



Review

Phenotypes and endotypes in eosinophilic esophagitis

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Key Messages

- Eosinophilic esophagitis (EoE) shares many features with other atopic diseases such as asthma, including heterogeneity in its presentation, natural history, and response to treatment.
- Clinical and molecular evidence suggests that different eosinophilic esophagitis patient phenotypes and endotypes exist.
- Phenotypic variations in EoE include the age of onset, degree of atopic comorbidity, response to different forms of therapy, and disease severity, among others.
- Biomarkers that may provide insight into the mechanisms of EoE for defining endotypes include the presence or absence of systemic Th2 inflammation, genetic risk factors, and histologic findings.

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ABSTRACT

Objective: To improve understanding of the heterogeneous presentation of eosinophilic esophagitis (EoE), and its different potential phenotypes and endotypes.

Data Sources: We reviewed studies addressing EoE genetics, risks, natural history, treatment, phenotype, or endotype to assess data relating to differences in the presentation of EoE in children and adults. This review was restricted to articles in the English language.

Study Selections: Data source abstracts, pertinent articles, and book chapters meeting the objectives were critically reviewed.

Results: Data to support differing phenotypes and endotypes in EoE are emerging, but findings are based on multiple studies and therefore sometimes incomparable. Like other atopic disorders EoE is a complex disease with diverse clinical presentations (phenotypes) based on response to therapy, natural history, and association with atopic comorbidities. Different pathogenetic mechanisms (endotypes) may drive the multiple phenotypes. T Helper type 2 inflammation, epithelial barrier defects, enhanced fibrosis, and association with rare monogenetic diseases are the most described endotypes in EoE.

Conclusion: Eosinophilic esophagitis is an atopic disorder that is increasing in prevalence and can be difficult to treat. Better understanding of phenotypes and endotypes in EoE may enable future care to be individualized more effectively, resulting in shorter time to remission and fewer endoscopies.

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Introduction

Atopic diseases such as atopic dermatitis (AD), asthma, allergic rhino-conjunctivitis (AR), and food allergy (FA) are increasingly prevalent in westernized developed societies. Traditionally they were defined as a group of conditions that develop because of an inherited tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of commonly tolerated proteins known as allergens.¹

Despite this narrow definition, it is now clear that atopic diseases are quite variable in terms of observable clinical characteristics at presentation, also known as *phenotypes*. Indeed, atopic diseases differ in severity, natural history, response to therapy, and triggers. Allergic disorders can be mild or severe, begin during childhood with transient or persistent clinical trajectories, or may begin in adulthood.² Atopic disorders occur in the same subjects (multimorbidity) more often than expected by chance, but can present in isolation.³

For example, cluster analysis of patients with asthma recognizes 5 different phenotypes: early-onset atopic, obese non-eosinophilic, early symptom-predominant, inflammation-predominant, and lastly, a benign asthma phenotype.⁴ Patients with *benign asthma* were identified only in the primary care cohort and not in the secondary care cohort, and were identified by little evidence of active disease. Two categories of patients were observed in both the primary care and secondary care settings. Patients with the *early-onset atopic asthma* phenotype were characterized by eosinophilic inflammation and good response to anti-inflammatory asthma therapies. *Obese, non-eosinophilic asthma* patients demonstrated decreased lung function, low levels of inflammation, and poor response to anti-inflammatory agents. The final 2 clusters of patients were identified only in the secondary care cohort and captured patients with asthma refractory to traditional therapies. *Early symptom-predominant asthma* had an early-onset, highly symptomatic disease with minimal eosinophilic airway inflammation. In contrast, patients in the *inflammation-predominant* group were mostly male and had few symptoms with late onset of eosinophilic inflammation—predominant asthma. As this work illustrates, different pathophysiology and prognostic differences can be encompassed within the diagnostic criteria for asthma.

In the last decade, research has progressed significantly in the field of atopic diseases, and it has become clearer that they consist in diverse complex inflammatory conditions.¹ Heterogeneity in the pathophysiology underlying these atopic disorders can explain the variable presentation of the phenotypes within atopic disorders. Whereas the inherited tendency to produce IgE antibodies in response to allergens was once considered the singular pathogenic mechanism in atopic disease, a growing body of evidence suggests that non-IgE-mediated mechanisms play essential roles in modulating the presentation of all types of atopic disorders.⁵ These distinct functional and immunological mechanisms are also called *endotypes*.

