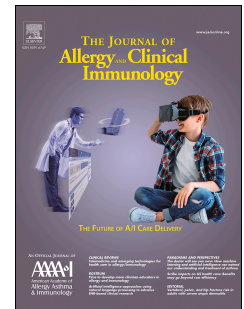


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Eosinophilic Esophagitis with Extremely High Esophageal Eosinophil Counts

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Conflict of interest:

M.E.R. is a consultant for Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Celgene, Astra Zeneca, Allakos, Arena Pharmaceuticals, Guidepoint and Suvretta Capital Management, and has an equity interest in the first four listed, and royalties from reslizumab (Teva Pharmaceuticals), PEESV2 (Mapi Research Trust) and UpToDate. M.E.R. is an inventor of patents owned by Cincinnati Children's Hospital. The other authors have no potential conflicts of interest to disclose.

Word Count: 1041**Key Words:** atopy, endotype, esophagus, eosinophil, histology, and IL-13

Capsule Summary

Patients with eosinophilic esophagitis (EoE) and extremely high esophageal eosinophilia have a distinct endotype defined by more severe atopic, endoscopic, histologic, and transcriptomic features.

To the Editor:

Eosinophilic esophagitis (EoE) is an inflammatory disease characterized by eosinophil infiltration into the esophageal mucosa with a peak count of ≥ 15 eosinophils per high-powered field (eos/hpf) following endoscopic biopsy. However, the range of esophageal eosinophilia can vary markedly from patient to patient. A key question in the field is to understand the relationship of eosinophil levels with disease features, especially since eosinophil-targeted therapies are now available. Patients with extremely high levels of esophageal eosinophilia have not previously been studied. It is unknown whether these patients exhibit different characteristics compared with EoE patients that have esophageal eosinophilia that is near the threshold of disease diagnosis. Given this, we aimed to establish whether any significant clinical, endoscopic, histologic, or transcriptomic features differ between patients with extremely high levels of esophageal eosinophilia and those with levels near the threshold of disease diagnosis.

Amongst a registry of patients with EoE, we identified a group of patients with the highest recorded levels of esophageal eosinophilia (eos/hpf >350), referred to as EoE-Hi. We subsequently identified a second group that had relatively low levels of esophageal eosinophilia (15-24 eos/hpf), referred to as EoE-Low. There were 74 patients in the registry with eosinophil counts of 15-24 eos/hpf on a distal esophageal biopsy. A random number generator was used to

select the 14 patients that comprised the EoE-Low group. Phenotypic and clinical characteristics were gathered on the basis of electronic medical records and detailed questionnaires as part of a research registry. Endoscopic characteristics were assessed on the basis of findings from EGD operative reports. Histologic characteristics were classified on the basis of the histologic scoring system (HSS).(1) Molecular analysis was performed using the 96-gene EoE Diagnostic Panel (EDP).(2) Age, demographics, esophageal eosinophil levels, absolute eosinophilia, IgE levels, atopic co-morbidities, and treatment modalities were assessed. Study population characteristics are summarized in Table E1 in this article's Online Repository at www.jacionline.org. The EoE-Low group was younger at the time of biopsy than the EoE-Hi group, with mean ages of 6.3 ± 3.4 years and 13.4 ± 10.3 years, respectively ($p = 0.02$). The EoE-Hi group had a disease duration that was significantly longer than the EoE-Low group, with mean duration of 6.0 ± 3.7 years and 1.9 ± 1.8 years, respectively ($p = 0.002$). Furthermore, there were more patients with atopic co-morbidities (100% vs. 64%) in the EoE-Hi group than the EoE-Low group ($p = 0.04$), and upon subcategorization there were significantly more patients in the EoE-Hi group with allergic rhinitis (93% vs. 50%) ($p=0.033$).

