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PII: S0091-6749(24)00242-2

DOI: <https://doi.org/10.1016/j.jaci.2024.03.004>

Reference: YMAI 16296

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 8 January 2024

Revised Date: 8 March 2024

Accepted Date: 8 March 2024

Please cite this article as: Constantine G, Khoury P, Overlap of Eosinophilic Esophagitis with Inborn Errors of Immunity and Immune Dysregulation, *Journal of Allergy and Clinical Immunology* (2024), doi: <https://doi.org/10.1016/j.jaci.2024.03.004>.

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Overlap of Eosinophilic Esophagitis with Inborn Errors of Immunity and Immune Dysregulation

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Keywords: EoE, immune dysregulation, IEI, Type 2 inflammation

Disclosure Statement: Dr. Constantine has received honoraria from PeerView. Dr.

Khoury has received grant funding from APFED.

Funding: This work was funded by the Division of Intramural Research, NIAID, NIH.

Eosinophilic esophagitis (EoE) is a chronic progressive disease of the esophagus characterized by aberrant type 2 (T2) inflammation and an impaired esophageal mucosal barrier. The etiology and pathophysiology of EoE remain incompletely understood and are likely multifaceted, involving impairment of the esophageal barrier, exposure to food and aeroallergens in susceptible individuals, and genetic and environmental risk factors. Emerging research suggests that aberrant T cell responses play a crucial role in the pathogenesis of EoE.¹ A dysregulated immune response results in the release of pro-inflammatory mediators central to EoE pathobiology including key cytokines, IL-4 and IL-13, that lead to eosinophil infiltration and inflammatory changes, damage to the epithelium and subsequent fibrosis. Simultaneously, compromised integrity of the epithelial barrier results in the release of alarmin cytokines (e.g., IL-33, TSLP, IL-25), downregulation of cellular adhesion molecules and tight junctions promoting increased permeability, recruitment of innate immune cells, and potentiation of the immune response initiated by T cells. The interplay between aberrant T cell responses and epithelial barrier dysfunction creates a vicious cycle in EoE, where immune activation and tissue damage perpetuate disease activity. Understanding drivers of EoE pathogenesis is critical for developing targeted therapeutic strategies that can break the cycle. Since inborn errors of immunity (IEI) often manifest with similar themes of aberrant immune responses and a compromised epithelial barrier, they provide an opportunity to inform our understanding of the intricate interplay between immune cell dysfunction and epithelial barrier compromise in EoE.

Dysregulation of the esophageal epithelium

Evidence from IELs affecting genes involved in intrinsic epithelial function and integrity play a significant role in EoE pathogenesis. Commel-Netherton syndrome caused by mutations in *SPINK5*, encoding the serine protease inhibitor LEKT1, results in severe atopic dermatitis and eosinophilic esophagitis as a result of an deregulated serine protease activity at epithelial barrier sites.² Recent research has further highlighted the importance of the tightly regulated epithelial environment via the balance of other epithelial proteases and their inhibitors. EoE-associated inflammation, namely IL-13, leads to decreased expression of SPINK7 (and SPINK5), leading to unrestrained kallikrein-5 (KLK5) activity and further epithelial barrier impairment.³ Similarly, IL-13 induced expression of the esophageal-specific cysteine protease calpain-14 (CAPN14) results in a compromised epithelial barrier associated with reduced desmoglein-1 expression.⁴ In contrast to epithelial barrier impairment, loss of esophageal epithelial cell-intrinsic TGF β R signaling in Loeys-Dietz syndrome (LDS) results in aberrant cell proliferation and differentiation, whereby basal keratinocytes display an immature phenotype likely as a result of defective cell cycle regulation. Additionally, LDS epithelial cells demonstrate signs of chronic activation including overexpression of inflammatory cytokines which promote the recruitment and activation of eosinophils and other immune cells.⁵ Increased TGF β expression has been well established in the pathogenesis of EoE however the data presented by Laky *et al* demonstrate that EoE can also be driven by decreased TGF β R signaling suggesting complex regulation of TGF β . Examining IEL disorders characterized by epithelial dysfunction offers a valuable framework for enhancing our understanding of EoE and may provide insights into therapeutic strategies.