One example of multiple pathogenesis in a single atopic disease is seen in asthma. Asthma patients can be broadly classified into 2 very different endotypes: those in whom airway inflammation is driven primarily by T helper 2 type (Th2) inflammation (Th2-high) and patients with minimal Th2 airway inflammation (Th2-low).^{6–8} The Th2-high endotype is most common, and the biologics currently approved for asthma treatment aim to treat this endotype. In contrast, the mechanisms driving the Th2-low endotype are currently less well understood, and treatment strategies specifically aiming at controlling the Th2 low endotype have not yet been proven to be effective.^{9,10} The development of endotypes such as Th2 inflammation depend on both genetic risk and environmental exposure factors, and therefore they may represent several complex steps of disease pathogenesis.⁵

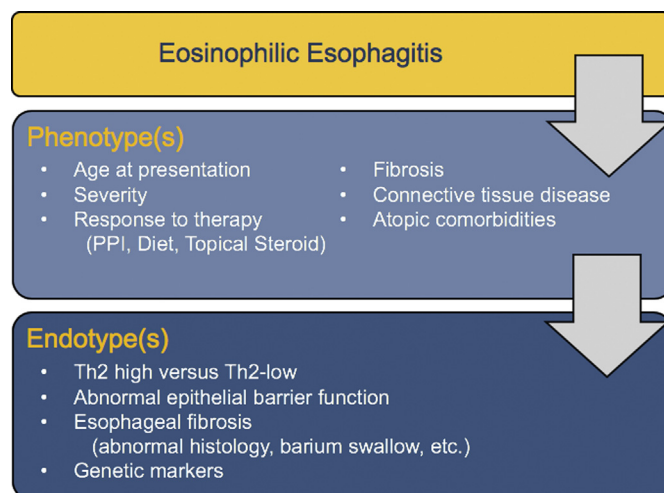


Figure 1. Schematic overview of potential considerations in phenotype and endotype classification in eosinophilic esophagitis.

Despite such complexity and diversity, treatment of atopic diseases has focused on guidelines that classify patients based on few clinical elements (“phenotype”) such as severity of disease, comorbidities, and response to therapy (ie, topical steroid and other anti-inflammatory therapies). Current efforts in the field have focused on advancing “precision medicine” by using both the patient’s phenotype and endotype to guide a truly individualized treatment.

Here, we analyze the current status of research regarding different phenotypes and endotypes in eosinophilic esophagitis (EoE), an increasingly described atopic disease. Several lines of evidence support the notion that EoE is an atopic disease. Eosinophilic esophagitis is characterized by Th2-predominant inflammation that tends to lead to fibrosis development. Cohort-based studies have shown that EoE is likely part of the atopic march, with increased risk of developing EoE if a prior comorbid atopic condition is present.¹¹ Chronic antigenic exposures from food and environmental allergens are a cause of EoE, and removing certain food antigens from the diet results in disease improvement.⁶

Because larger groups of EoE patients are being followed and described, EoE appears to be able to present with similar phenotypic heterogeneity to that seen in other atopic diseases. This variability is mirrored by multiple pathogenic pathways, or endotypes (Fig 1).^{7,8} Current efforts in the field have focused on advancing “precision medicine” in EoE. In this review, we analyze the current status of research regarding different phenotypes and endotypes in EoE, which in the future will form a foundation for truly individualized therapy in EoE.

Phenotypic Classification in EoE

Eosinophilic esophagitis is associated with symptoms of esophageal dysfunction and more than 15 eosinophils per high-powered field in at least 1 esophageal biopsy.¹² Based on the most current guidelines, the same type of initial treatment is offered to any patients diagnosed with EoE: proton pump inhibitor (PPI), swallowed topical steroids or various type of elimination diets.¹³ However, patients with EoE are not a homogeneous population, and different phenotypes exist.^{4,9,10} Indeed, EoE presents at different ages, and with varying clinical manifestations, comorbidities, natural history, biomarkers, and response to treatment.^{7,14,15} Recognizing and categorizing such different phenotypes is a critical step to choose the best management for specific

patients. Some emerging phenotypes can be proposed for EoE based on response to therapy, atopic status, and natural history of disease.

