peanut sensitization randomized to consume peanuts.[3] Among the participants with allergy, carriers of rs57265082 had greater peanut component spreading than the allergy-free noncarriers did.[3] This SNV falls in a region linked to *MALT1* expression, and it is possible that diminished expression is leading to the phenotype seen here; however, future work is needed to determine the exact impact of this SNV on *MALT1* expression and function.[3] In LEAP, *MALT1* status seems to be associated not only with higher levels of IgE but also with greater allergen-specific sensitizations that lead to true allergic disease through a pathway of PA risk that is not allergen component–specific.

The *MALT1* association with PA in LEAP is novel, and this is not a gene that has previously been implicated in PA or included in candidate gene investigations. Several key features of the LEAP study design likely explain why this variant may not have been detected in prior GWASs of PA. First, prior GWASs compared allergy-free controls with subjects with PA, whereas in contrast, the LEAP study included only participants who were at high risk for PA, many of whom were sensitized at baseline. The selection criteria of the LEAP study enriched specifically for the risk of PA and therefore may have created a unique cohort to discover novel genetic risk factors. Second, LEAP is the only setting in which a GWAS of PA modeling for oral peanut exposure in these high-risk children was performed. For example, we identified the *MALT1* association in those children who were at high risk and fully avoiding peanut exposure in early life. These unique aspects of LEAP likely led to a higher effect size of risk for *MALT1* with PA and therefore to higher power in this GWAS than in those prior.

Beyond the associations of the *MALT1* SNV with PA in the avoidance group and the relationship with higher peanut-specific IgE and noted component spreading, there are a few additional interesting observations to highlight in comparison with a general population frequency of this SNV of 8.6% (Table I), with a corresponding carrier rate of 16% (ie, proportion of the general population carrying at least 1 risk allele). We found that the overall carrier rate in the full group of LEAP participants (N = 559) is similar to that in the general population (12%); however, within the group of participants from the avoidance group who developed PA, this rate was considerably higher (35%), as previously published.[3] Interestingly, of the 7 participants within the consumption arm who had PA at baseline and therefore could not consume peanut, 3 were *MALT1* carriers, yielding a similarly higher carrier rate in this PA group of 43%. Only minimally higher carrier frequency was noted in those excluded from the trial on the basis of a baseline skin prick test result greater than 4 mm (16% in the Peanut Allergy Sensitization group IV [PAS IV] vs 12% in LEAP and 16% in the general Exome Aggregation Consortium [ExAC] population [Table I]). Moreover, within group IV, there was a lack of a positive association between *MALT1* and PA at 60 months of age (OR = 0.69 [95% CI = 0.12-4.1]). We also found a high carrier rate in the participants from the LEAP consumption arm who were unable to adhere to peanut consumption; 31% of the children who failed to sustain oral consumption were *MALT1* carriers in contrast to 12% of those who were randomized to consumption and successfully completed the trial, which is an almost triple carrier rate of enrichment. Collectively, all of these observations continue to support the role of *MALT1* in risk for PA, with a role for interaction with environment as originally reported.

There are some less-supporting observations to report for these carrier frequencies. Participants who were not included in the LEAP trial because of no severe eczema or egg allergy (Peanut Allergy Sensitization group I [PAS I]) had a higher carrier rate than the LEAP trial participants did (27% vs 12%). We did find an elevated carrier rate in the Peanut Oral Immunotherapy Study: Safety, Efficacy and Discovery (POISED) trial participants (carrier rate 19%), but we did not observe any elevation in the Oral Immunotherapy for Induction of Tolerance and Desensitization in Peanut-Allergic Children (IMPACT) trial (carrier rate 12%).[24,25] Although collectively the evidence for *MALT1* in LEAP points to elevated risk for PA, as described earlier, our estimated high risk (OR = 10.99)[3] is probably specific to the group of children who come from higher-risk backgrounds. With likely true population-based ORs in the range of those for the other identified PA genes (eg, *FLG* and *HLA* OR = ~2), these noted patterns of carrier rates among the high- and low-risk groups excluded from the LEAP study were not unexpected. Given the multiple strong observations across nonoverlapping participant samples from LEAP, our collective perspective on current data continue to support a role for *MALT1* in PA risk, especially in the context of oral peanut exposure avoidance.

