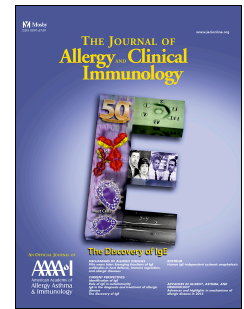


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Letter to the Editor, JACI

Eosinophilic Esophagitis vs Proton Pump Inhibitor-Responsive Esophageal Eosinophilia: Transcriptome Analysis

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on Intractable Diseases from the Ministry of Health, Labour and Welfare (#12103036
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conflicts of interest.

Short summary

Transcriptome analysis of eosinophilic esophagitis and proton pump
inhibitor-responsive esophageal eosinophilia suggests these are a single syndrome,
which casts doubt on the current guideline leading to the two distinct disease
examinations according to PPI responses.

48

49 Key words:

50 Eosinophilic esophagitis, Eosinophils, Microarray, Proton pump inhibitor-responsive
51 esophageal eosinophilia

52

53

54 Abbreviations:

55 EoE: eosinophilic esophagitis

56 EDP: EoE diagnostic panel

57 GO: Gene ontology

58 PPI: proton pump inhibitor

59 PPI-REE: PPI-responsive esophageal eosinophilia

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To the Editor:

The presence of dense eosinophilia in the esophageal epithelium, especially in the setting of unpleasant esophageal symptoms, suggests a diagnosis of eosinophilic esophagitis (EoE).¹ According to the current clinical consensus and guidelines, histological observation of > 15 eosinophils/HPF should be a confirming factor for EoE diagnosis by itself.^{1,2} Furthermore, based on the response to high-dose proton pump inhibitor (PPI) treatment, esophageal eosinophilia has been classified into two entities, known as EoE (PPI-resistant) and PPI-responsive esophageal eosinophilia (PPI-REE), each showing a frequency of about 50%. Therefore, being able to distinguish EoE from PPI-REE prior to PPI treatment would be clinically important for improving a patient's quality of life and initiating early, effective treatment. However, all the methods tested to date, including clinical characteristics, endoscopic/histologic findings, pH monitoring and tissue/genetic markers, have failed to distinguish EoE from PPI-REE.^{3,4} That suggests that EoE and PPI-REE may be variations of a single disease entity.

Previously, Wen et al. used an EoE diagnostic panel (EDP) and demonstrated that untreated PPI-REE shares a largely similar molecular transcriptome with EoE.⁵ Since the study was restricted to a set of 94 esophageal transcripts, there is a possibility that the remaining, unexamined transcripts contain differences between the two types of disease. The whole-genome mRNA expression profiles of esophageal biopsy specimens might provide an unbiased insight into the local inflammatory mechanisms at the molecular level. Therefore, we employed a genome-wide approach to investigate whether EoE and PPI-REE are the same disease entity.

Detailed information about the methods is described in this article's Online

Repository at www.jacionline.org. Briefly, esophageal biopsy specimens derived from EoE ($n = 4$) and PPI-REE ($n = 6$) patients before PPI treatment and control specimens ($n = 4$) were subjected to genome-wide transcriptome analysis. Consequently, we confirmed the absence of major differences between EoE and PPI-REE by several analytical methods. For instance, unsupervised principal-component analysis of EoE, PPI-REE and control specimens showed no separation between EoE and PPI-REE specimens (**Fig 1, A**). As shown in **Fig 1, B**, we identified 1,263 (red circle) and 1,947 (blue circle) differentially dysregulated transcripts in the EoE and PPI-REE patients, respectively, compared to the controls on the basis of the following criteria: > 2-fold change between the two groups and a P -value of $< .05$ with a false discovery rate (**Fig 1, B**). Moreover, cluster analysis showed no separation between EoE and PPI-REE specimens (**Fig 1, C**). We show a list of 2,097 dysregulated genes at our web site: <http://ee.shimane-u-internal2.jp/25.html>. Gene ontology (GO) analysis of each EoE and PPI-REE transcriptome also revealed significant overlap of GO terms (15/21 in EoE; 15/22 in PPI-REE) and a similar tendency for the P -value, suggesting shared basic biological functions, processes and components between EoE (red bars) and PPI-REE (blue bars) (**Fig 1, D**). To further examine these similarities, scatter plots comparing EoE to PPI-REE transcriptomes are shown for all genes (**Fig 2, A**), all transcription factor gene expression levels (**Fig 2, B**) and the 2,097 dysregulated genes (**Fig 2, C**). When we also directly compared EoE and PPI-REE, we found 35 significant genes ($P < .05$, > 2-fold change, with Westfall-Young false discovery rate correction) whose raw signals were relatively low (**Table EII**).