There were trends for more severe symptoms in the EoE-Hi group, although these did not reach statistical significance (see Table E2 in this article's Online Repository at www.jacionline.org). Endoscopically, there were significantly more patients with exudates seen on EGD in the EoE-Hi group compared with the EoE-Low group (11 [79%] vs. 0, $p < 0.0001$). This significant difference was also seen with regards to furrowing (14 [100%] vs. 4 [29%], $p = 0.0002$) and thickening (12 [86%] vs. 4 [29%], $p = 0.006$). However, there was no significant difference

between the two groups with regards to erosions, rings, and narrowing/strictures, likely due to the low prevalence of these findings in both groups.

The total score for each of the individual histologic parameters was higher (more severe) in the EoE-Hi than EoE-Low group ($p < 0.0001$). In addition, the average grade and stage of each histologic subcategory were significantly different between EoE-Hi and EoE-Low, with EoE-Hi demonstrating more severe disease histologically in every category except for dyskeratotic epithelial cells (Figure 1).

With regards to the molecular signatures between the two groups, there were substantial differences, including 30 upregulated and 13 downregulated genes (Figure 2A) (see Table E4 in this article's Online Repository at www.jacionline.org). The majority of upregulated genes were associated with inflammation, ion channels, and remodeling; whereas, the majority of downregulated genes were associated with epithelial barrier and proliferation (Figure 2B). Interestingly, 14 of the dysregulated genes are known to be regulated and/or associated with interleukin-13 (IL-13) (see Table E3 in this article's Online Repository at www.jacionline.org).

Previous studies have evaluated the long-term clinical progression of EoE and have shown significantly higher rates of dysphagia in patients with more severe esophageal eosinophilia and endoscopic disease.(3, 4) Another recent study used transcription profiling to evaluate relationships between histologic, endoscopic, and clinical features of patients with EoE with varying disease activity and severity and discovered 3 separate EoE endotypes that correlated in histologic, endoscopic, and clinical characteristics. Notably, the classification of these endotypes

was independent of peak eosinophil counts.(5) There is thus an active debate about whether the degree of esophageal eosinophilia in patients with EoE is consequential.

It is known that IL-13 is overexpressed in the esophageal tissue of patients with EoE and that IL-13 induces expression of the EoE transcriptome, at least in part.(6) Previous studies have demonstrated that IL-13 promotes esophageal eosinophilia via induction of eotaxins.(7, 8) A recent phase 2 clinical trial studying the effects of an anti-IL-13 monoclonal antibody in patients with EoE demonstrated a decrease in esophageal eosinophilia, further corroborating previous findings of the involvement of IL-13 in promoting esophageal eosinophilia.(9) We have found that IL-13-related pathways associate with esophageal eosinophil levels in individuals with extremely high levels of eosinophilia, suggesting the value of agents that interfere with IL-13 in this EoE subgroup.

There were several limitations to this study. First, the sample size was small. This limited the power of the study to detect differences that may be present. In addition, this was a retrospective study, and symptoms reported were based upon clinical documentation and, therefore, were subject to what was discussed during clinic appointments. Furthermore, given the average age of the patients in this cohort, certain symptoms, such as dysphagia and food impaction are less likely to occur. The age differences between the two groups may have impacted the prevalence of co-morbid atopic disease as certain atopic diseases manifest later in life. In addition, an increased incidence of atopic disease may contribute to genetic differences between patients. Expansion of RNA analysis may yield interesting and novel results and can be considered in the future. Further limitations of the study include a lack of evaluation of patient race, ethnicity, or

geographical region, all of which can affect the generalizability of the results. Finally, it is important to note that the EoE-Hi population is the only one with co-existing EGIDs. When we removed these three patients, the results still showed that all previous similarities and differences remained, with two exceptions; there is no longer a statistical difference between the histologic characteristic, dilated intercellular spaces, and the clinical characteristic, steroid resistance, becomes statistically significant between the two groups.

