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# One march, many paths: Insights into allergic march trajectories

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## Abstract

**Objective:** The classical allergic march model posits that atopy begins in infancy with atopic dermatitis and progresses to asthma and allergic rhinitis in a subset of individuals. The growing prevalence and severity of allergic diseases has prompted renewed interest in refining this model. This review outlines epidemiologic evidence for the existence of allergic march trajectories (distinct paths of atopy development in individuals), reviews the roles that genetics, environment, and disease endotypes play in determining trajectory outcomes, and discusses the clinical utility of the trajectory model.

**Data Sources:** PubMed search of English-language articles and reviews without date limits pertaining to the epidemiology, genetics, and immunologic mechanisms of allergic march trajectories and disease endotypes.

**Study Selections:** Studies and reviews were selected based on their high quality and direct relevance to the review topic.

**Results:** Recent work in the field has shown that IgE-mediated food allergy and eosinophilic esophagitis are components of the allergic march. Further, the field is acknowledging that variability exists in the number and sequence of allergic manifestations that individuals develop. These allergic march pathways, or trajectories, are influenced by genetic, environmental, and psychosocial factors that are incompletely understood.

**Conclusion:** Continued elucidation of the landscape and origins of allergic march trajectories will inform efforts to personalize allergic disease prevention, diagnosis, and treatment.

### Keywords

Allergic march; allergic march trajectories; atopic dermatitis; food allergy; asthma; allergic rhinitis; eosinophilic esophagitis

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## Introduction

Allergic diseases are among the most prevalent and increasing chronic medical conditions in both children and adults.[1] The allergic (or atopic) march serves as an important paradigm for understanding the natural progression of T helper type 2 ($T_H2$) cell-mediated allergic diseases. Classically, the march begins in infancy with atopic dermatitis (AD) and progresses to IgE-mediated food allergy (IgE-FA), asthma, and allergic rhinitis (AR). Recent work indicates that eosinophilic esophagitis (EoE) is also a manifestation of the allergic march that is typically diagnosed towards the latter portion of the progression.[2] This paradigm has provided important insights into the relationship between these highly prevalent and immunologically-linked conditions.

Though it has some utility in gauging a child's risk of developing allergic multimorbidity,[3] the classical march sequence also has limitations.[4] Most notably, it was historically informed by population-level studies which suggested a stereotyped progression that began with AD.[5] To the practicing allergist, however, it has long been apparent that there is considerable variability in the number and sequence of allergic conditions that individuals develop.[3,5] The basis for this heterogeneity in allergic march pathways, or trajectories, is not well understood and is likely the result of a complex interplay of environmental, genetic, and psychosocial factors (Figure 1).

Here we review epidemiologic evidence supporting the existence of distinct allergic march trajectories, as well as insights into the major genetic and environmental factors that influence allergic outcomes. We discuss clinical applications for this paradigm and highlight important knowledge gaps including those relating to mechanisms of allergic sensitization and allergic march progression, as well as the need for a more nuanced understanding of the role that allergic disease endotypes play in determining trajectory outcomes. This review is relevant to both clinicians and experimental scientists, as it provides a framework for understanding march trajectories and pursuing investigations of their cause and consequence.

## Epidemiologic evidence for allergic trajectories

A seminal study that highlighted heterogeneity in allergic developmental profiles used Bayesian machine learning and latent class analysis to analyze data from two pediatric birth cohorts.[6] The authors reported eight distinct developmental profiles of AD, wheeze, and AR. While 48.3% of children exhibited some form of allergic disease, only 7% followed trajectory profiles resembling the classical allergic march. Limitations of this study included cohort size, survey-based nature of diagnosis, and number of allergic conditions considered. Nevertheless, this study was among the first to highlight the existence of distinct allergic trajectories among individuals.

A number of epidemiologic studies that utilize heterogenous methods and disease definitions have since been published that further support the concept of allergic march trajectories. As AD onset often occurs early in life, most longitudinal prospective cohort studies of children have considered AD as the origin of the allergic march and considered trajectories

that emerge after AD diagnosis. Supporting this approach, AD was found to be the first allergic manifestation in 60.7% of UK children who were followed through age 18.[7] In the same study, AD-asthma-AR was the most common allergic trajectory, though IgE-FA and EoE were not considered. Of note, this study identified 14 additional trajectories, with asthma and AR occurring as the first allergic manifestation in 20.4% and 10.5% of allergic children, respectively.[7] A second pediatric cross-sectional analysis also supported a strong relationship between AD and subsequent development of respiratory allergy, as the authors observed that AD, asthma, and AR coexist to a greater degree than would be expected due to chance alone.[8] Moreover, this study found that allergic comorbidity at age four was associated with comorbidity four years later in a dose-dependent fashion.[8] Together, these studies support the sequence of AD to respiratory allergy (asthma and/or AR) as a predominant allergic trajectory (Figure 1), while simultaneously challenging the notion that it is the only pattern of allergy development.