Here, our comprehensive microarray data obtained from PPI-REE patients substantially overlapped with the data from EoE patients, strongly suggesting that they are the same or at least variations of a single disease. In good agreement with Wen et al.'s report,⁵ our microarray data also showed similar increases in inflammatory markers, including eotaxin-3 (*CCL26*), cadherin 26 (*CDH26*), periostin (*POSTN*), carboxypeptidase A (*CPA3*) and desmoglein-1 (*DSG1*) (**Fig 2, C** and gene list at <http://ee.shimane-u-internal2.jp/25.html>). In addition, our analysis demonstrates that none of the transcription factor genes showed significant differences between the two groups (**Fig 2, B**). These observations further support our conclusion that EoE and PPI-REE should be considered to be the same disease entity.

We speculate several reasons for why only half of esophageal eosinophilia patients respond to PPI. First, PPI-REE might comprise less severe cases of the same disease that are mild enough to respond to PPI treatment. Indeed, in PPI-REE patients, the 2,097 significant expression profiles were reversed by PPI therapy (see gene list at <http://ee.shimane-u-internal2.jp/25.html> and **Fig E1, A** in this article's Online Repository at www.jacionline.org). In particular, the reduction in eosinophils/HPF, as well as *CCL26* levels, has been reported by multiple groups on different continents.^{4,5} Moreover, commonly dysregulated genes showed no major differences, but were slightly shifted to EoE, indicating minor differential molecular reactions (**Fig 2, C**). Recent studies also revealed that patients with more severe histological findings showed a lower response rate to PPI treatment.^{6,7} Importantly, our data also showed that both the *CCL26* level (**Fig 2, D**) and eosinophil count (**Fig 2, E**) were higher in EoE than in PPI-REE. Furthermore, the *CCL26* level and eosinophil count (of each individual) were positively and significantly correlated ($r = .91$, $P < .0001$) (**Fig E1,**

B).

Second, esophageal eosinophilia might be heterogeneous due to the time passed since disease onset. Since the primary clinical symptoms are mild to moderate in most patients, it is difficult to investigate the development of acute esophageal eosinophilia. However, a long term follow-up study of PPI-REE reported that typical features of EoE were observed in 86% of patients at some time during the course.⁸ Thus, successful PPI treatment at an earlier clinical visit by these patients might have been reflected in a shorter disease duration.

Third, the composition of immune cells other than eosinophils might be slightly different. For instance, the number of group 2 innate lymphocytes in the esophageal epithelium was reported to be higher in EoE patients than in PPI-REE patients.⁹ Such lymphocytes might be responsible for PPI-resistant inflammation, resulting in PPI-unresponsiveness.

Compared to Wen et al.'s study,⁵ we observed minor differences, probably due in part to our smaller sample size, genetic and environmental factors, and the use of different array platforms between the studies. For instance, *KCNJ2* expression—a candidate gene for distinguishing EoE from PPI-REE—showed a tendency to be highly expressed in EoE compared to PPI-REE (**Fig 2, F**), but the difference was not significant in our study. While smaller in scale, a strength of our study is that we performed genome-wide transcriptome analysis, providing an unbiased insight.

In conclusion, the gene expression profiles of mucosal biopsy specimens showed no major differences between EoE and PPI-REE before PPI treatment. Accordingly, our data suggest a single syndrome, which calls into question the current guideline position that the PPI response points to the existence of two distinct diseases. Finally,

we note that this study has a small sample size, which means that it may lack the power to detect true effects. A follow-up study with a larger sample size is thus warranted.

This work was funded by Health and Labor Sciences Research Grants, Research on Intractable Diseases, from the Ministry of Health, Labour and Welfare, Japan (#12103036 to IN) and Grants from the Agency for Medical Research and Development, Japan (#27280401 to IN and #27280301 to KM). We express our sincere gratitude to all the members of the Japanese Research Group for Eosinophilic Gastrointestinal Disorders. We thank Ms. Kazue Takeda and Ms. Michiko Yamada (National Research Institute for Child Health and Development) for their fine technical support, and Lawrence W. Stiver (Tokyo, Japan) for proofreading the manuscript.

FIGURE LEGENDS

FIG 1. Expression profiles of esophageal biopsies and microarray analysis.

A, Unsupervised principal-component analysis of esophageal eosinophilia (EoE and PPI-REE) and the controls. **B,** Venn diagrams comparing the number of genes identified as dysregulated in both EoE and PPI-REE, each primarily compared to Control. **C,** Heatmap of 2,097 differentially dysregulated genes' expression profiles ($P < .05$, > 2 -fold). Clustering analysis within each group; each column represents an individual patient or control. **D,** Gene ontology analysis of each EoE and PPI-REE transcriptome.

