

Supplementary Tables and Figures:

Supplementary Table 1. Validated damaging *de novo* variants identified in EoE patients by WES

Chr	Position ¹	Classification	Gene symbol	Transcript	Exon	Base change	Amino acid change
3	38182638	Nonsynonymous	<i>MYD88</i>	NM_002468	5	c.791G>A	p.Arg264Gln
4	149356614	Frameshift deletion	<i>NR3C2</i>	NM_000901	2	c.1399delT	p.Tyr467fs
6	33170716	Nonsynonymous	<i>SLC39A7</i>	NM_001077516	7	c.970G>C	p.Ala324Pro
6	36926963	Nonsynonymous	<i>PI16</i>	NM_001199159	3	c.214C>T	p.Arg72Trp
9	286591	Nonsynonymous	<i>DOCK8</i>	NM_203447	3	c.287C>T	p.Thr96Met
12	48459414	Frameshift deletion	<i>SENP1</i>	NM_001267595	11	c.1084delG	p.Glu362fs
12	133219189	Nonsynonymous	<i>POLE</i>	NM_006231	37	c.4855T>C	p.Tyr1619His
13	95860082	Nonsynonymous	<i>ABCC4</i>	NM_005845	7	c.883T>C	p.Phe295Leu
14	68244292	Nonsynonymous	<i>ZFYVE26</i>	NM_015346	25	c.4958T>G	p.Leu1653Arg

¹Genome build hg19 coordinates

Abbreviations used: Chr, chromosome; EoE, eosinophilic esophagitis; WES, whole-exome sequencing

Supplementary Table 2. Validated compound heterozygous variants identified in EoE patients by WES

Chr	Position ¹	Classification	Gene symbol	Transcript	Exon	Base change	Amino acid change	ESP MAF ²	No. Hets ³
17	4535035	Nonsynonymous	<i>ALOX15</i>	NM_0011140	14	c.1849C>T	p.Pro617Ser	0.0037	4
17	4535314	Nonsynonymous	<i>ALOX15</i>	NM_0011140	13	c.1679C>T	p.Thr560Met	0.0167	5
18	64172434	Nonsynonymous	<i>CDH19</i>	NM_021153	12	c.1934G>C	p.Gly645Ala	0.0255	8
18	64218391	Nonsynonymous	<i>CDH19</i>	NM_001271028	5	c.715A>G	p.Thr239Ala	0.0033	2
3	3143465	Nonsynonymous	<i>IL5RA</i>	NM_000564	6	c.278G>A	p.Gly93Asp	N/A	2
3	3144388	Nonsynonymous	<i>IL5RA</i>	NM_000564	5	c.199G>A	p.Val67Met	0.0047	2
20	60902022	Nonsynonymous	<i>LAMA5</i>	NM_005560	39	c.5113G>A	p.Val1705Met	0.0005	2
20	60910124	Nonsynonymous	<i>LAMA5</i>	NM_005560	20	c.2435A>C	p.Lys812Thr	0.0305	4
18	44098219	Nonsynonymous	<i>LOXHD1</i>	NM_001145472	16	c.1939G>T	p.Val647Phe	N/A	2
18	44146406	Nonsynonymous	<i>LOXHD1</i>	NM_144612	17	c.2251C>T	p.Arg751Trp	0.0025	2
4	38775794	Nonsynonymous	<i>TLR10</i>	NM_001017388	2	c.1418T>C	p.Ile473Thr	0.0373	9
4	38776104	Stopgain	<i>TLR10</i>	NM_001017388	2	c.1108C>T	p.Gln370*	0.0001	2
5	110428060	Nonsynonymous	<i>WDR36</i>	NM_139281	1	c.74T>C	p.Leu25Pro	0.0116	4
5	110434448	Nonsynonymous	<i>WDR36</i>	NM_139281	4	c.488C>T	p.Ala163Val	0.0057	2

¹Genome build hg19 coordinates; ²NHLBI ESP European MAF; ³Number of heterozygous EoE patients at the specified variant position (includes unrelated and related patients)

Abbreviations: Chr, chromosome; EoE, eosinophilic esophagitis; ESP, Exome Sequencing Project; MAF, minor allele frequency; N/A, not available; No., number; Hets, heterozygotes; WES, whole-exome sequencing

Supplementary Table 3. *DHTKD1* rare variant burden analysis in EoE

Chr	Start ¹	Stop ¹	Gene symbol	Transcript	No. <i>DHTKD1</i> variants (n)		<i>p</i> -value (one-sided) ³
					Cases (n = 37)	Controls (n = 379) ²	
10	12110916	12165227	<i>DHTKD1</i>	NM_018706	5	15	0.01