Subsequent studies have provided more nuanced information regarding potential modifiers of the AD-to-respiratory allergy trajectory. In a prospective pediatric birth cohort study, very early-onset AD and persistent AD significantly increased risk of developing asthma and AR.[9] Interestingly, late-onset AD in this study also increased risk of asthma, but not AR. In another prospective study examining children with AD, 43% developed asthma and 45% developed AR by age seven.[10] In this case, severe and early-onset AD were both associated with increased risk of sensitization to food and aeroallergens.[10] These findings echo those of a multi-ethnic population-based prospective cohort study that found that early and persistent AD increased risk of physician-diagnosed food allergy.[11] There are also alterations to the skin that occur in the absence of clinically apparent AD that may facilitate allergic sensitization.[12,13] For example, compared to non-allergic individuals, subjects with peanut allergy and no AD history have reduced skin content of cis-urocanic acid and pyrrolidone carboxylic acid, features typically seen in non-lesional skin of AD patients.[13] Together, these observations suggest that certain AD endotypes may alter progression on the march (Figure 1).

Allergic landscapes in adulthood are less clear than in childhood. Conceptually, childhood allergic disease that is outgrown may be distinct from disease that either develops or persists later in life. It is likely that non-allergic co-morbidities influence allergic trajectories and outcomes in adulthood. These complexities are highlighted in a latent class analysis of subjects aged seven to 53 with asthma and comorbid allergies (AD, IgE-FA, and/or AR) in the Tasmanian Longitudinal Health Study.[14] Data on lung function and presence of chronic obstructive pulmonary disease (COPD) was also considered. In this study, five trajectories with varying severities and durations of asthma and allergies were reported. Two trajectories ("early-onset persistent asthma and allergies" and "late-onset asthma and allergies") were specifically associated with COPD. The latter was also associated with the presence of other co-morbidities such as psychiatric illness, hypertension, and gastroesophageal reflux disease.[14] This study highlights the need to account for comorbid disease, and the possibility of allergic disease misdiagnosis, when studying the course of allergic trajectories in adulthood.

Although allergic asthma and AR are often clinically associated, the existence of comorbid AD, asthma, and AR is rare in adults. A recent study of Swedish adults showed that about 2% of the general population have concomitant AD, asthma, and AR, a rate that increased to about 6% in sensitized adults.[15] The finding that sensitization modifies disease risk was also found in a multiplex component analysis of European adults with AR, in which total IgE levels and IgE polysensitization to aeroallergens were most predictive of allergic multimorbidity (AR plus AD and/or asthma).[16] Polysensitization was associated with allergic multimorbidity (AD, asthma, and AR) to a larger extent in children than in adults in a Polish cohort.[17] In a separate study, latent class analysis identified five patterns of sensitization and pediatric allergic morbidity (AD, asthma, or AR).[18] Early onset and persistent sensitization were associated with AD, while early onset and transient sensitization were associated with increased asthma risk. Finally, sensitization to house dust mite allergen was linked to increased risk for both asthma and AR.[18] Together, these studies further demonstrate the importance of age of onset and the modulatory role of allergic sensitization in predicting allergic multimorbidity.

Characterizing respiratory allergy endotypes has recently been facilitated through the use of cluster analyses. Examining children with differential profiles of wheeze and/or asthma, Tang *et al* identified a high-risk group with persistent wheeze, very early allergic sensitization, and frequent respiratory infections.[19] Two lower-risk clusters were collectively associated with lower IgE levels, minimal allergic sensitization, and infrequent wheeze.[19] Recapitulating the challenge of characterizing allergic disease outcomes in adults, a recent cluster analysis identified three distinct endotypes (C1–C3) of adult asthmatics.[20] C1 asthmatics exhibited active asthma, poor lung function, elevated body mass index, and high blood neutrophil count and had poor outcomes. In contrast, C2 asthmatics exhibited mild asthma and rhinitis symptoms, while C3 asthmatics had inactive or mild untreated childhood-onset asthma with high IgE levels.[20] The distinctive characteristics reported for pediatric versus adult respiratory allergy endotypes further support the concept of heterogeneity in allergic trajectories and highlight the need to identify clinical and molecular features that correlate with specific disease outcomes.