Aberrant immune response

A growing subset of IEI disorders present with predominate allergic manifestations and have been termed primary atopic disorders (PADs). A collection of PADs have been reported in association with EoE (**Table 1**) but the underlying etiology of these associations remains to be fully explored. PADs associated with EoE have been largely characterized by exuberant T2-driven inflammation as a result of impaired T cell receptor (TCR) signaling and cytoskeletal remodeling (e.g., DOCK8, CARD11, CARMIL2), altered cytokine signaling (e.g., STAT3 LoF, ERBIN deficiency, STAT5B GoF), T cell repertoire restriction (e.g., SCID), and tolerance failure (e.g., IPEX).⁶ Many EoE-associated PADs including STAT3 LoF and ERBIN deficiency are characterized by increased IL4R α expression and enhanced Th2 differentiation leading to amplified release of IL-4, IL-5, and IL-13 – all likely contributing to EoE pathogenesis.⁷

To better understand the association of EoE in IEIs, a recent study utilized the U.S. Immunodeficiency Network (USIDNET)⁸ database to characterize diagnoses of EoE in a diverse cohort of IEI. The dataset of voluntary case submissions included 5,484 individuals, of whom 61 (1.1%) were diagnosed with EoE. Considering the reported prevalence of EoE (0.06%) in a combined adult and pediatric population⁹, EoE may be overrepresented in IEI. Among the EoE cases identified, the majority of IEI were represented by common variable immune deficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS), combined immunodeficiency, hyper-IgE syndromes, and chronic granulomatous disease (CGD). While histopathology, symptom

assessments or methods to reduce ascertainment bias were not assessed, this survey provides new insight highlighting several IEIs previously unrecognized in association with EoE.

Future research including detailed assessment of clinical characteristics, tissue-based assessments including transcriptomics, metabolomics, microbiome, and other mechanistic studies are needed to determine the mechanisms that promote EoE within the context of IEI.

Given the reported prevalence of EoE in available datasets, there should be a heightened suspicion for EoE and other eosinophilic GI disorders (EGIDs) in patients with IEI experiencing gastrointestinal symptoms.¹⁰ While significant symptoms often prompt an evaluation for inflammatory bowel disease in IEI; it is essential to also consider obtaining biopsies and screening for EoE and/or other EGIDs. Additionally, evaluation of multicenter consortia data or large claims databases is needed to identify additional immunodysregulatory disorders that may be associated with EoE and EGIDs and to guide further investigation into pathomechanisms unique to EoE.

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Table 1. Inborn Errors of Immunity reported in association with Eosinophilic Esophagitis

IEI associated with EoE	Gene(s)	Inheritance pattern	Molecular consequence	IUIS major category	IUIS subcategory	IEI subcategory	Proposed/possible mechanism of EoE association	Observed in USIDNET (6)
Adaptive Immunity								
Enhanced TH2 differentiation/activity								
Autosomal dominant hyper IgE syndrome	STAT3	AD	LoF	Combined immunodeficiencies with associated or syndromic features	Hyper IgE syndromes	PAD	Skewed TH2 differentiation, enhanced expression of IL-4, IL-5, and IL-13, cytokines	X
DOCK8 Deficiency	DOCK8	AR	LoF	Immunodeficiencies affecting cellular and humoral immunity	Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency	PAD	Skewed TH2 differentiation, enhanced expression of IL-4, IL-5, and IL-13, cytokines	X
IPEX Syndrome	FOPX3	XL	LoF	Diseases of Immune Dysregulation	Regulatory T Cell Defects	PAD, PIRD	Impaired regulatory T cell development and function, TH2 skewing	X
STAT5B GoF	STAT5B	Somatic	GoF	NA	NA	PAD	Aberrant TH2 cytokine production, possible enhanced sensitivity to IL-3 and TSLP signaling	
CARD11 DN LoF	CARD11	AD	LoF	Combined immunodeficiencies with associated or syndromic features	Hyper IgE Syndromes	PAD	Unknown, impaired mTORC1 activation leading to poor TH1 and enhanced TH2 differentiation	