FIG 2. Comparison between EoE and PPI-REE transcriptome genes identified by microarray analysis.

A, B and C, Spearman's correlation comparing absolute raw values for: **(A)** all genes subjected to microarray, **(B)** all transcription factor gene expression levels and **(C)** the 2,097 differentially dysregulated. Black, $P < .05$, > 2 -fold; orange, EDP gene. **D, E and F,** Eotaxin-3 (*CCL26*) mRNA expression, esophageal eosinophil counts and *KCNJ2* mRNA expression in indicated groups are shown (**** $P < .0001$, *** $P = .001$ and ** $P < .01$).

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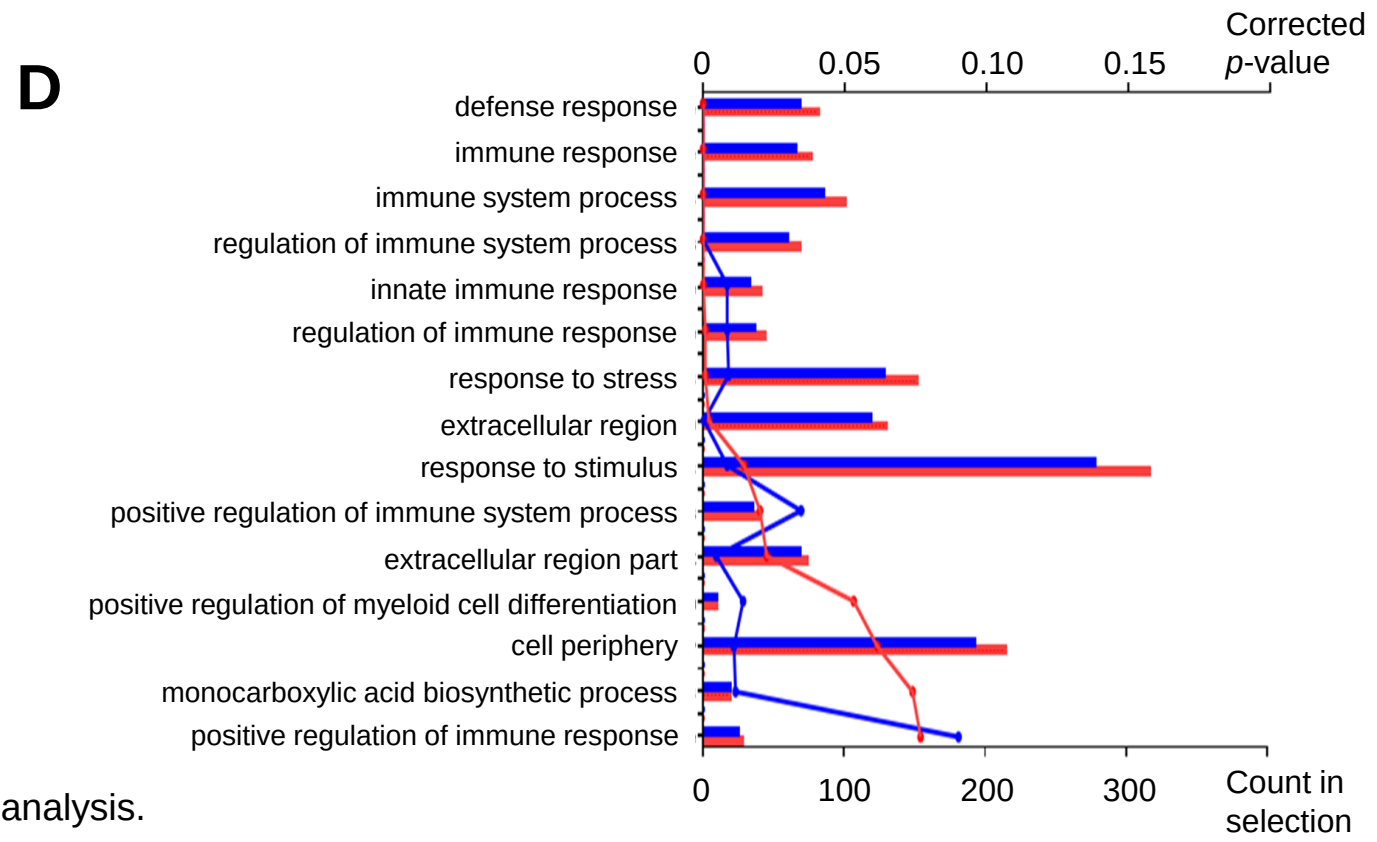
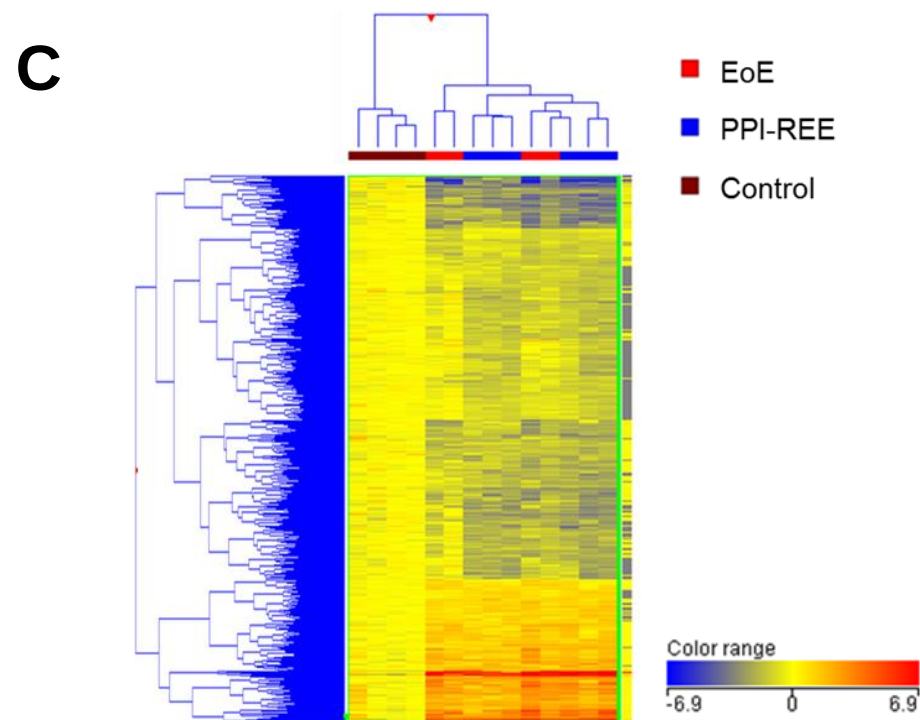
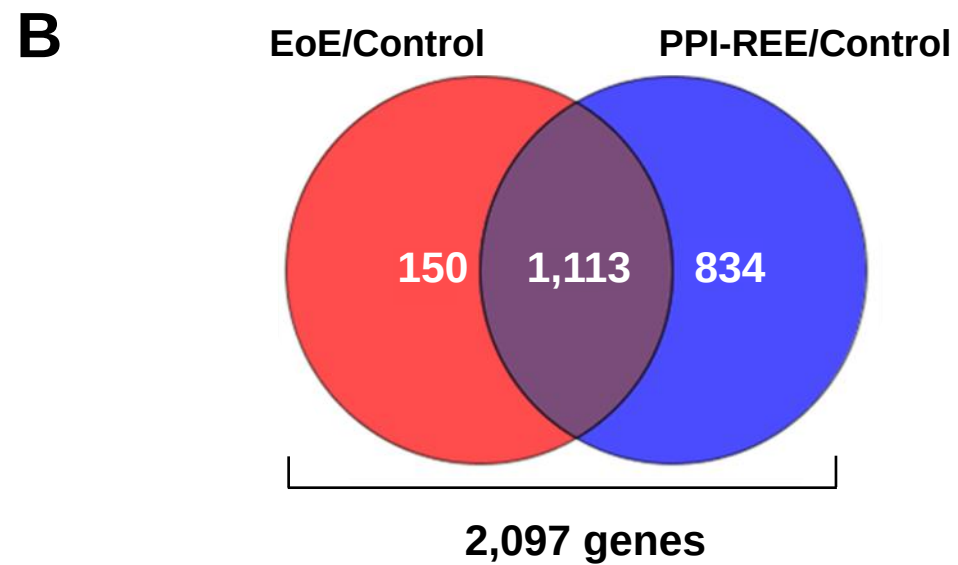
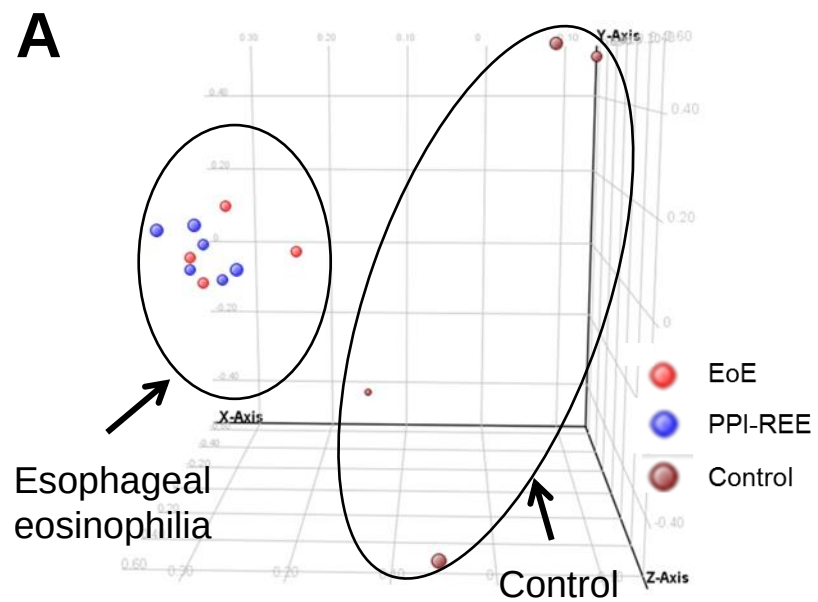