Response to Therapy

As proposed by Atkins et al.,¹⁶ understanding the extent of a patient's response to therapy could add information to their phenotype and disease severity.¹⁶ In work by Shoda et al.,¹⁷ 3 groups of EoE patients could be identified.^{17,18} A mild form was identified that responded to all forms of treatment, including PPIs (these patients may have been defined as PPI-responsive esophageal eosinophilia or PPI-REE in the recent past). The second is a classic form of EoE largely unresponsive to PPI monotherapy but responsive to food antigen elimination (dietary treatments) or swallowed steroids, whereas the third subtype is characterized by severe fibrosis and largely unresponsive to PPI, swallowed steroids, and diet. However, these 3 phenotypes are difficult to distinguish before treatment initiation. Furthermore, whether these represent 3 distinct phenotypes with distinct disease prognosis, or whether these patients are presenting at different points in time during the natural progression of EoE, is unclear.

Atopic vs Non-atopic Phenotype

As in many allergic conditions, EoE patients have high levels of atopic comorbidity such as allergic rhinitis, bronchial asthma, eczema, and IgE-mediated food allergies.^{19–21} Similarly, patients with multiple food allergies, are at risk of developing EoE.²²

Epidemiologic data from pediatric cohorts demonstrating that EoE follows other atopic conditions in the allergic march confirm the common pathogenetic mechanism.²³ Chronic antigenic exposure drives EoE inflammation in most patients by triggering a specific Th2 inflammation.^{24,25} Growing evidence suggests that esophageal inflammation is impacted by seasonal aeroallergens in patients with comorbid EoE and allergic rhinitis, leading to increased esophageal mucosal inflammation.^{26,27}

However, a significant proportion of patients with EoE do not demonstrate signs of allergy, suggesting that this may be a different phenotype.²⁸ Indeed, other non-atopic diseases, such as inflammatory bowel disease,²⁹ connective tissue disorders,³⁰ autism,³¹ attention deficit hyperactivity disorder,³¹ and additional monogenic disorders,^{31,32} have been shown to be associated with EoE. These factors may modulate the presentation of EoE, leading to additional aspects of inflammation or fibrosis that differ from the classical atopic pathway. This suggests that in some patients, the development of EoE is not conditional on prior atopic disease. Future studies will need to take into account these differences to see whether atopic and non-atopic patients have different response to therapy and natural history of disease to determine more appropriate and personalized therapies. Defining these phenotypes also would enable identification of risk factors leading to EoE development in atopic and nonatopic patients, which could then be employed to design studies of secondary prevention.

Natural History

Most evidence suggests that EoE is a chronic disease, which relapses once treatment is stopped and if left untreated is associated with development of fibrosis.^{21,33} For example, in 30 adult EoE patients followed off of treatment over time, 60% had unchanged or worsening dysphagia.²¹ Data also suggest that delays in EoE diagnosis increase the risk of fibrosis development.³⁴ The odds of developing fibrostenosis increased 5% for each year of symptoms before diagnosis. Additional studies have identified that younger patients are more likely to present with an inflammatory phenotype, whereas older patients present with a fibrostenotic phenotype, with risk of fibrostenosis doubling for every decade of life.²¹

However, we and others have described a small minority of EoE patients who may have periods of remission after several years of therapy for EoE.^{35,36} Most patients that achieved sustained remission appeared to be very responsive to therapy and achieved complete absence of esophageal mucosal eosinophils while on therapy.³⁶ Similarly, 23% of untreated adults had improved dysphagia over time.²¹

Therefore, the long-term prognosis of EoE in patients is unknown. Further studies defining the prognosis of EoE based on clinical phenotype are necessary to establish those patients who need aggressive treatment to prevent fibrosis or those who may be able to attempt a milder therapeutic regimen. Similarly, additional study is needed to define which patient characteristics may predict a period of disease remission without therapy.