While initial definitions of the allergic march did not consider IgE-FA, it is now clear that it is an important constituent. In a systematic review, a strong and dose-dependent association was observed between AD and IgE-FA.[21] In some population studies, clinically proven IgE-FA occurred in up to 15% of subjects with AD.[21] AD has been linked to sensitization to food allergens, which occurs earlier in life as compared with sensitization to aeroallergens.[22] IgE-FA may also be an allergic trajectory modifier. In a Canadian birth cohort study, there was a strong positive additive interaction between AD and IgE-FA.[23] In addition, AD increased risk for asthma seven-fold but only in individuals sensitized to food or aeroallergens.[23] A subsequent study found that food sensitization in the first two years of life was associated with increased risk of asthma and AR, regardless of aerosensitization status.[24]

The fact that some children with IgE-FA, without a history of AD, progress on the allergic march begs the question of whether IgE-FA is an alternative mode of initiation on the march (Figure 1). Indeed, IgE-FA is an independent risk factor for AR and asthma, in

particular IgE-FA to peanut, milk, and egg.[25] Tolerance at the gut is mediated by a distinct milieu of immune cells (e.g. tolerogenic dendritic cells) and cytokines that collectively favor differentiation of T regulatory ($T_{Reg}$) cells and suppression of allergic responses (Figure 2A).[26,27] When this system of tolerance fails, immune mechanisms similar to those observed in cutaneous sensitization become relevant, including roles for the cytokines thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33 (Figure 2B,C).[27–29] The prospect of allergic sensitization at the gut as a distinct mechanism for allergy would expand the popular dual allergen exposure hypothesis that posits that food allergen-skin interactions promote IgE-FA, whereas food allergen-gut interactions yield allergic tolerance.[25,28] However, the genetic and/or environmental factors (e.g. microbiome, dietary exposures) that skew immune responses to favor gut sensitization necessitate further investigation.

Finally, recent studies have uncovered a particularly strong relationship between IgE-FA and the chronic esophageal disorder EoE. In a pediatric virtual birth cohort study, children with IgE-FA exhibited a nine-fold increased risk of ultimately developing EoE.[2] The study also found that personal history of AD, IgE-FA, and asthma independently and cumulatively associated with increased rate of developing EoE, findings that collectively support a role for EoE as a late-diagnosed member of the allergic march.[2] The increased prevalence of the major allergic conditions in patients with EoE is corroborated by recent studies, including a meta-analysis and a multisite registry analysis examining children and adults with EoE.[30,31] Continued investigations of the immunopathology of EoE will likely uncover additional mechanistic links between it and the other allergic manifestations.

## Influence of genetic factors on allergic trajectories

The importance of inherited genetic factors in predisposing to atopy is well established, although it is not fully clear how they contribute to specific allergic trajectories. In one study, mother-child dyads demonstrated a dose-dependent association between maternal and childhood allergic diseases; the strongest associations were seen for identical allergic disease (asthma and AR), whereas non-identical diseases exhibited weaker associations.[32] In another prospective cohort study performed in Sweden, history of allergy in both biological parents predicted allergy development at 10 years of age, though heredity did not associate with allergic disease burden.[33] These studies highlight the role of genetics as a critical, though not exclusive, determinant of allergic outcomes.

The availability of large-scale genome wide association studies (GWAS) has revolutionized the ability to identify allergic risk loci. To date, these have uncovered an array of genes and intergenic variants with predicted functions that encompass innate and adaptive immunity, epithelial barrier integrity, cellular signaling, and gene regulation (Table 1).[34–37] Of note, many genetic variants identified in these studies are associated with multiple allergic manifestations. Despite this, it is challenging to determine the impact of specific genetic variants on distinct allergic trajectories, as individuals with various combinations of allergic manifestations are often grouped into a single disease outcome category. Additionally, temporal disease relationships are unclear, disease phenotypes are often self-reported, and all known allergic march manifestations are rarely studied simultaneously.

Despite these shortcomings, important insights into how genetic factors may shape allergic trajectories can be gleaned from existing genomic studies. For example, focusing on susceptibility variants previously associated with AD and EoE, Hirota *et al* investigated their associations with childhood IgE-FA. 14 genetic loci exhibited significant associations (Table 1).[38] The strongest association for subjects with AD and IgE-FA occurred for a *KIF3A/IL13* variant, consistent with the critical role of IL-13 in IgE-mediated allergic responses.[38] Notably, the IL13-dependent locus *CAPN13* has been more recently associated exclusively with EoE.[39] It is plausible that such differences in gene pleiotropy contribute to differences in allergic outcomes and, thus, heterogenous allergic trajectories.