FIG 1. Expression profiles of esophageal biopsies and microarray analysis.

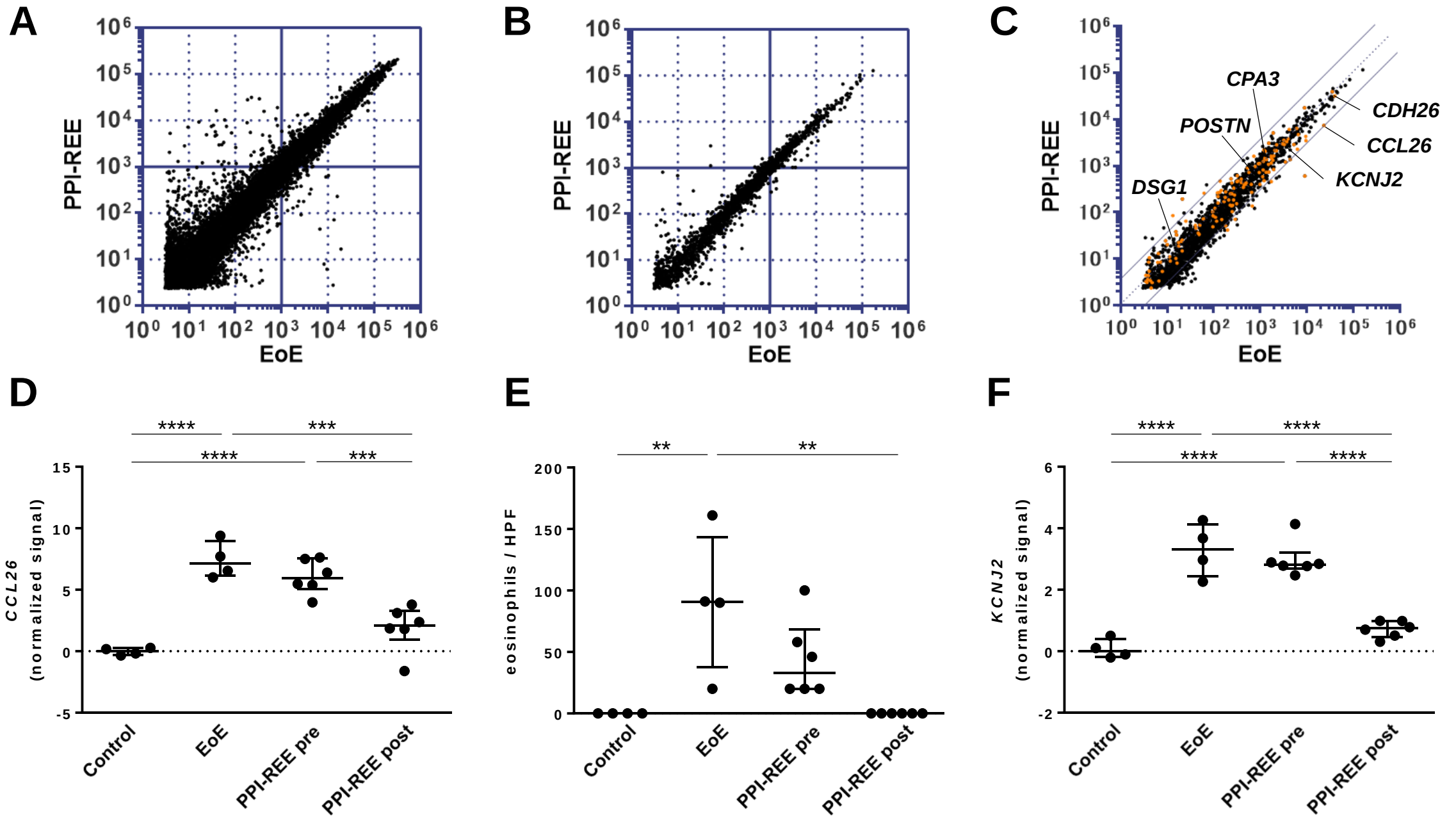


FIG 2. Comparison between EoE and PPI-REE transcriptome genes identified by microarray analysis.