In conclusion, patients with EoE with high esophageal eosinophilia have distinct clinical, endoscopic, histologic, and transcriptomic features from those with near-diagnostic levels of esophageal eosinophilia, suggesting that they may represent a unique endotype, although we cannot completely exclude the possibility that they are a more severe common endotype. Compared with patients with EoE with relatively low esophageal eosinophilia, patients with extremely high levels of esophageal eosinophilia present with (1) increased incidence of atopic co-morbidities (specifically atopic rhinitis upon subcategorization); (2) older age at the time of esophageal biopsy; (3) longer disease duration; (4) more severe endoscopic effects; (5) more severe histologic disease; and (6) a distinct molecular signature, especially enriched for IL-13-regulated genes. Molecular analysis revealed that multiple genes are significantly differentially expressed between the two cohorts, especially those regulated by IL-13, indicating that IL-13 likely has a key role in esophageal eosinophilic infiltration in patients with EoE. By examining the subset of patients with this extreme phenotype, our findings support that esophageal eosinophils are causally associated with disease pathology and that these patients likely require more aggressive therapeutic intervention, including anti-IL-13-based agents.

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171 have no potential conflicts of interest to disclose.

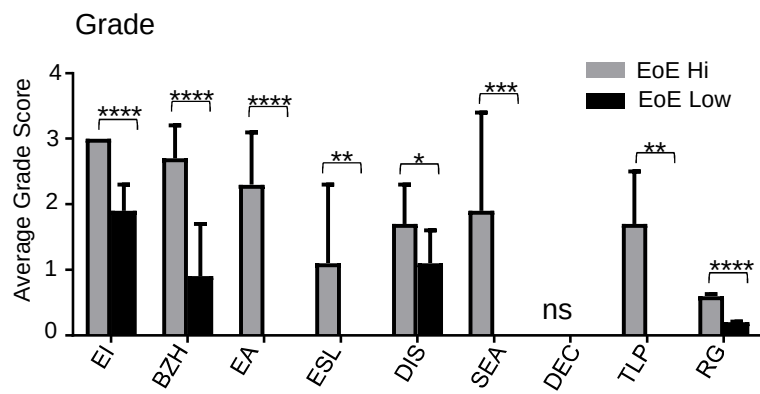
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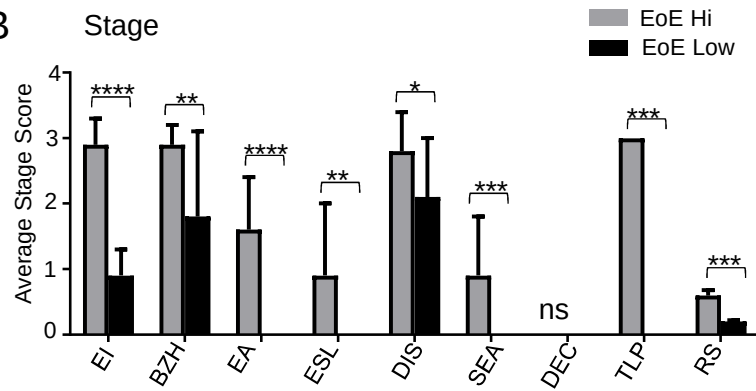
Figure 1. Histologic characteristics assessed by the HSS. In A, average grade (severity) score and in B, average stage (extent) score comparing EoE-Hi vs. EoE-Low in each subcategory. Characteristics were combined and divided by the composite score to calculate the relative grade/stage. P-values were calculated with 2-sided, unpaired t-test and Mann-Whitney U test. EI, eosinophilic infiltration; BZH, basal zone hyperplasia; EA, eosinophil abscess; ESL, eosinophil surface layering; DIS, dilated intercellular spaces; SEA, surface epithelial alteration; DEC, dyskeratotic epithelial cells; TLP, thickened lamina propria; RG, relative grade; RS, relative stage. **** $p \leq 0.0001$, *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$; ns, not significant.

Figure 2. Comparative gene expression of EoE-Hi and EoE-Low. In A, a volcano plot reflects a bidirectional fold change ($\log_2$) and negative $\log_{10}$ p-value (EoE-Hi vs. EoE-Low) for 96 genes. The 14 genes that previously have been reported to be regulated by IL-13 are labeled. FC, fold change. In B, when individual expression of the EoE Diagnostic Panel genes was compared between the 2 groups, there were 43 genes with significantly different expression ($p < 0.05$, fold change > 2.0). This graph displays gene expression by category and negative $\log_{10}$ p-value.