*HLA-DQA1*0102* AND PEANUT EXPOSURE: A QUALITATIVE INTERACTION FOR PA RISK

The HLA locus is one of the most replicated genomic regions for allergy. Notably, whereas the locus is generally implicated for allergic phenotypes across the atopic march, specific HLA alleles themselves tend to be associated with specific allergen response. Given that HLA alleles are involved in peptide antigen presentation to T cells, the observation of specific risk alleles for PA[1,26,27] is expected. In the LEAP study, a particular polymorphic HLA class II gene allele, which may actually be reflective of a haplotype, *HLADQA1*0102*, had an OR of 1.99 (P = .04) for PA in those LEAP participants who avoided peanut, similar to previously reported GWAS findings for this allele.[2,26] Unexpectedly, this allele was also shown to have a potentially protective effect against the development of PA in the context of peanut consumption.[2] A strong genetic association was identified between rise in *Arapis hypogaea* 2–specific IgG4 and *HLA DQA1*0102*, a relationship seen only in children who regularly consumed peanut, all of whom were tolerant of peanut in the LEAP outcome assessment (β = 0.42 [P = 1.69E–05]). The fact that this same HLA allele was also associated with PA in LEAP participants who avoided peanut—and has previously been reported as a PA susceptibility gene—suggests a functional role for specific HLA genes as a peanut recognition restriction element, consistent with the known role of this locus in antigen presentation. Thus, a strong gene-environment. interaction in

TABLE I. Frequency of the minor (T) allele and carrier rate (TT/TG genotype) at the MALT1 SNP (rs57265082) across relevant data sets

	Data set					
Frequency	**ExAC***	**LEAP (N = 559)**	**PAS I† (N = 49)**	**PAS IV‡ (N = 55)**	**IMPACT (N = 126)**	**POISED (N = 118)**
T allele frequency	8.56%	6.35%	13.27%	8.18%	7.14%	10.17%
Carrier frequency (TT or TG)	16%	12%	27%	16%	12%	19%

ExAC, Exome Aggregation Consortium; *PAS,* Peanut Allergy Sensitization.
*In ExAC the carrier rate was calculated by using the Hardy-Weinberg equation.
†PAS I is characterized by the absence of egg allergy and severe AD, excluded from the LEAP trial.
‡PAS IV is characterized by a skin prick test result greater than 4 mm, excluded from the LEAP trial.

the form of peanut consumption may be an indication of a direct structural interaction between an HLA molecule and peanut peptide epitopes delivered through the oral route, resulting in immunomodulatory IgG4 responses.

This protective role of *HLA-DQA1*0102* appears to be dependent on age at which peanut consumption is initiated. An interaction between HLA genetic risk alleles and age of onset of disease is not unique to PA and has been described in autoimmunity as well.[28-32] Age is a critical factor in OIT, with durable nonresponsiveness to peanut achieved in LEAP through initiation of OIT during the first year of life, and partially in IMPACT through initiation of OIT between 18 and 48 months of age.[15,25] Notably, in the latter study, although most children were successfully desensitized by OIT, remission after discontinuation of therapy was predominantly achieved by initiating therapy in the 18- to 30-month time frame, not in children between 30 and 48 months of age. This same time juncture, approximately age 30 months, corresponds to the acquisition of additional epitope specificities in the peanut-specific IgE response.[33] The *HLA-DQA1*0102* findings were echoed in the IMPACT trial, in which carriers had higher peanut-specific IgG4 levels and were more likely than noncarriers to achieve desensitization and remission of PA (93% vs 78% and 35% vs 22%, respectively).[34] In the POISED trial, carriers were more likely to achieve desensitization and sustained unresponsiveness; however, there was no association with peanut-specific IgG4 level, and the results were not statistically significant.[34] The fact that the *HLA-DQA1*0102* genetic association with therapeutic response seen in LEAP and IMPACT was not recapitulated in POISED, a peanut OIT study conducted in adolescents and adults suggests that genetic influence for peanut OIT is most relevant during very early childhood, waning in older subjects coincident with determinant spreading, likely in conjunction with environmental modulation that abrogates this genetic predisposition.