Letter to the Editor, JACI

Online Repository Materials

**Eosinophilic Esophagitis vs Proton Pump Inhibitor-Responsive
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Online Repository Methods

Patient selection

We prospectively recruited patients with esophageal eosinophilia from April 2014 to July 2016. Among 16 patients who underwent GI endoscopy before PPI treatment, 10 patients showed dense eosinophilia in the esophageal epithelium and were included in this study. RNA specimens extracted from esophageal biopsy specimens from patient Nos. 1~10 were of suitable RNA quality and quantity for microarray analysis. Patient Nos. 5~10 were paired PPI-REE post-treated patients. As healthy volunteer controls, previously reported subjects (n = 4, Nos. 11~14) were also enrolled for microarray analysis.^{E1} The clinical characteristics for the patients are shown in Table EI.

Microarray analysis Inclusion criteria

EoE and PPI-REE were diagnosed in accordance with the 2011 consensus guidelines,^{E2} and subjects with other possible causes of esophageal eosinophilia were excluded. Control specimens were defined as < 1 eosinophil/HPF histologically, with no history of EoE or treatment with oral or systemic steroids. All esophageal biopsy specimens were obtained at the Department of Gastroenterology and Hepatology, Shimane University Hospital (Shimane, Japan). Informed consent was obtained from each study subject.

Specimens were placed in RNeasy[®] solution (QIAGEN, Valencia, CA, USA) at room temperature after biopsy and then stored at -80°C until gene expression profiling. As described previously,^{E1, E3} microarray analysis (Agilent Technologies, Santa Clara, CA, USA) was performed according to the manufacturer's instructions. Briefly, total RNA was extracted using an RNeasy Micro kit (Qiagen) and then evaluated with an Agilent Bioanalyzer and an RNA 6000 Nano kit (Agilent Technologies). The gene expression profiles were assessed using microarray technology with Agilent SurePrint G3 Human GE 8 x 60k. Data analysis was performed using GeneSpring software ver. 12.5 (Agilent Technologies). To normalize variation in the staining intensity between microarrays, the average difference for all genes on a given microarray was divided by the median of all measurements on the microarray. Genes in the EoE or PPI-REE patients that showed a significant difference in signal intensity compared with the same genes in the Controls ($P < .05$, t test with Benjamini–Hochberg false discovery rate correction) were considered to be up-regulated or down-regulated. Hierarchical clustering was performed using the gene expression data, contrasting EoE, PPI-REE and Controls.

Statistical analyses

Differences between the study groups were determined using the 1-way ANOVA followed by the Bonferroni multiple comparison post-test. Correlations were calculated using Spearman's r value. Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA). A $P < .05$ was considered significant.

Ethical approval

67 This study was performed according to a protocol approved by the institutional review
68 board of National Center for Child Health and Development, Tokyo, Japan (Acceptance
69 Number #725).
70

FIGURE LEGENDS

FIG E1. Comparison of esophageal transcriptomes using 2,097 genes.

A; Heatmap showing 2,097 differentially dysregulated gene expression profiles ($P < .05$, > 2 -fold). Clustering analysis within each group was performed; each column represents an individual patient or control. **B;** Correlations between the *CCL26* level and eosinophil count for all the samples included in this study ($r = 0.91$, $P < .0001$).

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TABLE EI. Clinical characteristics

No.	Age (y)	M/F	Race	Medication at biopsy	Diagnosis	Response to PPI therapy	Clinical symptoms			Endoscopic findings				Eosinophils		Atopic history			
							Dysphagia	Heartburn	Other esophageal symptom	Furrow	Concentric ring	White plaque	Stricture	Histology eosinophils/HPF	Peripheral blood eosinophils (μ l)	BA	AR	AD	FA
1	71	F	Asian	-	EoE	-	-	-	+	-	-	-	-	161	868	+	-	-	-
2	66	F	Asian	-	EoE	-	+	-	+	+	-	-	-	91	546	-	-	-	+
3	38	M	Asian	-	EoE	-	+	-	+	+	-	+	-	90	720	-	+	+	-
4	43	F	Asian	-	EoE	-	+	-	-	-	+	-	-	20	218	-	+	-	+
5	53	M	Asian	-	PPI-REE	+	+	+	-	+	+	+	-	20	298	-	+	-	-
6	43	M	Asian	-	PPI-REE	+	+	+	-	+	-	+	-	58	179	-	+	-	+
7	41	M	Asian	-	PPI-REE	+	-	-	-	+	+	+	-	46	319	-	+	+	-
8	76	F	Asian	-	PPI-REE	+	-	-	+	-	+	+	-	20	80	-	-	-	-
9	71	M	Asian	-	PPI-REE	+	+	-	-	+	+	+	-	100	81	-	+	-	+
10	48	M	Asian	-	PPI-REE	+	+	-	-	+	+	-	-	20	280	-	+	-	-
11	59	M	Asian	-	Control	NA	-	-	-	-	-	-	-	< 1	NA	-	-	-	-
12	42	M	Asian	-	Control	NA	-	-	-	-	-	-	-	< 1	NA	-	-	-	-
13	44	M	Asian	-	Control	NA	-	-	-	-	-	-	-	< 1	NA	-	-	-	-
14	53	F	Asian	-	Control	NA	-	-	-	-	-	-	-	< 1	NA	-	-	-	-