Endotypes in EoE

Recognition of disease phenotype can be useful to characterize atopic conditions such as EoE as a tool for guiding clinical care or clinical trials. However, disease phenotypes can frequently overlap, may change as time passes, and do not necessarily give insights into the underlying pathogenetic mechanisms.³⁷ Thus, a rational next step in defining patients with similar presentations of atopic disease has been to identify disease endotypes based on distinct pathological mechanisms. This has been of particular interest in atopic disorders such as EoE, because potential therapies to target specific immunological pathways are being developed at a rapid pace.^{9,38} The phenotypes associated with significant inflammation and other atopic conditions may have higher T helper 2 type (Th2) inflammation and may be associated more commonly with a defect in the epithelial barrier affecting multiple organs; conversely, the phenotypes associated with fibrosis, low inflammation, and monogenetic disorders may be linked to predisposition to enhanced fibrosis and other poorly understood molecular mechanisms.

Th2-High vs Th2-Low

Two main endotypes of allergic disease have been defined. The first is a T helper 2 type (Th2)—high endotype that is characterized by typical Th2 inflammation with high levels of eosinophils, interleukin (IL)-5, IL-4, IL-13, thymic stromal lymphopoietin (TSLP), and eotaxins. Th2-high is the most common type of inflammation described in atopic diseases, and the current available drugs and biologics are best at treating this endotype. These patients tend to be classic atopic patients with elevated IgE and eosinophilia. Patients with multiple atopic comorbidities tend to cluster in this endotype.

The second main allergic endotype that has been described has been termed “Th2-low,” because of the lack of prominent Th2 inflammation, elevated IgE, or prominent eosinophilia.^{6,7,10} Th2-low endotypes are emerging in atopic diseases as more difficult to treat, despite sharing similar phenotypes with Th-2 high ones.^{9,10} Low Th2 endotype is associated with neutrophil-predominant inflammation in asthma and Th17 inflammation in AD.

Eosinophilic esophagitis is defined in all cases by the presence of eosinophil infiltration in the mucosa, and molecular studies confirm the presence of Th2-high inflammation in EoE.^{11,12} Not surprisingly, as in many atopic diseases, a low Th2 endotype is also emerging. For example, Mulder et al.³⁹ have shown that intra-epithelial mast cell density was increased significantly in biopsy specimens from patients with EoE when compared with patients with gastroesophageal reflux disease or normal control esophagus tissue, as expected in an atopic disease.³⁹ However, a subgroup of non-atopic EoE patients not only were phenotypically distinct but also had significantly lower IgE-positive mast cells, suggesting that the non-atopic EoE phenotype may be associated with a different

endotype. Similarly, an EoE-like disease, with similar symptom presentation, strong familial aggregation, but absence of eosinophilic infiltration and low Th2 inflammation has been described in a limited number of patients with hereditary presentation of EoE-like disease.⁴⁰ This suggests that a primary Th2-low endotype may exist in EoE similarly to what is seen in other atopic diseases. Given the current definition of EoE based solely on eosinophilic infiltration, the low-Th2 endotype may be significantly under-recognized. Furthermore, even among Th2-high atopic diseases, there may be additional subsets in patient endotype. Blood eosinophilia and elevated serum IgE are common in all Th2-high endotypes in atopic diseases but not equally essential for the development of all allergic disease manifestations.^{41,42} Indeed, anti-IgE therapy (omalizumab) and anti-eosinophil treatment such as anti-IL-5 antibodies have been shown to benefit Th2-high asthma^{43,44} but are most beneficial in patients with allergic sensitization and an eosinophilic endotype, respectively. These biologics have been less successful in nasal polyps,⁴⁵ atopic dermatitis,⁴⁶ or EoE.^{47,48}