Focusing on susceptibility to AD, asthma, and AR, a series of seminal GWASs have uncovered a shared set of risk genes with functions that include immune cell signaling and epidermal differentiation (Table 1). In two separate GWASs, Ferreira *et al* previously reported over 150 associated genetic variants.[35,36] Remarkably, very few variants (affecting *FLG, IL2RA, GSDMB*, and several intergenic regions) exhibited differential disease-specific effects.[35] The observed association between AD and variants of *FLG*, which encodes the keratin-binding protein filaggrin, corroborate the knowledge that *FLG* variants are permissive for progression of atopy specifically in the setting of AD.[40,41] Another GWAS performed by Johansson *et al* identified 41 additional novel loci.[37] While most risk loci were associated with the combined phenotype of AD, asthma, and AR, 20 loci were more significantly associated with AD and AR, and 16 loci had stronger effects on asthma.[37] Among the variants with differential disease effects were two SNPs in the intron of *IL2RA*; rs12722547 was more strongly associated with asthma than rs61839660.[37] These studies indicate that a set of immunologically important genes is shared in predisposition to multiple allergic manifestations, with some genetic variants exhibiting differential effects on allergic outcomes.

Using a reductionist approach, a recent analysis examined genotype associations with pediatric allergic trajectories that begin with AD.[42] Four single nucleotide polymorphisms (SNPs) were associated with distinct allergic trajectories and were also linked to specific demographic features, including self-identified race and sex.[42] Interestingly, all identified SNPs affect non-coding parts of the genome, suggesting regulatory functions. One of the SNPs, rs60242841, was associated with the AD-to-asthma trajectory and was more common in individuals of African ancestry than European ancestry.[42] This study sheds light on the complex role of genetics in driving heterogenous allergic outcomes. As race is a social construct, the study also highlights the need to consider concomitant modifying factors, including psychosocial factors. In sum, while important progress has been made in identifying allergic risk loci, studies that examine genotype associations with specific allergic trajectories of interest are warranted.

## Influence of environmental factors on allergic trajectories

The growing prevalence of allergic disease has sparked interest in understanding how exogenous and potentially modifiable factors facilitate allergy. As infants are uniquely vulnerable to the effects of dysbiosis,[43] there has been particular interest in identifying early-life modifiers of microbial colonization that predispose to allergy. While there are

varying degrees of evidence for vaginal delivery, breastmilk-based diet, and early-life avoidance of antibiotics and/or antacids in preventing atopy,[43–46] there is paucity of data on how these factors impact specific allergic disease trajectories. In a recent study examining effects of these factors on allergic multimorbidity (AD, IgE-FA, asthma, and/or AR), vaginal delivery, breastmilk feeding, and avoidance of antibiotics and antacids were associated with reduced rate of developing at least three allergic manifestations.[47] Whether early-life factors favor specific allergic trajectories, and what their impacts are on EoE, remain to be determined.

The effects of dysbiosis extend beyond the gastrointestinal tract. For example, analysis of *Staphylococcus aureus* colonization in the nares revealed a direct correlation between colonization and sensitization to either egg or peanut, regardless of AD severity.[48] Other examples of dysbiosis in allergy include the esophageal microbiome in EoE, which exhibits high prevalence of *Haemophilus* species.[49] In the respiratory tract, pharyngeal colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxhella catarrhalis* has been associated with early-life asthma.[50] Longitudinal analyses with sampling at various mucosal sites will be needed to further dissect microbial effects on specific allergic trajectories.

Another important environmental factor that can influence allergic trajectories is infant diet and timing of allergic food introduction. The hallmark Learning Early About Peanut (LEAP) Allergy trial motivated recommendations for early peanut introduction in patients with high risk of peanut allergy.[51] The success of this approach is likely due to anatomical differences in immunologic responses that mediate tolerance versus sensitization (Figure 2). While early study of the effects of peanut consumption by at-risk infants does not appear to support a role in reducing allergic disease burden beyond peanut allergy,[51] further studies of early food introduction cohorts is warranted.