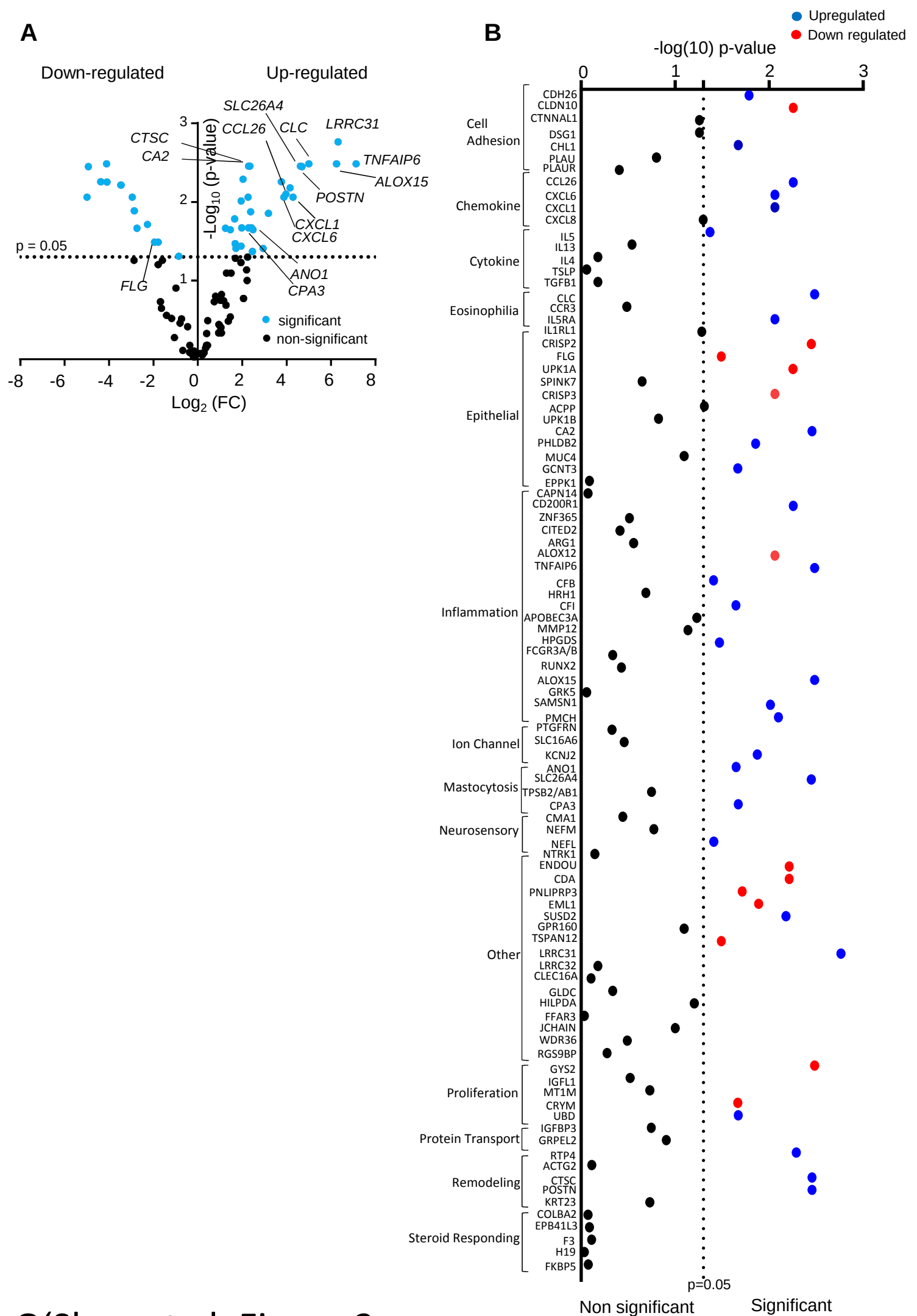
A



B



O'Shea, Figure 1



O'Shea et al, Figure 2

Table E1. Characteristics of subjects

	Eos/hpf >350 (n=14)	Eos/hpf 15-24 (n=14)	P-value
Male sex, no (%)	11 (78.6)	11 (78.6)	>0.99
Age at time of Biopsy (y)	13.4 ± 10.3	6.3 ± 3.4	0.02*
Age at Diagnosis (y)	7.3 ± 9.2 (n=12)	4.4 ± 2.6 (n=12)	0.33
Duration of Disease* (y)	6.0 ± 3.7 (n=12)	1.9 ± 1.8 (n=12)	0.002**
Eosinophils per HPF (mean eos/hpf)	433 ± 96.6	18.6 ± 2.9	<0.0001***
Absolute Eosinophilia (mean)	686 ± 353 (n=13)	482 ± 269 (n=13)	0.11
IgE (mean)	426 ± 451 (n=9)	339 ± 548 (n=5)	0.75
History of other EGIDs [†] , no. (%)	3 (23.1) (n=13)	0	0.23
Atopic Co-morbidities, no. (%)	14 (100)	9 (64.3)	0.04*
Atopic Dermatitis	10 (71.4)	6 (42.9)	0.25
Allergic Rhinitis	13 (92.8)	7 (50)	0.033*
Asthma	9 (64.3)	8 (57.1)	>0.99
Food Allergy	9 (64.3)	6 (42.9)	0.45
History of Anaphylaxis	5 (35.7)	4 (28.6)	>0.99
Treatment at time of Biopsy, no. (%)	14 (100)	14 (100)	>0.99
Elimination Diet	11 (78.6)	10 (71.4)	>0.99
Elemental Diet	0	0	>0.99
PPI	5 (35.7)	12 (85.7)	0.018*
Swallowed Glucocorticoids	8 (57.1)	5 (35.7)	0.45
More than one treatment modality	10 (71.4)	11 (78.6)	>0.99