Similarly, EoE patients with classical eosinophil infiltration and Th2-high inflammation can have different type of clinical manifestations, because children tend to have more inflammatory manifestations and adults more fibrotic ones.^{15,49} Shoda et al¹⁷ demonstrated different endotypes within EoE, using a machine learning approach to examine histological, endoscopic, and molecular features in the Consortium of Eosinophilic Gastrointestinal Disease Researchers Database.¹⁷ They identify 3 potential endotypes of EoE, using a discovery and validation approach. The first, EoEe1, represented 35% of all patients, and had the mildest features with minimal gross endoscopic changes, a pauc-inflammatory pattern of histology, and fewer differential gene expression changes, and was associated with steroid-responsiveness. The second group, EoEe2, represented 29% of all patients and was associated with pediatric-onset, steroid-refractory disease with features of gross endoscopic edema, basal cell hyperplasia, and high expression of inflammatory and steroid-responsive genes. Eosinophilic esophagitis e3 had especially low expression of epithelial differentiation genes and a greater frequency of patients with a narrow-caliber esophagus, and represented 36% of patients. These 3 different endotypes of patients may account for the diverse natural history and response to therapy. However, they may represent the natural evolution of untreated Th2 inflammation, which becomes more severe and fibrostenotic with time. The relevance of these 3 endotypes and the clinical characteristic in each group need to be prospectively studied.

Genotype Correlations in EoE

A number of factors argue that environmental risks play an important role in the pathogenesis of EoE. The rapid increase in EoE prevalence experienced in the Western Countries, the fact that fraternal twins are more at risk of developing EoE than siblings, and yet identical twins are not always equally affected, suggest a strong environmental component in EoE development.⁵⁰ Nonetheless, 1 reason for the presence of different endotypes may be attributable to differing genetic backgrounds of patients. Like other atopic disorders such as atopic dermatitis, IgE-mediated food allergy, allergic rhinitis, and asthma, EoE has complex causes. Genetic predisposition and environmental factors both play a major role in disease development.⁵¹

Strong evidence suggests that genetic predisposition is an important risk factor in development of EoE. Siblings and twins have increased risk of EoE compared with the general population.⁵⁰ Several genetic loci have been linked to EoE risk by genome-wide association studies, confirming that inheritability is associated with genetic predisposition.^{52–55} Gene loci associated with EoE

Altered Epithelial Barrier:

Desmoglein 1
Desmoplakin
Calpain 14 (CAPN14)
SPINK5
Filaggrin (FLG)

Increased Fibrosis:

TGF- β 1, 2, & 3
TGF- β receptor
Fibrillin
PTEN

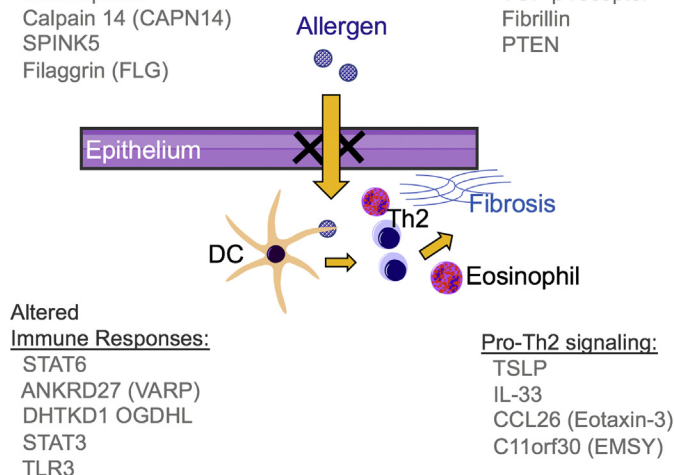


Figure 2. Genetic risks that may influence EoE endotype. Gene loci associated with increased risk of developing EoE relate to esophageal epithelial barrier function, inflammatory signaling, and development of fibrosis.

development fall into 4 major categories: genes associated with enhanced Th2 inflammation, genes associated with maintenance of epithelial barrier genes associated with enhanced fibrosis, and genetic defects associated with multiple comorbidities, including EoE (Fig 2). The characterization of the correlation between genotype, endotype, and phenotype are still in preliminary stages for EoE. However, data accumulated thus far points to 4 different endotypes, associated with Th2 inflammation, fibrosis, epithelial barrier dysfunction, and the last associated with rare genetic disorders.