Various ambient exposures (e.g. pollutants, endotoxin, dust, and viruses) have also been found to modulate allergic susceptibility.[52] For example, air pollution associated with urban environments is thought to cause epigenetic changes and immune dysregulation that lead to increased risk of AD and asthma.[52,53] Conversely, elevated endotoxin levels observed in rural environments and in the setting of early-life animal exposure are associated with lower risk of respiratory allergy and allergic sensitization.[52] This effect was validated in a landmark study that examined allergic outcomes in Hutterites and the Amish, who share a similar genetic background but have distinct farming practices.[54] As further evidence of the importance of microbial exposures to allergic outcomes, asthma risk is decreased in children living in urban areas where microbial composition of dust resembles that of children living in rural areas.[55]

It is well established that allergic diseases are associated with significant economic costs and impairments in quality of life, factors that disproportionately affect socioeconomically disadvantaged groups.[56] Highlighting an important role for racial disparities in driving differential health outcomes, black children suffer from higher allergic burden than white children, even when accounting for socioeconomic status.[57] Further, structural determinants (e.g. housing policies) are known to contribute to allergic health disparities.[58] Relevant

future directions for the field include standardizing methods used to assess disease burden, considering impacts of structural health determinants on differential allergic trajectories, and ensuring that future investigations of allergic march trajectories maximize socioeconomic and racial diversity.

## Relevance of allergic march trajectories to patient risk stratification and treatment

How genetic and environmental factors dictate allergic progression is a question of considerable scientific and clinical interest, as it is relevant to determining disease risk, prevention, and treatment. The ability to accurately model gene-environment interactions to predict an individual's allergic profile represents a holy grail of personalized medicine that may be coming within reach. This is primarily due to the recent revolution in "big data" approaches that have allowed the identification of novel allergic disease risk factors, endotypes, and biomarkers.[59] These data are especially valuable when partnered with unbiased machine learning methods that reveal otherwise unappreciated and testable patterns.[42] Through these efforts, it is conceivable that the next decade will see the introduction of a new generation of clinical risk assessment and disease stratification systems. In the following section, we provide some examples of clinical practices supported by current evidence and identify areas where more research is needed to inform clinical decision making.

Given that AD is the most common initiation point on the march, there is particular focus on identifying interventions that alter allergic progression of children with AD.[60,61] Compelling evidence demonstrates that risk of allergic sensitization to foods and environmental allergens correlates with AD presence and severity.[10–11,62] Further, multiple studies have now shown that early introduction of allergenic foods in children with AD prevents IgE-FA.[51,62] Despite this, evidence showing a benefit of AD treatment has been more elusive. A recent Cochrane review found that skin care interventions during infancy did not change an individual's risk of developing AD or the amount of time to onset of AD.[63] Recent studies specifically examining the role of AD treatment in preventing allergic progression demonstrate mixed results.[64,65] It is possible that such studies have not focused on the appropriate disease endotype(s) as outcomes. It is even less clear how such efforts will influence march trajectory outcomes later in life.

The realization that IgE-FA is a manifestation of the allergic march has increased the complexity and utility of the paradigm. For example, IgE-FA increases risk for being diagnosed with asthma and AR later in life,[23] which may help with patient risk stratification. Further, the risk relationship between IgE-FA and EoE is particularly strong, an observation that is useful both clinically and with regard to understanding the immunopathology of this condition.[66,67] As EoE is sometimes a complication of sublingual immunotherapy (SLIT) and oral immunotherapy (OIT), it should be considered in children who develop consistent symptoms during these treatments.[68] Given that some patents exhibit IgE-FA as their first allergic manifestation, it is conceivable that IgE-FA unpreceded by AD represents a distinct IgE-FA endotype. It is not known if early introduction of allergenic foods modifies

risk of development of allergic manifestations other than IgE-FA. Specifically designed prospective studies are needed to better understand how various IgE-FA endotypes associate with distinct allergic trajectories.[69]

Immunomodulation has long been an approach used in clinical allergy, and there is evidence that its benefits may extend beyond the primary condition(s) being treated. Indeed, a systematic review and meta-analysis of allergen immunotherapy observed a short-term benefit in preventing asthma in children with AR.[70] The introduction of several new biologics that block inflammatory pathways shared among multiple allergic manifestations holds additional promise for modifying allergic march trajectories. For example, the anti-IL4-alpha receptor antibody dupilumab has demonstrated efficacy in the treatment of AD, asthma, and EoE, and is being investigated for use in treating peanut allergy.[71,72] Similarly, the anti-TSLP monoclonal antibody tezepelumab is in clinical trials for the treatment of asthma.[73] As TSLP is an early regulator of $T_H2$ responses, it is conceivable that it may confer additional clinical benefits. Finally, there is an ongoing trial assessing the efficacy of the anti-IgE biologic omalizumab in preventing asthma in high-risk 2–3-year-olds,[74] the results of which are eagerly awaited. In sum, the potential for immunomodulatory therapies to affect, and possibly halt, the allergic march is high, though more detailed studies will be needed to ascertain effects on specific allergic trajectories.