Swallowed Glucocorticoids + Diet	6 (42.9)	1 (7.1)	0.077
PPI + Diet	4 (28.6)	9 (64.3)	0.13
Swallowed Glucocorticoids + PPI	2 (14.2)	4 (28.6)	0.65
Swallowed Glucocorticoids + Diet + PPI	1 (7.1)	1 (7.1)	>0.99

HPF, high-power field; SD, standard deviation; EGIDs, eosinophilic gastrointestinal disorders; PPI, proton-pump inhibitors

*Duration of Disease defined as the time interval between Age at Diagnosis and Age at time of Biopsy

[†] 2 patients have additional diagnoses of eosinophilic colitis and 1 patient has a diagnosis of eosinophilic gastroenteritis

Table E2. Clinical characteristics

	EoE-Hi (n = 14)	EoE-Low (n = 14)	P-value
Symptoms at time of Biopsy: no. (%)			
Abdominal Pain	8 (57.1)	5 (35.7)	0.45
Vomiting	5 (35.7)	1 (7.1)	0.16
Dysphagia/Food Impaction	2 (14.3)	2 (14.3)	>0.99
Failure to Thrive [¥] (%)	5 (35.7)	1 (7.1)	0.16
Steroid Resistance ^Ψ (%)	11 (78.5)	5 (35.7)	0.054

EoE, eosinophilic esophagitis

[¥]Failure to thrive was defined as a weight decline over 2 major percentiles or a weight that falls below the 3rd percentile for age.

^ΨHistory of steroid resistance was defined as evidence of histologic disease (eos/hpf>15) despite prescribed steroid treatment.