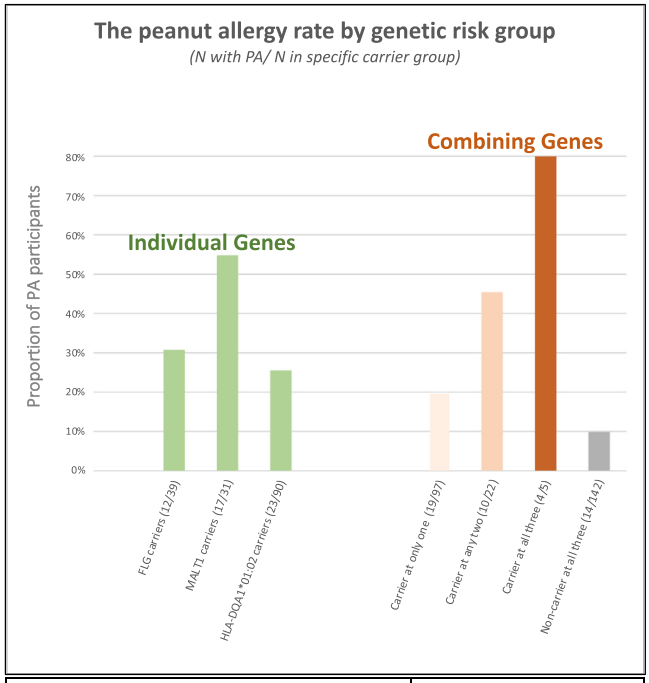
A CUMULATIVE GENETIC SCORE FOR PA RISK

To develop a PA genetic risk score that may have translational value, cumulative risk across multiple genetic loci needs to be considered. The utility of genetic risk scores to risk stratify individuals and tailor intervention is now an often-discussed aspect of complex disease risk prediction[35] and has been most recently applied to AD, showing value in predicting not only AD risk but also severity.[36] The full idea behind polygenic risk scores is to leverage large well-powered GWASs and sum across numerous genetic loci accounting for the small but additive genetic risk effect size for the specific disease of interest.[37] Here, to offer some perspective on the potential utility of a genetic risk score for PA, we examine the scenario of LEAP participants carrying risk alleles at *FLG*, *MALT1*, and *HLA-DQA1* in an informal summative risk analysis. We first defined the carrier and noncarrier status at each of the 3 genes based on the prior findings described earlier and in detail previously.[2,3,16] We then combined carrier status across the 3 genes within the peanut avoidance group. Within each group of study participants defined on the basis of individual-gene or combined-gene carrier status, we determined the proportions of participants with PA and PA-free participants and obtained OR and *P* values (Fig 1 [see detailed note for carrier definitions and analysis]).

The highest single-gene risk for PA in the absence of sustained oral peanut exposure is for *MALT1*, followed by for *FLG* and *HLA-DQA1*0102*; the effect sizes differ slightly from those in the original reports, as here the genetic model is carrier versus noncarrier and not additive (0, 1, or 2 copies of risk allele). We observe a strong building of evidence for cumulative risk when looking at the proportion of subjects with PA within each carrier category: of who carry only 1 risk gene, 20% had PA; in those who carry any 2 risk genes, 45% had PA; in those who carry all 3 risk genes, 80% had PA; and in the group of participants that had no genetic risk at the 3 genes considered here, only 10% went on to develop PA (Fig 1). We are limited in our ability to generate formal risk prediction scores for PA; for that, one needs to use discovery and validation samples that are well powered to have more precise effect sizes that can be used to weight each risk allele carried by an individual. Our informal illustration here, just counting carrier status across 3 genes in the small LEAP study, does however reveal a pattern in which the greatest risk was noted in the participants who carry risk variants for all 3 genes (*MALT1*, *FLG*, and *HLA-DQA1)* (OR = 25.12 [*P* = 7.33E–03]) in contrast to those who carry risk variant at only 1 (*MALT1* or *FLG* or *HLA-DQA1)* (OR = 3.13 [*P* = 1.94E–03]). This offers some perspective on the potential for such types of approaches in the future.