Several single-nucleotide polymorphisms (SNPs) near immune signaling genes have been identified to be associated with increased risk of developing Th2 inflammation as well as EoE. These include thymic stromal lymphopoietin (TSLP) on 5q22, eotaxin-3 (CCL26) on 7q11.23, and Toll-like receptor 3 (TLR3) on 4q35.1.^{28,52,55} Epithelial-derived pro-Th2 inflammatory signaling is highly dysregulated in EoE. Blanchard et al⁵⁶ found that CCL-26 (eotaxin-3) is overexpressed by 50-fold in EoE patients compared with healthy controls or patients affected by gastroesophageal reflux.⁵⁵ This is likely attributable to the genetic polymorphism present in approximately 13% of patients with EoE.^{51,54} This suggested for the first time how dysregulated esophageal epithelial signaling promotes eosinophil chemotaxis in a subgroup of genetically predisposed individuals.

Similarly, the TSLP risk allele (AA) on 5q22 is correlated with increased risk of EoE development, increased epithelial TSLP expression, and mucosal basophil recruitment.^{52,55,57} The importance of TSLP in EoE pathophysiology is not surprising. Thymic stromal lymphopoietin plays a crucial role in other atopic diseases such as asthma and eczema by instructing antigen-presenting cells to induce a Th2 effector response, and by inducing Th2-cytokine production from adaptive and innate cells.⁵⁸ The central role of TSLP in EoE has been confirmed in animal studies, where TSLP inhibition leads to a prevention in EoE development in an animal model.⁵⁷ Martin et al⁵⁴ have shown that SNPs' TSLP locus is associated with significantly increased EoE when control subjects with atopic disease were used as the comparator group; other loci were associated with atopy and not EoE.⁵⁴ Furthermore, Sherrill et al⁵⁹ demonstrated a nonsynonymous polymorphism in the TSLP receptor gene on Xp22.3 and Yp11.3, which could explain the male preponderance of EoE.⁵⁹

Our group demonstrated that pediatric EoE patients with the TSLP risk allele (rs3806932 AA) have increased food allergen triggers, regardless of the degree of background atopic disease.^{57,60} These children are less likely to respond to single-food elimination diets than children who are not homozygous for the risk allele.⁶⁰ Other SNPs that modulate inflammatory Th2 signaling are associated with different EoE clinical phenotypes. Indeed, Ávila-Castellano et al²⁸ demonstrated that EoE patients with TLR3 SNP (CC or CG at rs3775292) are more frequently sensitized to both environmental and food allergens.²⁸ In summary, these inherited risk loci may account for which patients present with Th2-high EoE endotypes, EoE associated with atopic condition and therapeutic response to anti-inflammatory therapy. Furthermore, these are genes that may be associated with EoE1 and EoE2 subtypes of EoE as described by Shoda et al.¹⁷

Th2 inflammation leads to fibrosis in some allergic patients, including in EoE patients. However, Th1 cytokines such as tumor necrosis factor alpha may lead to a similar effect.⁶¹ Several lines of evidence support the importance of the transforming growth factor beta (TGF- β) in EoE fibrosis development. Transforming growth factor-beta on 19q13,^{62,63} is a pro-fibrotic factor in the setting of Th2 inflammation, and clinical studies correlate SNPs in the TGF- β locus as well as connective tissue disorders with EoE.^{30,64} Connective tissue disorders such as Loeys-Dietz, Marfan's, and Eros Danlos' syndrome are thought to share a set of common pathogenic mechanisms in the development of EoE through dysregulated TGF- β signaling. Aceves et al^{62–65} have shown that those EoE patients responsive to steroid therapy are more likely to have the CC genotype at the -509 position in the TGF- β promoter than were nonresponders, suggesting that TGF- β , could be responsible for a specific endotype.^{62–65} Additional evidence implicating the TGF- β pathway as important in EoE comes from recent studies demonstrating that STAT3 negatively regulates TGF- β signaling via ERBB2-interacting protein, an SMAD anchor for receptor activation.⁶⁶ This mechanism is clinically significant, because individuals with dominant-negative STAT3 mutations (autosomal dominant hyper-IgE syndrome) have increased incidence of EoE.⁶⁷ Therefore, some evidence suggests that a predisposition to develop fibrosis may be at the basis of the EoE fibrostenotic phenotype.