## Conclusion

The concept of the allergic march is critical for understanding the natural patterns of allergic disease development as well as the pathophysiologic relationships shared among major allergic manifestations. The heterogeneity of allergic march pathways is attributable to the existence of multiple allergic disease endotypes, which reflect a critical and incompletely understood interplay between hereditary and exogenous factors. Despite this, evidence for two predominant trajectories is emerging: 1) AD to respiratory allergy (asthma and/or AR) and 2) AD to food allergy (IgE-FA and/or EoE). There may also be reason to consider trajectories starting with IgE-FA as a distinct entity. Several questions remain about the mechanistic underpinnings and clinical implications of allergic trajectories:

- To what extent is allergic sensitization in the gut responsible for distinct disease endotypes and march trajectories?
- How do genetic variants interact with each other and with environmental factors to yield specific allergic outcomes?
- Which patients warrant close surveillance for disease development, and how can the march be prevented?

Such questions will benefit from systems medicine studies that integrate epidemiologic, clinical, and “omics” data and further inform mechanistic experimental studies. It is also essential that future investigations include prospective, longitudinal studies that consider geographically and demographically diverse patient populations. Collectively, these efforts have the potential to revolutionize approaches in allergic disease prevention, diagnosis, and treatment.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

| | |
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| **AD** | atopic dermatitis |
| **AR** | allergic rhinitis |
| **COPD** | chronic obstructive pulmonary disease |
| **EoE** | eosinophilic esophagitis |
| **GWAS** | genome wide association study |
| **IgE-FA** | IgE-mediated food allergy |
| **IL** | interleukin |
| **LEAP** | Learning Early About Peanut |
| **OIT** | oral immunotherapy |
| **SLIT** | sublingual immunotherapy |
| **SNP** | single nucleotide polymorphism |
| **$T_H2$** | T helper type 2 |
| **TSLP** | thymic stromal lymphopoietin |

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### Learning Objectives

1. Recognize epidemiologic evidence supporting the existence of allergic march trajectories.
2. Be aware of the major genetic and environmental determinants of allergic march trajectories.