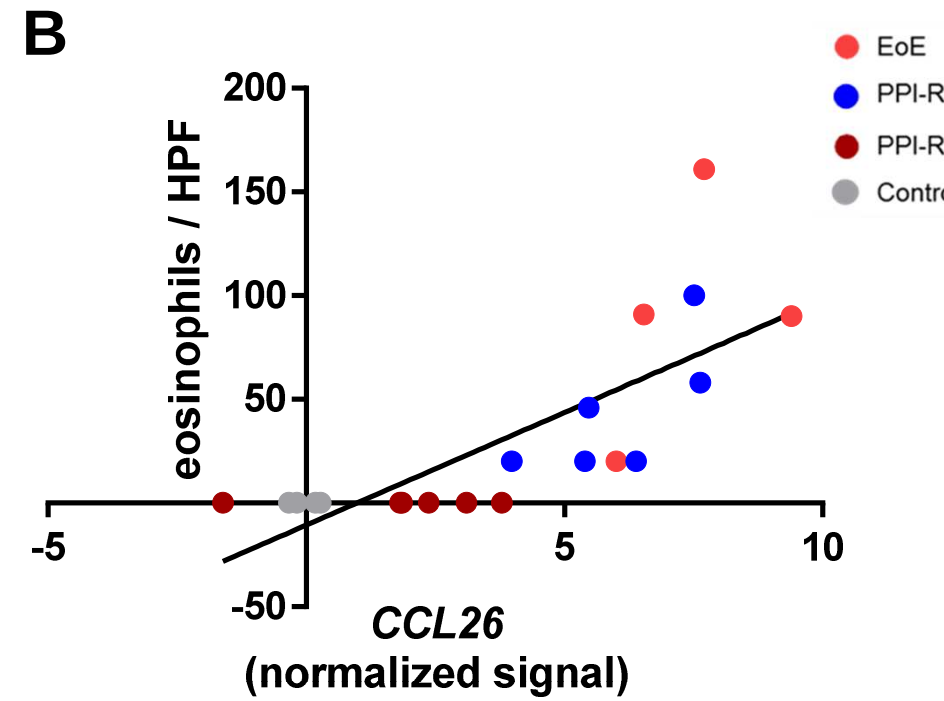
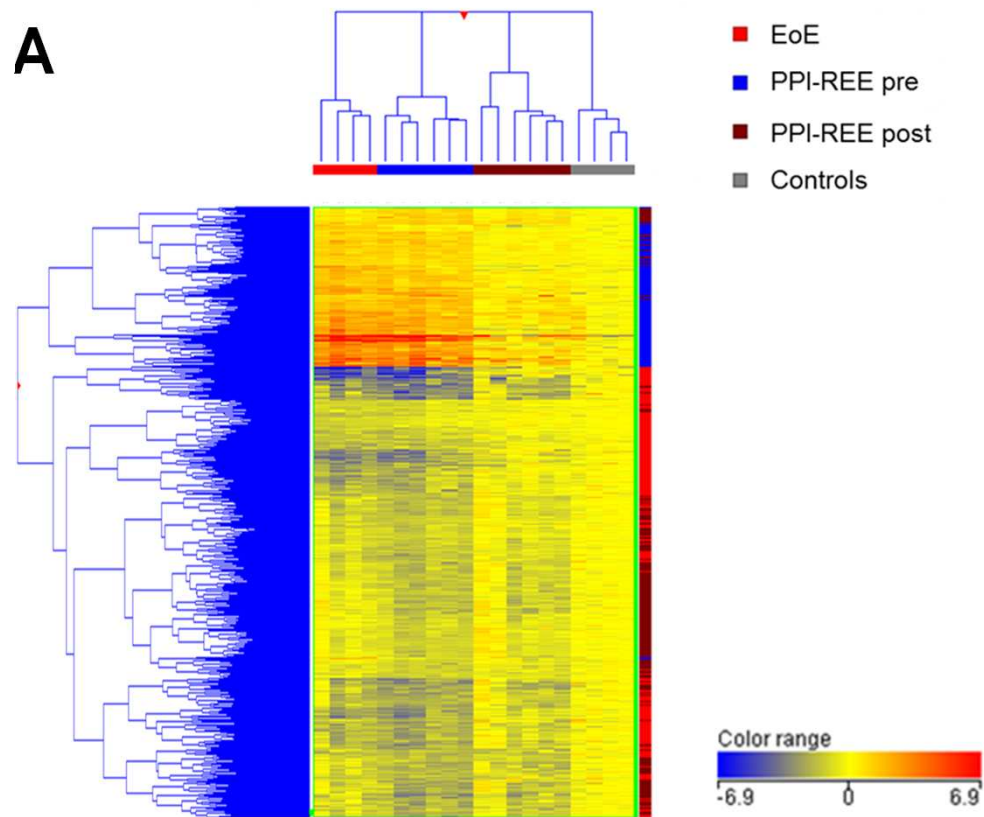
EoE, eosinophilic esophagitis; *PPI-REE*, Proton Pump Inhibitor-responsive esophageal eosinophilia; *PPI*, Proton Pump Inhibitor; *NA*, not applicable; *BA*, bronchial asthma; *AR*, allergic rhinitis; *AD*, atopic dermatitis; *FA*, food allergy.