¹Genome build hg19 coordinates; ²Individuals of European ancestry from the 1000 Genome Project (Phase 1 v3); ³One-sided *p*-value from KBAC testing with 1,000 permutations as described by Li and Leal (2010).
Abbreviations: Chr, chromosome; EoE, eosinophilic esophagitis; KBAC, kernel-based adaptive cluster

Supplementary Table 4. Differentially regulated EoE transcriptome genes in family 443

Gene Symbol	<i>p</i> -value ¹	Fold change		
		[EoE] vs [CTL]	[CTL] vs [family 443]	[EoE] vs [family 443]
<i>SFRP1</i>	2.84E-06	5.28	-11.76	-2.23
<i>APOL1</i>	7.77E-06	14.37	-28.94	-2.01
<i>RNASE1</i>	1.46E-05	4.37	-12.73	-2.91
<i>AADAC</i>	2.09E-05	3.79	-10.66	-2.82
<i>CCL26</i>	2.09E-05	327.05	-759.89	-2.32
<i>CTSW</i>	2.09E-05	2.04	-4.99	-2.45
<i>S100A12</i>	2.09E-05	-5.60	12.70	2.27
<i>RSAD2</i>	3.95E-05	2.78	-6.91	-2.48
<i>RARRES3</i>	6.12E-05	4.27	-8.60	-2.01
<i>RDH12</i>	6.76E-05	-2.58	7.24	2.80
<i>TPSAB1</i>	1.17E-04	16.31	-58.39	-3.58
<i>UBD</i>	1.17E-04	18.13	-36.35	-2.00
<i>SLC15A3</i>	2.34E-04	2.33	-5.58	-2.39
<i>LY6K</i>	2.50E-04	-2.68	7.60	2.83
<i>FTH1</i>	2.66E-04	-10.33	3.94	-2.62
<i>IFI27</i>	3.86E-04	5.67	-11.59	-2.04
<i>ENDOU</i>	1.38E-03	-11.01	45.10	4.10
<i>CPA3</i>	1.65E-03	49.98	-122.59	-2.45
<i>S100A8</i>	2.45E-03	-4.00	9.50	2.37
<i>CFB</i>	2.95E-03	7.71	-15.74	-2.04
<i>TPSB2</i>	3.04E-03	14.62	-60.03	-4.11
<i>SLURP1</i>	3.31E-03	-11.55	34.31	2.97
<i>CXCL14</i>	3.84E-03	-2.84	11.60	4.09
<i>IGFL1</i>	3.84E-03	-15.02	33.21	2.21
<i>ZNF365</i>	4.43E-03	-13.51	29.52	2.18
<i>ALOX12</i>	8.16E-03	-10.89	27.92	2.56
<i>HLA-A</i>	8.16E-03	2.22	-4.99	-2.25
<i>ACSL5</i>	8.35E-03	3.81	-7.73	-2.03
<i>LOX</i>	1.27E-02	6.99	-3.38	2.07
<i>NSG1</i>	1.28E-02	-2.38	4.99	2.10
<i>KRT6B</i>	1.75E-02	-6.31	25.00	3.96
<i>RNASE7</i>	2.03E-02	-14.16	5.41	-2.62
<i>IL36A</i>	2.51E-02	-7.88	3.08	-2.56
<i>OR2A7</i>	2.51E-02	2.45	-7.86	-3.21
<i>CWH43</i>	3.42E-02	-5.35	12.41	2.32
<i>KRT6C</i>	3.43E-02	-4.82	9.95	2.07

¹Corrected *p*-values using ANOVA unequal variance with Tukey post-hoc test and Benjamini-Hochberg false discovery rate.

Abbreviations: EoE, eosinophilic esophagitis; NL, control

Supplementary Figure 1. Sequence homology between DHTKD1 and OGDHL

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DHTKD1      1      10      20      30
OGDHL      MSQRLRLPSRLGVQAARLLAAHDVPVFGWRSSSGPPNPPSSRGCGSSYMEEMYFAWLENPQSVHKSWSDFRASEEAFSGSAQDRP
consensus>50 msqrlrlpsrlgvaarllaaahdvvpvfgwrssrsmmapATfaaakgGIGssymeemyfawlenpqavhlfWdgfrEagvyafsGsyqPRK

DHTKD1      40      50      60      70      80      90      100
OGDHL      PESRE.PQGALER.....PPVDHGLARLVTVYCEHGHKAAKINPFTTGOALTENVPEIQAL.....VQTQGPPE.HHAGL
consensus>50 PevveepqgAverrtktsklvevdlaqvrL!rvYqihGHhAqi#PLfil#ALL#nvvei#littidklafydlqvqdl#gefqlhTagl