IMPLICATIONS FOR PREVENTION AND TREATMENT

There are several potential direct clinical implications of the genetic findings from the aforementioned trials. The first is that there appear to be stages of PA dependent on genetics and age that determine the trajectory of PA (Fig 2). Variants in *FLG* present a very early genetic risk stage, associating strongly with the first steps of the atopic march, AD, and allergen sensitization. Variation in *MALT1* adds the risk for rapid allergen-specific component spreading and the development of food allergy. Finally, *HLADQA1*0102*, although a risk factor for PA in the context of avoidance, presents the possibility of favorable outcomes through early consumption. Elucidating an individual's genetic risk factors provides a unique opportunity for personalized medicine



Genetic Carrier Status	OR	P-value
MALT1 (rs57265082)	10.97	3.04E-07
*HLA-DQA1*0102*	2.10	3.83E-02
FLG (score)	2.54	3.06E-02
Carrier at one or more	3.13	1.94E-03
Carrier at any 2 or more	7.86	1.57E-05
Carrier at all three: *MALT1*&*HLA*&*FLG*	25.12	7.33E-03

FIG 1. Genetic determinants of PA in the peanut avoidance, per-protocol group from LEAP. *Upper box,* Green bars represent the proportion with PA among carriers of each individual gene. Peach bars represent the proportion with PA collapsing across 3 candidate genes (*FLG*, *MALT1*, and *HLA-DQA1*). *Bottom box,* OR estimates for PA within each single gene and multi-gene carrier category. *Detailed note*: Definitions of carrier were created for each of the 3 genes on the basis of prior findings[2,3,16]: for *MALT1,* carrier was defined as participants carrying at least 1 copy of the T allele at rs572650820; for *FLG,* carrier was defined as participants carrying at least 1 deleterious allele of 4 variants (p.R1798*, p.R501*, p.S126*, and p.S761fs); and for *HLA,* carrier was defined as participants carrying at least 1 copy of the *HLA-DQA1*01:02* allele. A simple combined carrier status across the genes was also generated, creating 4 groups of individuals: *G0,* noncarrier across all 3 genes (n = 142); *G1,* carrier at any 1 of the genes (n = 97); *G2,* carrier at any 2 of the genes (n = 22); and *G3,* carrier at all 3 genes (n =5). We generated ORs and *P* values for PA by using logistic models adjusting for trial inclusion criteria (egg allergy and eczema severity), age at baseline, sex, and the first 5 genetic principal components as covariates as previously described.[2,3,16] To provide an understanding that higher genetic score thresholds yield greater ability to risk stratify, ORs for PA are calculated for 3 types of gene carrier thresholds: carrier at any 1 or more (*G1* + *G2* + *G3* vs *G0*), carrier at any 2 or more (*G2* + *G3* vs *G0* + *G1*), and carrier at all 3 (*G3* vs *G0* + *G1* + *G2*). Participants with missing *HLA-DQA1*01:02* calls (n = 12) were not included in the *HLA*-only and combined gene analyses.

and allows for more informed medical decisions both before and after disease onset.

Identification of an individual's genetic risks may also present several potential therapeutic considerations, but there remain limitations and uncertainties before genetic prognosis becomes clinically actionable. Although FLG variants pose a risk for development of AD and food allergy, whether early control of AD will prevent the development of allergic disease remains unknown. Trials of emollient use in the prevention of AD and food allergy have had mixed results, potentially owing to differences in emollients used, identification of participants, and other factors.[38] The currently active Stopping Eczema and Allergy (SEAL) study is comparing the effect of preventive versus reactive management of AD flares in young infants on the impact of progression of AD and development of food allergy (ClinicalTrials.gov identifier NCT03742414). For those with the greatest risk, skin barrier protection plus consistent oral consumption may be necessary to prevent the progression to allergic disease.