TABLE EII. List of the 35 significant expression profiles ($P < .05$, > 2 -fold change)* of EoE / PPI-REE pre

Probe Name	Fold Change EoE / PPI-REE pre	Raw Signal		Gene Symbol	Gene name
		EoE	PPI-REE pre		
A_33_P3350306	10.4	39.8	3.6	ZNF589	zinc finger protein 589
A_19_P00317960	6.3	21.7	3.2	KC6	keratoconus gene 6
A_19_P00806092	5.3	19.5	3.4		
A_19_P00327175	4.9	20.2	3.8		
A_33_P3272493	4.9	32.4	6.2	CD209	CD209 molecule
A_19_P00315832	4.7	151.0	30.2		
A_19_P00806685	4.6	52.5	10.6		
A_24_P13831	4.4	15.4	3.3	SNX20	sorting nexin 20
A_19_P00322426	4.0	14.4	3.4	LOC441204	hypothetical LOC441204
A_19_P00807468	3.8	39.1	9.6	lnc-HIST1H1A-1	lnc-HIST1H1A-1:2
A_33_P3397127	3.7	27.2	6.9		
A_23_P22761	3.7	20.9	5.3	SHOX	short stature homeobox
A_33_P3234031	3.6	21.0	5.5	lnc-TBC1D29-1	lnc-TBC1D29-1:1
A_33_P3389336	3.6	20.6	5.4	LOC101929918	hypothetical LOC101929918
A_19_P00808669	3.2	49.6	14.4		
A_33_P3365142	3.2	27.5	8.2	GAD1	glutamate decarboxylase 1
A_19_P00331739	3.1	16.9	5.1		
A_33_P3423171	3.1	9.1	2.7	WDR6	WD repeat domain 6
A_33_P3318642	3.1	11.9	3.6	MC1R	melanocortin 1 receptor
A_33_P3228600	3.1	11.2	3.4	CPA5	carboxypeptidase A5
DCP_20_7	2.9	99.7	32.1		
A_33_P3404566	2.9	21.0	6.9		
A_23_P397391	2.8	49.9	16.6	FFAR2	free fatty acid receptor 2

A_33_P3225507	2.8	109.3	36.5	OR10G2	olfactory receptor, family 10, subfamily G, member 2
A_19_P00811814	2.7	8.9	3.1		
A_19_P00326972	2.6	169.1	60.6		
A_33_P3272628	2.6	21.5	7.7	FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide
A_33_P3327818	2.6	1452.7	524.4		
A_33_P3295690	2.5	31.4	12.0	C16orf90	chromosome 16 open reading frame 90
A_23_P208373	2.5	81.7	31.3	CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6
A_33_P3287105	2.4	565.0	221.6		
A_19_P00322337	2.4	42.8	17.1	lnc-CBLB-4	lnc-CBLB-4:1
A_24_P132633	2.2	19.5	8.5	TMEM252	transmembrane protein 252
A_33_P3341154	2.1	40.3	17.7	INTS1	integrator complex subunit 1
A_19_P00316288	-3.0	7.4	21.2	IPW	imprinted in Prader-Willi syndrome

*With Westfall-Young false discovery rate correction.



. Comparison of esophageal transcriptomes using 2,097 genes.