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PGM3 Deficiency	<i>PGM3</i>	AR	LoF	Combined immunodeficiencies with associated or syndromic features	Hyper IgE Syndromes	PAD	Unknown, reduction in N-glycosylation may impair IL6ST-dependent cytokine signaling	X
Common Variable Immunodeficiency (CVID)	Heterogenous genetic defects	Variable	Various	Predominantly Antibody Deficiencies	CVID Phenotype	NA	Unknown, altered antibody production	X
NEMO deficiency (ectodermal dysplasia with immune deficiency)	<i>IKBKG</i>	XL	LoF	Combined immunodeficiencies with associated or syndromic features	Anhidrotic Ectodermal dysplasia with Immunodeficiency	NA	Unknown	X
ALPS	<i>FAS</i>	AD	LoF	Diseases of Immune Dysregulation	Autoimmune Lymphoproliferative Syndrome (ALPS, Canale Smith syndrome)	PIRD	Unknown	X
Epithelial function/development								
Loeys-Dietz Syndrome	<i>TGFβR1</i> and <i>TGFβR2</i>	AD	Deregulated TGFβ signaling	Combined immunodeficiencies with associated or syndromic features	Hyper IgE Syndromes	PAD	Decreased TGFβR1 signaling leads to impaired epithelial cell differentiation, hyperproliferation and release of inflammatory mediators	
Comel-Netherton syndrome	<i>SPINK5</i>	AR	LEKTI-1 LoF	Combined immunodeficiencies with associated or syndromic features	Hyper IgE Syndromes	PAD	Increased proteolytic activity as a result of impaired protease inhibitor (LEKT1) activity resulting in barrier dysfunction	
SAM Syndrome	<i>DSG1</i>	AR	DSG1 LoF	NA	NA	PAD	Impaired cell-to-cell adhesion resulting from aberrant desmosome formation in the epidermal and epithelial sites	

IL33 gene duplication	<i>IL33</i>	NA	Possible GoF secondary to gene dosage effect	NA	NA	NA	Increased IL-33 production and activity leading to inflammation at epithelial sites	
Innate immunity								
CGD	<i>CYBB, CYBA, NCF1, NCF2</i>	XL (<i>CYBB</i>), AR	LoF of NADPH oxidase subunits	Congenital defects of phagocyte number or function	Defects of Respiratory Burst	PIRD	Unknown	X
STAT1 GoF	<i>STAT1</i>	AD	GoF	Defects in intrinsic and innate immunity	Predisposition to Mucocutaneous Candidiasis	PIRD, PAD	Unknown, aberrant STAT1 activity may impair of STAT3 promoter binding activity, may lead to increased IL-5 signaling in eosinophils, and/or have intrinsic effects on esophageal epithelial and T cell activity	X
DADA2	<i>ADA2</i>	AR	Unknown	Autoinflammatory Disorders	Type 1 Interferonopathies	PIRD	Unknown, impaired expansion of immunomodulatory M2 macrophages, increased TNF- α	
TRAPS	<i>TNFR1</i>	AD	Unknown	Autoinflammatory Disorders	Non-Inflammasome Related Conditions	PIRD	Unknown, enhanced TNF responses, aberrant IL-1 cytokine production	
CANDLE	<i>PSMB, PSMA3, PSMB4, PSMB9</i>	AR	LoF	Autoinflammatory Disorders	Non-Inflammasome Related Conditions	PIRD	Unknown, exuberant type 1 interferon release	

USIDNET, United States immunodeficiency network; AD, autosomal dominant; LoF, loss-of-function; PAD, primary atopic disorder; AR, autosomal recessive; IPEX, immune dysregulation; XL, x-linked; PIRD, primary immune regulatory disorders; GoF, gain-of-function; NA, not available; TSLP, thymic stromal lymphopoietin; DN, dominant negative; SCID, severe combined immunodeficiency; TCR, t-cell receptor; CVID, common variable immunodeficiency; ALPS, autoimmune lymphoproliferative syndrome; EBV, Epstein-Barr virus; SAM, severe skin dermatitis, multiple allergies and metabolic wasting; CGD, chronic granulomatous disease; DADA2, deficiency of adenosine deaminase 2; TRAPS. tumor necrosis factor receptor-1 associated periodic syndrome; CANDLE. chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature