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Title: Association of Eosinophilic Esophagitis and Hypertrophic Cardiomyopathy

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Supplementary Figure 1. Relative expression of calreticulin 3 (CALR3) is decreased by 17% (p=0.001) by microarray in the epithelial biopsies of EoE patients (n = 18) compared to normal control biopsies (n = 14). Error bars represent standard error of the means (s.e.m.)

Supplementary Table 1. Summary of patients with hypertrophic cardiomyopathy and eosinophilic esophagitis

Patient Identifier (Sex)	Cardiology History			Gastroenterology History				Genetics		Other Significant History
	Diagnosis	TTE Findings	Age at Diagnosis (years)	Diagnosis	Peak Intraepithelial Count (Eos/hpf)	Failed PPI	Age at Diagnosis (years)	Locus	Mutation	
1[a] (M)	HCM	basal septal hypertrophy of 19 mm, LVOT obstruction	33; symptom onset age 28	EoE	120	Yes	30; symptom onset age 23	*MYPBC3*	c.1624G>C, p.E542Q	allergic rhinitis asthma
2 (M)	HCM	LV diastolic septal thickness Z score of 5.13, LV diastolic wall thickness Z score of 2.93, LV systolic wall thickness Z score of 2.95	1	EoE	93	Yes	17	Unknown	N/A	familial osteogenesis imperfecta I (grandmother, mother, sister, and brother affected) septal myomectomy
3 (M)	HCM	LV diastolic wall thickness Z score of 2.39	21	EoE	15 (on GJ tube feeds)	Yes	20	Chr 1 deletion	10.88-Mb deletion, 1p36.33 to 1p36.22	1p36 syndrome septal myomectomy

Abbreviation: EoE, eosinophilic esophagitis; Eos, eosinophils; HCM, hypertrophic cardiac myopathy; hpf, high-power field; M, male; TTE, transthoracic echocardiography; PPI, proton pump inhibitor; Chr, chromosome; N/A, not applicable, mm, millimeters; LVOT, left ventricular outflow tract; LV, left ventricular; GJ, gastrojejunostomy.

[a] Index patient

Supplementary Table 2. Demographics of eosinophilic esophagitis and control cohorts of candidate-gene association study

	CCHMC EoE	CoFAR EoE	CGCC Control	dbGaP Control
Sex (n)				
Males	376	150	376	3,479
Females	138	72	384	5,007
Age Range	3 months - 60 years	6 months - 65 years	2-18 years	> 50 years

Abbreviation: CCHMC, Cincinnati Children's Hospital Medical Center; CGCC, Cincinnati Genomic Control Cohort; CoFAR, Consortium of Food Allergy Research; dbGAP, Database of Genotypes and Phenotypes; EoE, eosinophilic esophagitis

30% of CCHMC and 51% of CoFAR cases had proton pump inhibitor (PPI) therapy before diagnostic endoscopy. Control subjects (without EoE) included the self-reported Caucasian subjects in the Cincinnati Genomic Control Cohort (CGCC) (*n* = 760; age range of 2-18 years) and an external control cohort (without EoE) acquired from a Database of Genotypes and Phenotypes (dbGaP) University of Michigan study (*n* = 8,486). In the CCHMC and CoFAR cohorts, 73% and 68% of EoE cases were male, respectively, and EoE cases had an age range of 3 months-60 years. The external control cohort (dbGaP) was collected through an aging and retirement study; subjects in this control cohort were typically older than the patients with EoE at the time of DNA collection.

Supplementary Table 3. Association between single-nucleotide polymorphisms in the *MYBPC3* gene and eosinophilic esophagitis[a]

SNP	Genomic Region	Affected MAF	Unaffected MAF	*Permutated*[b] *P* value	Adjusted OR
rs11570053	47371261	0.001	0.000	0.0004	NA
rs182114979	47319500	0.001	0.000	0.0011	12.60
rs34937994	47389638	0.395	0.352	0.0020	1.20
rs141947880	47385350	0.035	0.022	0.0038	1.63
rs3824869	47378245	0.382	0.343	0.0041	1.18
rs11601200	47395209	0.035	0.022	0.0041	1.62
rs2278890	47399602	0.390	0.353	0.0071	1.17
rs12801188	47388214	0.385	0.349	0.0078	1.17
rs11570094	47359706	0.267	0.303	0.0110	0.84
rs118134583	47323727	0.014	0.024	0.0121	0.57
rs200416580	47332836	0.014	0.024	0.0122	0.57
rs75994385	47310397	0.014	0.024	0.0136	0.57
rs3729986	47371598	0.083	0.064	0.0138	1.33
rs3740689	47380593	0.428	0.477	0.0140	0.82
rs11570041	47374633	0.014	0.025	0.0144	0.58
rs117847273	47379023	0.014	0.025	0.0146	0.58
rs75958295	47347644	0.010	0.019	0.0166	0.54
rs202076451	47377516	0.081	0.101	0.0222	0.78
rs10747	47376544	0.018	0.028	0.0253	0.63
rs11570034	47375889	0.018	0.028	0.0253	0.63
rs6485749	47332875	0.001	0.000	0.0317	5.04
rs11039176	47339169	0.011	0.019	0.0377	0.59
rs6485752	47374911	0.016	0.024	0.0444	0.65
rs75350544	47333729	0.011	0.018	0.0449	0.60

Abbreviation: SNP, single-nucleotide polymorphism dbSNP ID; MAF, minor allele frequency; *P* value, probability from a logistic regression analysis; OR, odds ratio; *MYBPC3*, cardiac myosin-binding protein C3.

[a]Genome-wide association study using 736 eosinophilic esophagitis cases and 9,246 control cases

[b] Data represents one locus tested by an a priori hypothesis for MYBPC3's association with EoE. Therefore, permutation analysis, rather than multiple testing correction, was performed.

Supplementary Table 4. Hypertrophic Cardiomyopathy–Causing Genes having Common Variants Associated with Eosinophilic Esophagitis

Gene	Function	Chr	SNP[a]	BP	Minor Allele	MAF EoE	MAF Control	Major Allele	*P* Value	OR
Actin, alpha, cardiac muscle 1 (*ACTC1*)	found in muscle tissues and a major constituent of the contractile apparatus	15	rs113887107	35108264	A	0.063	0.083	G	0.0201	0.75
Actinin, alpha 2 (*ACTN2*)	actin-binding protein with multiple roles in different cell types	1	rs10925210	236906807	T	0.387	0.352	A	0.0171	1.16
Calreticulin 3 (*CALR3*)	calcium-binding chaperones localized mainly in the endoplasmic reticulum	19	rs45510495	16620302	A	0.017	0.027	G	0.0456	0.63
Calsequestrin 2 (*CASQ2*)	calcium-binding protein that stores calcium for muscle function	1	rs3810998	116311924	A	0.265	0.305	C	0.0046	0.82
Caveolin 3 (*CAV3*)	component of the caveolae plasma membranes found in most cell types	3	rs12631502	8803700	G	0.166	0.135	A	0.0035	1.27
Cysteine- and glycine-rich protein 3 (*CSRP3*)	may be involved in regulatory processes important for development and cellular differentiation	11	rs74756565	19215569	C	0.033	0.018	A	0.0001	1.84
Junctophilin 2 (*JPH2*)	junctional complexes between the plasma membrane and endoplasmic/sarcoplasmic reticulum ,which mediate cross talk between cell surface and intracellular ion channels	20	rs6017273	42778766	G	0.145	0.179	A	0.0033	0.78
LIM domain binding 3 (*LDB3*)	interacts with alpha-actinin-2 through its N-terminal PDZ domain and with protein kinase C via its C-terminal LIM domains	10	rs12570666	88510097	G	0.252	0.288	A	0.0099	0.83
Myosin, heavy chain (*MYH7, MYH6*)	changes in the relative abundance of this protein and the alpha (or fast) heavy subunit of cardiac myosin correlate with the contractile velocity of	14	rs11465523	23845754	A	0.050	0.037	G	0.0278	1.37

	cardiac muscle									
Myosin, light chain 2 (*MYL2*)	regulatory light chain associated with cardiac myosin beta (or slow) heavy chain	12	rs116876453	111341702	C	0.026	0.038	A	0.0462	0.68
Troponin C type 1 (*TNNC1*)	central regulatory protein of striated muscle contraction	3	rs62257617	52492601	A	0.066	0.052	G	0.0398	1.29
Tropomyosin 1 (*TPM1*)	provides stability to actin filaments	15	rs2414814	63362379	A	0.054	0.041	C	0.0348	1.33
Titin (*TTN*)	adhesion template for the assembly of contractile machinery in muscle cells	2	rs2054708	179645577	G	0.052	0.075	A	0.0053	0.68

Abbreviation: Chr, chromosome; EoE, eosinophilic esophagitis; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism; BP, base pair

[a]The listed SNP is the most significant association in each region

Supplementary Figure 1