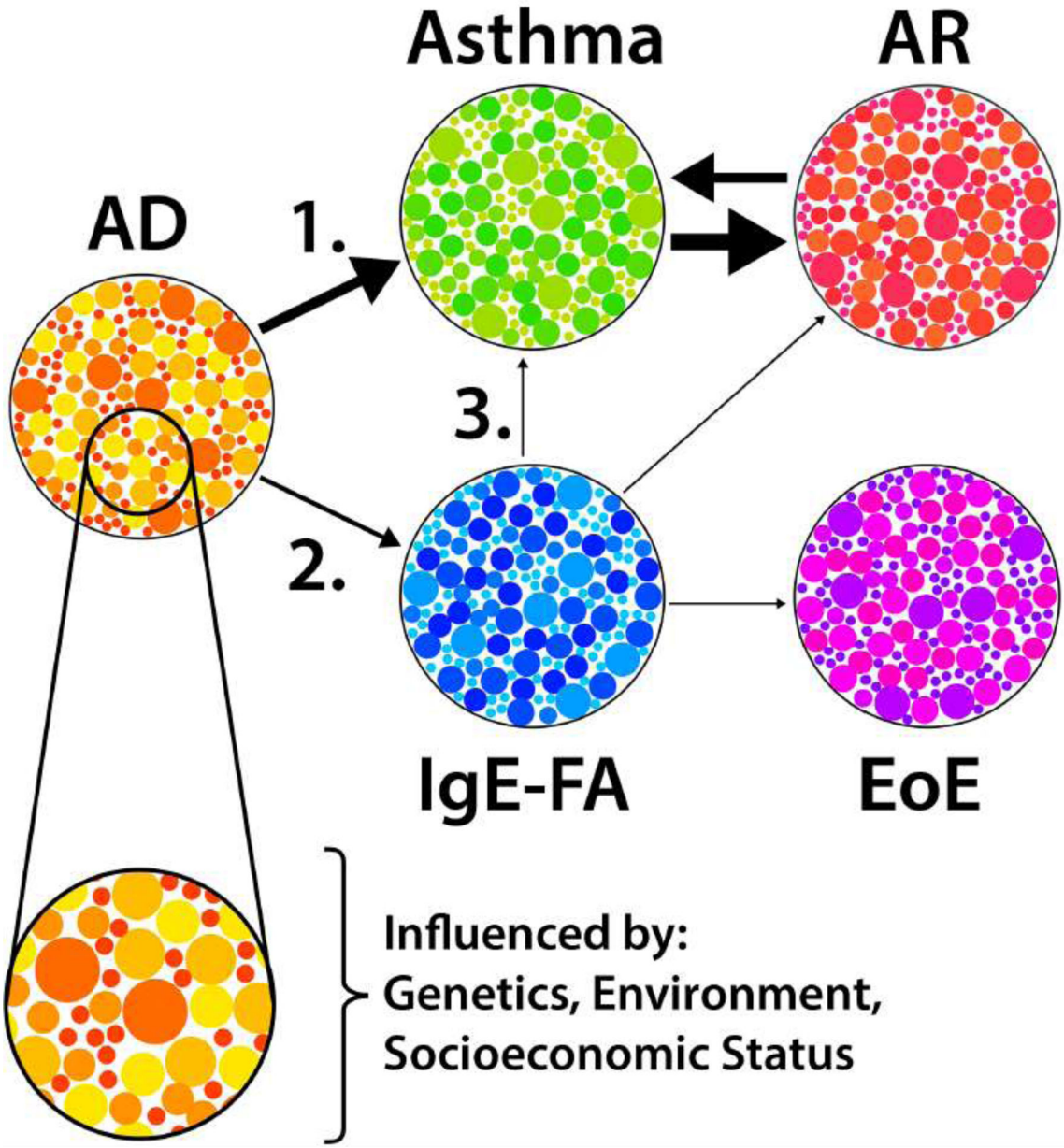


**Figure 1: Allergic march trajectories.**

Allergic diseases have distinct endotypes (small circles), and developmental trajectories (arrows) that are influenced by genetic, environmental, and psychosocial factors. The most common trajectories are shown. Arrow weight represents relative prevalence at our institution. AD, atopic dermatitis; IgE-FA, IgE-mediated food allergy; AR, allergic rhinitis; EoE, eosinophilic esophagitis.

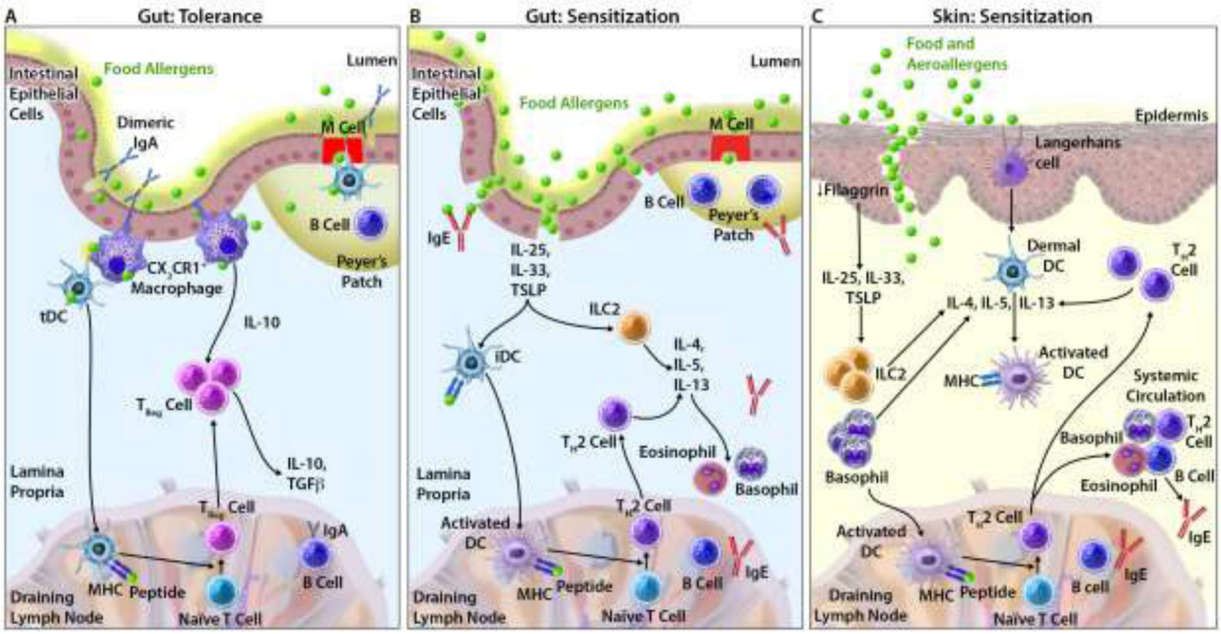


**Figure 2. Mechanisms of tolerance and sensitization.**

(**A**) Oral tolerance in the gut. (**B**) Allergic sensitization in the gut. (**C**) Allergic sensitization via the skin.