Table E3. 14 Genes Associated with IL-13

Gene	Reference
ANO1 (anoctamin-1)	(1)
CLC (Charcot-Leyden crystal protein)	(2)
CPA3 (carboxypeptidase A3)	(2)
CCL26 (eotaxin-3)	(3)
ALOX15 (arachidonate 15-lipoxygenase)	(4)
POSTN (periostin)	(4, 5)
LRRC31 (leucine-rich repeat-containing 31)	(6)
TNFAIP6 (TNF alpha-induced protein 6)	(3)
FLG (filaggrin)	(7)
SLC24A4 (pendrin)	(8)
CXCL1 (chemokine (CXC motif) ligand 1)	(2)
CXCL6 (chemokine (CXC motif) ligand 6)	(2)
CA2 (carbonic anhydrase 2)	(2)
CTSC (cathepsin C)	(3)

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Table E4. Genes Differentially Expressed Between EoE-Hi and EoE-Low

Gene	Regulation	P-value	Fold Change
ALOX15 (arachidonate 15-lipoxygenase)	Up	0.0033	76
ANO1 (anoctamin 1)	Up	0.023	5.6
CA2 (carbonic anhydrase 2)	Up	0.0035	4.9
CD200R1 (CD200 receptor 1)	Up	0.036	3.9
CCL26 (exotaxin 3)	Up	0.0055	14
CDH26 (cadherin 26)	Up	0.016	3.2
CFB (complement factor B)	Up	0.039	3.3
CFI (complement factor I)	Up	0.023	2.8
CHL1 (cell adhesion molecule L1-like protein)	Up	0.021	3.9
CLC (Charcot-Leyden crystal protein)	Up	0.0033	32
CPA3 (carboxypeptidase A3)	Up	0.021	4.9
CTSC (cathepsin C)	Up	0.0035	5.1
CXCL1 (chemokine (CXC motif) ligand 1)	Up	0.0087	20
CXCL6 (chemokine (CXC motif) ligand 6)	Up	0.0087	15
GCNT3 (glucosaminyl (N-acetyl) transferase 3, mucin type)	Up	0.022	2.4
HPGDS (hematopoietic prostaglandin D synthase)	Up	0.034	3.2
IL5 (interleukin 5)	Up	0.043	5.5
IL5RA (interleukin 5 receptor subunit alpha)	Up	0.0087	4.8
KCNJ2 (potassium inwardly rectifying channel subfamily J member 2)	Up	0.013	5.2
LRRC31 (leucine-rich repeat-containing 31)	Up	0.0017	80
NEFL (neurofilament light)	Up	0.039	7.7
PHLDB2 (pleckstrin homology-like domain family B member 2)	Up	0.014	9.1
PMCH (pro-melanin concentrating hormone)	Up	0.0080	16
POSTN (periostin)	Up	0.0035	25
RTP4 (receptor transporter protein 4)	Up	0.0052	4.1
SAMSN1 (SAM domain-containing protein)	Up	0.010	3.9
SLC26A4 (pendrin)	Up	0.0036	26
TNFAIP6 (TNF alpha-induced protein)	Up	0.0033	140
UBD (ubiquitin D)	Up	0.021	5.3
ALOX12 (arachidonate 12-lipoxygenase)	Down	0.0087	7.8
CDA (cytidine deaminase)	Down	0.0061	11
CLDN10 (claudin 10)	Down	0.0055	21
CRISP2 (cysteine rich secretory protein 2)	Down	0.0036	31
CRISP3 (cysteine rich secretory protein 3)	Down	0.0087	32
CRYM (crystallin mu)	Down	0.022	6.7
EML1 (echinoderm microtubule-associated protein-like 1)	Down	0.013	7.3
ENDOU (poly(U)-specific endoribonuclease)	Down	0.0061	11
FLG (filaggrin)	Down	0.032	3.9
GYS2 (glycogen synthase 2)	Down	0.0033	17
PNLIPRP3 (pancreatic lipase related protein 3)	Down	0.019	4.8
TSPAN12 (tetraspanin 12)	Down	0.032	3.5
UPK1A (uroplakin 1A)	Down	0.0056	17

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