A group of genes that are associated with epithelial barrier function have been implicated in EoE pathogenesis. These include calpain 14 (CAPN14) on chr2p23.1, Filaggrin (*FLG*) on 1q21, and epithelial serine protease inhibitor SPINK5 on 5q32. Similar to the model proposed in atopic dermatitis, in EoE, the epithelium may be genetically predisposed to be more permeable. This is thought to increase the amount of contact between antigens and the immune system, and predispose to inappropriate loss of tolerance for these antigens.³⁶ Calpain 14 (CAPN14) is a protease in the calpain family that is expressed at the highest level in the esophageal epithelium and upper gastrointestinal (GI) tract. Interleukin-13 induces Calpain 14 expression in EoE, causing damage of the esophageal epithelium and loss of barrier function.⁶³ Case control analysis suggested that breast feeding infants with the pathogenic CAPN14 variant may reduce the risk of EoE development.⁶⁴ This highlights how knowledge of disease-associated genotypes may be a useful clinical marker to predict clinical response to differing exposures or therapies. Loss-of-function variants in filaggrin (*FLG*) have been identified in both asthmatic and atopic dermatitis patients.^{68,69} *FLG* variant 2282del4 has been shown to be associated with EoE development in a cohort of 365 patients even when restricted to a subset of nonatopic EoE patients ($P = .03$).⁷⁰ Netherton's syndrome, which is caused by a defect in the epithelial serine protease inhibitor SPINK5, has also been described as an EoE risk as well as severe atopic dermatitis.^{71,72}

An ever-expanding group of rare monogenic diseases have been associated with an increased risk of developing EoE. These

associations represent opportunities to understand nonobvious associations that contribute to pathogenetic mechanisms in EoE. Germline mutations of the tumor suppressor PTEN, the tumor suppressor lipid phosphatase, and tensin homolog, on 10q23.31. Mutations in PTEN have been associated with eosinophilic GI disorders, with 10% of patients developing EoE.⁶² These patients have additional clinical findings and risks, including macrocephaly, developmental delay, autism, and increased cancer susceptibility that warrant additional clinical screening for complications. Additionally, five rare, damaging variants in dehydrogenase E1 and transketolase domain-containing 1 (DHTKD1 on 10p14) as well as 7 variants in the DHTKD1 homolog oxoglutarate dehydrogenase-like (OGDHL on 17q21.2) have been described in kindreds with familial EoE.⁷³ These genes play a role in maintaining normal mitochondrial function in esophageal epithelium. Understanding why these genes maintain esophageal health will lead to a better future understanding of EoE.

Linking genotype with clinical presentation may over time enable clinicians to further understand the correlations between endotype and response to therapy. For example, recent data suggest that therapeutic response to PPIs in EoE patients is negatively correlated with single-nucleotide polymorphisms in *CYP2C19* and has variable correlation with different *STAT6* variants.⁷⁴ Future prospective work may enable clinical testing that predicts response to different therapeutic approaches, which may help to reduce the number of endoscopies required for EoE patients.

Conclusion

Significant developments in understanding the underlying cause behind the varying presentations of EoE have been seen. However, prospective prediction regarding the phenotype or endotype for a particular patient remains a significant clinical challenge. Prospective studies are needed to define the value of biomarkers in identifying clinically meaningful groups of patients with sensitivity and specificity.

Several areas of EoE patient care could benefit from improved definitions of patient phenotype or endotype. The long-term risks of fibrosis, stricture, and impaction in EoE are not well understood and may vary from patient to patient based on underlying endotypes. Whether all untreated patients have equal risk of stricture formation over time is unclear, and defining patient groups based on phenotype or endotype may help to categorize which patients require more aggressive treatment to prevent these complications. Additionally, the current data do not clarify whether available therapies effectively prevent fibrosis for all patients, and work thus far implies that therapeutic response may vary based on phenotype. Considering patient phenotype and endotype in the design of future trials of therapeutics for EoE offers 1 strategy to maximize benefit for patients. Increasing understanding and use of phenotypes and endotypes in EoE will help to integrate accurate, individualized predictive and therapeutic approaches into the care of EoE.

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