**Table 1.**

Susceptibility genes associated with two or more allergic march manifestations.[a]

| Allergic diseases | Susceptibility genes |
|---|---|
| AD, IgE-FA | *CCDC80, DEXI, IL21, KIF3A, NLRP10, OR10A3* |
| AD, IgE-FA, Asthma, AR | *CLEC16A, FLG, GLB1, IL2, LRRC32, OVOL1, SLC25A46, TNFRSF6B, ZNF365, ZNF652* |
| AD, IgE-FA, Asthma, AR, EoE | *EMSY (C11orf30), STAT6, TSLP, WDR36* |
| AD, IgE-FA, AR | *TMEM232* |
| AD, Asthma, AR | *AAGAB, ABCB9, ABO, AC004893.11, ACTR1A, ADAMTS4, AHI1, AK056081, ALOX15, APC1, APOBR, AQP5, ARHGAP15, ARHGAP27, ARL3, ARL6IP4, ASCL2, ATXN2L, B4GALT3, BATF3, BCL2L11, BCL6, BOLL, C1orf54, C22orf46, C5orf56, CAMK4, CCDC134, CCL20, CCR7, CD200R1L, CD247, CEP57, COL15A1, CRTC3, CSDC2, CSF2RB, CTC-551A13.2, CXCR5, D2HGDH, DC86, DLEU1, DYNAP, EAF2, EFEMP2, ERBB3, ERMP1, ETS1, F11R, FAM105A, FAM177A1, FAM76B, FBXW2, FCER1G, FOSL2, FOXO1, GFRA3, GNGT2, GPANK1, GSAP, GSDMB, HDAC3, HDAC7, HHEX, HIS1H2BD, HLA-C, HLA-DQA1, IKZF2, IL13, IL18R1, IL18RAP, IL1B, IL1RL1, IL27, IL2RA, IL4R, IL6R, IL7R, INPP5D, IPCEF1, IQCB1, IQGAP1, ITGB8, ITPKA, JAZF1, KIAA0391, KIAA1109, KLF2, LAT, LINC00284, LINC00299, LINC00393, LPP, MANBA, MAP3K14-AS1, MARS2, MCCD1P1, ME11, MFSD13A, MFSD9, MIR146A, MYC, MYL6B, NAB2, NCF4, NDFIP1, NDFIP1, NEK6, NFATC2, NFKBIA, NHP2L1, NOD2, NRROS, NSMCE1, NUDT12, OGFOD2, OR10J5, ORMDL3, PAG4, PAPOLG, PHF5A, PIGN, PITPNM2, PLCL1, PMM1, POLI, PPCDC, PPOX, PPP2R1B, PPP2R3C, PRR5L, PRRC2A, PSMD5, PTGER4, PTPRC, PTPRK, PVALB, PVT1, RAB24, RAD51B, RASA2, RASGEF1A, RBM15B, REL, RERE, RFTN2, RGS14, RIN3, RORA, RORC, RP11-132N15.1, RP11-132N15.2, RP11-24N18.1, RP11-264B17.4, RP11-534L20.5, RP11-554D20.1, RP11-770G2.5, RP11-94L15.2, RP4-1115A15.1, RPRD2, RPS26, RTEL1, RTF1, RUNX3, RYBP, SBNO1, SDK1, SENP7, SERPINB7, SH2B3, SIK2, SLC15A2, SLC22A4, SLC22A5, SMAD4, SMAD7, SNX32, SPATA32, SPNS1, SPPL3, STAT5B, STMN3, SULT1A1, SUOX, TARS2, TBL1XR1, THEM4, TIAM2, TLR1, TMEM180, TNC, TNFAIP3, TNFAIP8, TNFRSF14, TNFRSF8, TNFSF4, TRAF3, USF1, VDAC1, VPRBP, ZBTB38, ZDHHC12, ZNF217, ZPBP2* |
| AD, AR | *ANKRD46, ATXN2, BNC2, ETV7, HSPE1, IL31, LRRC43, MOB4, NOS3, TLR10* |

[a]Gene-disease associations were identified in previous genome-wide association studies.[34–39] Individuals with gene variants did not necessarily exhibit all listed allergic manifestations for a given gene. AD, atopic dermatitis; IgE-FA, IgE-mediated food allergy; AR, allergic rhinitis; EoE, eosinophilic esophagitis.