Identification of *MALT1* carrier status aids in differentiating those who will progress from sensitization to development of PA.[3] Further research is needed to understand and replicate *MALT1*'s association with PA in high-risk cohorts with severe eczema and/or egg allergy and then determine whether modulating the activity of *MALT1* will prevent PA or other allergic diseases.

The peanut-specific *HLA-DQA1*0102* allele perhaps has the most direct and actionable therapeutic implications. Data from LEAP suggest that this PA risk allele provides the unique opportunity for prevention of PA in the context of peanut consumption, as well as an increased risk of PA with avoidance.[2] Early OIT in PA carriers may even lead to tolerance.[34] The bidirectionality of this allele provides an intriguing opportunity to harness genetic risk to develop specific therapeutics, potentially in the form of peanut peptide immunotherapy.

These individual genetic risks are best interpreted in combination with each other, the age of the individual, and the opportunity for peanut consumption (Fig 2). The LEAP trial demonstrated that oral consumption prevents PA for most children; however, some children develop PA very early, before introduction of solid food, or shortly thereafter. Carriers of multiple genetic risk alleles may increase this risk, as demonstrated by the increasing risk of PA with increasing carrier burden (Fig 1). Therefore, early introduction is paramount in genetically susceptible individuals. It may be that for those with the greatest risk, early introduction alone is insufficient to prevent PA. Further, as age increases, the window for modification of risk through peanut consumption seems to close. For older children and adults with established PA or highest-risk genetics, the addition of tolerogenic adjuvants, such as mAbs, other biologic agents, or other immunomodulatory drugs, in conjunction with peanut consumption are likely needed to allow for desensitization and durable clinical benefit to occur.

FUTURE DIRECTIONS

Much remains unknown about how the aforementioned genetic risks lead to the development of allergy, and further work is needed to develop a broadly applicable PA risk prediction score. First, there are likely other relevant genes for PA, including those described in a recent comprehensive review of the genetics of allergic disease,[1] which may be key for the development of a PA genetic risk score applicable to the general population. It may be that the varying clinical phenotypes of PA will provide important clues in the development of risk prediction tools. A recent analysis of the LEAP and the Enquiring about Tolerance (EAT) study described participants with several phenotypes of PA, including those who develop persistent PA in the first year of life, those who develop PA after the first year of life, and those in whom