DHTKD1      110     120     130     140     150     160     170     180     190
OGDHL      LNMGKEEAStEVLVYINQIYCGGTSITSQLQSQDEKDFAKRFEELQKETFTTERKHISKLMLESQEDHFLAKTKESTVKRYGGEA
consensus>50 inmge#elSLeE!ivyL#iYcqqIgiEfmf#dv#ch#WiaqfEelqvmqFssEEkhlLal$veSmeF#dFlArKfSsvKR#GLEGA

DHTKD1      200     210     220     230     240     250     260     270     280
OGDHL      ESMGMFFHELLKMSAYSGITDVIIGMPHGRRLNLITGLLQFPPLMFRKMRGLSEFPENFSATGDVLSHLTSSVD.LYFGAHHPLHVTML
consensus>50 EvMigflheiidmSaymGie#ViIGMPHGRRLNvLanviqfdliEliFqcmdgllEfaenfeasGDVlyHLgmyv#riyfvannhihs$V

DHTKD1      290     300     310     320     330     340     350     360     370
OGDHL      PNPShLEAVNPVAVGKTGRGRQSSRDGDYSPDNSAQPPGDRVICLVHGDAASCGQCIVPETFTLSNLEHFRIGGSVHLVNNQLGYTTPA
consensus>50 aNPShLEAVNPVvvgKTkaeQfyRqDgdyspdsnaqqGdkViciLVHGDAaFaGQG!VyETfHLS#LPh#rinGsVhV!VNNQIG#TTda

DHTKD1      380     390     400     410     420     430     440     450     460
OGDHL      ERGRSSLYCSDIgKLVGCAIIVHVGDSPEPVVRAIRLAFEYQROFRKDVLLIDL CYRQWGHNELDEPFYTNPI MYKITRARKSPD TYAE
consensus>50 emaRSSlYcsD!akvVnaaIiHVNaDdPEeV!yvcrvAfEyqngFnKDV!!DLvCYRqrGHNE$DEPM#T#PI MYKiIhaqvp!ldkYA#

DHTKD1      470     480     490     500     510     520     530     540
OGDHL      HLIAGCLMTOEVS3IKSSYYAKLNDHLNNMAHY..RPPALNLQAHWQGLAQPE...AQIHTWSIGVPLDLRLRFVGMKSVEVPRQL.QMB
consensus>50 hLIAGClvTl#EveEiiakYyail#alnmmadykihihialnL#ahWqGlfv#gepaqiTcpaTG!PiD$Lf!GmvaveVPlelfiqH

DHTKD1      550     560     570     580     590     600     610     620     630
OGDHL      SHLLKTHYQSRMEKMDGIGKLDAWATLALALGSLLAQCFNVRISGQDVGRGTFSSQRHAIVVCQETD.DHYIPLNHMDENCKGFLVSNPS
consensus>50 sgllksh!lrgmedMmdnikvDWAIAEY$AlGSLLa#GinVRLSGQDVGRGTFSSQRHa!vvdQEvDrdy!P$NH$dP#Qag!leVcNSp

DHTKD1      640     650     660     670     680     690     700     710     720
OGDHL      LSEEAVLGFELGMAIESPnllVLEAQQGDFfNgAQiLiDqFISgC#AKWvlnqGIViLLPHGm#GmGP#HSSARiERFLQMc#dde#av
consensus>50 LSEyaVLGFELGmaieSPnllVLEAQQGDFfNgAQiLiDqFISgC#AKWvlnqGIViLLPHGm#GmGP#HSSARiERFLQMc#dde#av

DHTKD1      730     740     750     760     770     780     790     800
OGDHL      DG.....DTVNMFPVHPTTPAQYFELLRROMVRNFRKPLIVASPKMILRLPAVSTLOEAPGTTFNPIVIGD...SSVDPKKVK
consensus>50 daftkdfevsqlydvNmiVvncsTPA#YFHvLRRQivlnFRKPLI!fsPKMLRLlPeAvSsl#MvpGTSF#pVigfdgaaavdPeqVqr

DHTKD1      810     820     830     840     850     860     870     880     890
OGDHL      LVFCSGKHfYSLVKQRESLGAKKHDFAIIRVEELCPFFLDLSLQRMSSKYKHVKDHIWQOEPQNMGPWSFVSPRFEEKQLA..CKLRLVGR
consensus>50 L!FCsGKvYdLVK#ReSlidlkeedvAIIRvE#icPPF1DliQeMeKYkgvk#liWcQEEhQNMgyd%!SPRFmkiLarackirlVGR

DHTKD1      900     910
OGDHL      PPLPVPAVIGITVHIHQHEDI LAKTFA.....
consensus>50 dPlavPAvGignvHLvqlediLdkaFnlqafegktf

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Supplementary Figure 2. *DHTKD1* sequence conservation across multiple species