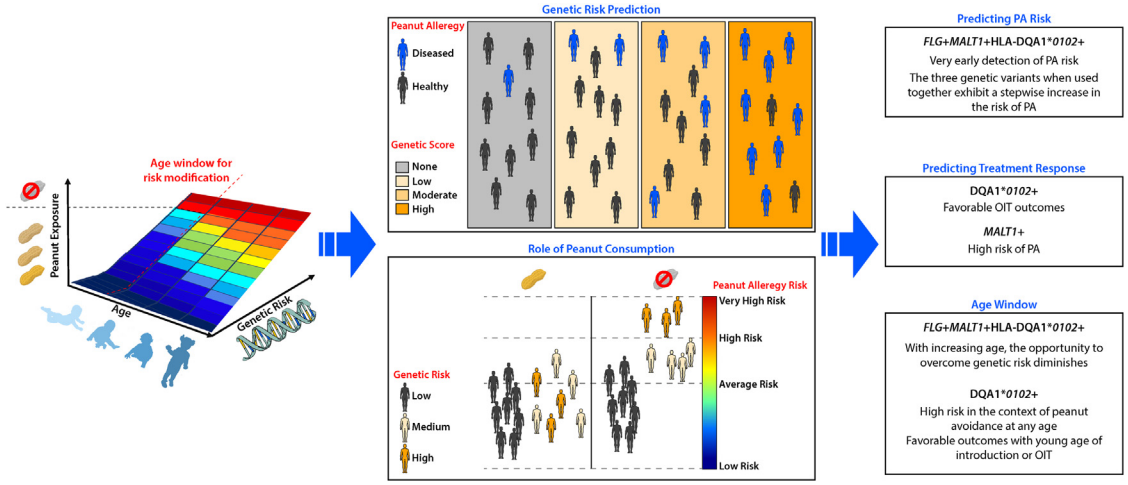


FIG 2. Interplay of the effects of peanut consumption, age, and genetic risk on the development of PA and response to OIT. A perspective on the relationship between genetic risk for PA (z-axis), the age at oral exposure to peanut (x-axis), and the environment interaction that modifies genetic risk (y-axis) is offered (*left panel*). Low risk for PA is presented in dark blue, with a gradation to high risk for PA in dark red. This panel is a simplification that does not cover the entirety of the 3 axes but instead serves to show the complex interplay of these variables. The *upper center panel* illustrates the enrichment of subjects with PA by genetic risk prediction, and the *bottom center panel* demonstrates modified risk with oral exposure. The *right panel* offers perspective on the utility of incorporating genetics in PA based on lessons learned from LEAP. The bottom center panel is adapted from Torkamani et al.[35]

PA resolves.[39] Overlaying genetics on the different phenotypes of PA will further our understanding of how these genetic risk factors may influence the trajectory of PA.

Importantly, any genetic score for PA, or food allergy in general, needs to consider a much wider range of genetic variants genome-wide and potentially consider other risk signatures derived from multi-omics integration characterizing molecular profiles beyond genetic risk.[40] Although GWASs for PA and food allergy that can be leveraged for these genetic scores are available (reviewed in Kanchan et al[1]), evidence from larger well-powered resources (eg, newer, larger GWASs that address environmental exposure or existing biobank data integrating genetics with electronic medical records) need to be considered. An approach to overcome this current limitation in existing GWASs for food allergy may be to "borrow" evidence across atopic march genetics, as much larger studies exist for other phenotypes such as AD and asthma.[41-44] For example, it has been recently shown that there is greater accuracy to predicting AD risk and AD severity when genetic risk prediction is built by including GWAS evidence from multiple atopic march phenotypes (ie, asthma, AD, and allergic rhinitis) in contrast to GWASs from only AD.[36] To address the current limitations in genetic studies available for PA, approaches such as these that consider genetic evidence across the atopic march may similarly assist not only in predicting PA risk but also in identifying those individuals who may have the greatest benefit from OIT. Yet another approach to borrow evidence could come from systems biology studies such as those proposed within the National Institute of Allergy and Infectious Diseases–funded Systems Biology of Early Atopy (SUNBEAM) study (ClinicalTrials.gov identifier NCT 04798079). As demonstrated recently for asthma, multi-omics approaches combining genetics, transcriptomics, and epigenetics can reveal context-specific (eg, rhinovirus) genetic mechanisms for childhood onset,[45] and omics signatures can help identify disease endotypes.[46] Similarly, an integrative multi-omics approach to defining genes for food allergy and PA can be a powerful tool to hone in on additional risk profiles for PA, but importantly it can also identify additional genomic signatures that can be integrated with genetic scores to improve their utility in predicting risk, severity, and even response to therapy.[40]

Second, the role of the environment cannot be discounted, as evidenced by the impact of early introduction to overcome much of the genetic risk of *FLG*, *MALT1*, and *HLA-DQA1* in the LEAP peanut consumers. In addition to age, genetics, and oral consumption, other factors should be considered, including household exposure, colonization with *Staphylococcus aureus*, microbial diversity, among the many environmental factors that likely contribute to the development of PA.[47,48] Considering how other environmental variables and the microbiome influence development of allergy or tolerance will be important, and incorporating age with all of these compartments of evidence will be critical to understanding how to tailor therapy to genetic risk.

Finally, a better understanding of the mechanistic pathways by which PA develops and persists is needed to derive targeted therapeutics for established disease. We need better understanding of mechanisms of antigen presentation, whether by skin or gut, that lead to the development of allergy or tolerance. We need to understand why peanut and other food allergies persist even in the absence of continued antigen exposure. Further, we need to understand why genetic risk appears to be modifiable by oral exposure in only the first few years of life. By understanding the mechanisms by which PA develops, persists, and resolves, we may be able to identify adjuvants to OIT that make older children and adults immunologically similar to their younger, more malleable counterparts and thus more likely to achieve long-term tolerance.

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