

Supplementary Information

Medical Records-based Genetic Studies of the Complement System

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Note: Supplementary Tables S6-9, S11-S13 are too large to present in this format, and are provided as Excel files.

Supplementary Tables.

Table S1: Basic characteristic of study subjects in eMERGE-III by study site.

Sites	Sample Size (N)	Mean Visits* (SD)	Mean Age (SD)	% Female
Boston Children's	884	32.57 (42.08)	17.69 (5.71)	42%
CCHMC	6,402	29.02 (29.05)	23.13 (103.31)	42%
CHOP	10,186	27.70 (27.99)	19.72 (6.47)	42%
Columbia	2,035	71.70 (75.08)	64.52 (20.86)	48%
Geisinger	3,037	102.61 (61.28)	71.60 (16.28)	47%
Harvard	30,036	90.44 (79.35)	59.14 (17.30)	54%
Kaiser/GHC/UW	3,279	131.03 (76.29)	93.95 (12.29)	57%
Mayo Clinic	10,048	93.08 (70.04)	72.45 (42.31)	50%
Marshfield clinic	4,045	213.87 (89.49)	80.11 (9.98)	61%
Mt. Sinai	6,032	66.28 (53.24)	62.16 (16.87)	58%
Northwestern	4,792	82.58 (67.60)	62.18 (15.18)	83%
Vanderbilt	21,362	79.49 (71.31)	66.31 (17.14)	55%
Overall	102,138	83.58 (78.47)	58.15 (37.32)	54%

CCHMC: Cincinnati Children's Hospital Medical Center, CHOP: Children's hospital of Philadelphia,

Visits*: Clinic visits.

Table S2: Distribution of eMERGE-III participants by the number of C3/C4 tests performed.

Test Counts	No autoimmune diagnosis		With autoimmune diagnosis	
	C3 Levels	N (%)		N (%)
1	1315 (33.29)		1221 (30.92)	
2	215 (5.44)		389 (9.85)	
3	4 (1.03)		144 (3.64)	
4	11 (0.27)		102 (2.58)	
5	6 (0.15)		79 (2.00)	
6	5 (0.12)		43 (1.08)	
7	2 (0.05)		32 (0.81)	
8	0 (0.00)		33 (0.83)	
9	9 (0.22)		21 (0.53)	
10	2 (0.05)		31 (0.78)	
> 10 tests	15 (0.37)		241 (6.10)	
C4 Levels				
1	1352 (33.81)		1246 (31.16)	
2	220 (5.50)		390 (9.75)	
3	40 (1.00)		144 (0.60)	
4	12 (0.30)		102 (2.55)	
5	5 (0.12)		74 (1.85)	
6	4 (0.10)		44 (1.10)	
7	2 (0.05)		37 (0.92)	
8	0 (0.00)		30 (0.75)	
9	0 (0.00)		24 (0.60)	
10	1 (0.02)		30 (0.75)	
> 10 tests	14 (0.35)		227 (5.67)	

Table S3: The overall distribution of autoimmune and inflammatory disorders among GWAS participants with C3 and C4 levels.

Autoimmune and Inflammatory Disease Sub-phenotypes (eMERGE autoimmunity algorithm)	Number of participants with C3 Levels (% overall cohort)	Number of participants with C4 Levels (% overall cohort)
		N (%)
Arthritis Rheumatoid arthritis (RA)	1026 (26.06)	1031 (26.11)
Connective Lupus erythematosus	340 (8.63)	338 (8.56)
Vasculitis Arteritis	301 (7.64)	298 (7.54)
Connective Sjogren's syndrome	240 (6.09)	235 (5.95)
Skin Raynaud	209 (5.30)	209 (5.29)
Skin Psoriasis	187 (4.74)	192 (4.86)
Connective Scleroderma	173 (4.39)	173 (4.38)
GI Ulcerative colitis (UC)	153 (3.88)	152 (3.85)
GI Crohns disease	120 (3.04)	126 (3.19)
Arthritis Polymyalgia rheumatica	113 (2.87)	117 (2.96)
Endocrine Hashimotos thyroiditis	110 (2.79)	112 (2.83)
Connective Mixed Connective Tissue Disease (MCTD)	104 (2.64)	104 (2.63)
Vasculitis Granulomatosis	66 (1.67)	66 (1.67)
Neuro Multiple sclerosis	64 (1.62)	65 (1.64)
Heme Antiphospholipid syndrome (APS)	63 (1.60)	64 (1.62)
Connective Sarcoidosis	61 (1.54)	61 (1.54)
Vasculitis Giant Cell Arteritis	61 (1.54)	59 (1.49)
Heme Thrombocytopenic purpura (TTP)	60 (1.52)	59 (1.49)
Muscle Polymyositis	59 (1.49)	57 (1.44)
Arthritis Psoriatic arthritis	41 (1.04)	43 (1.08)
Muscle Dermatomyositis	41 (1.04)	41 (1.03)
Skin Pyoderma	30 (0.76)	32 (0.81)
Heme Autoimmune hemolytic anemia (AIHA)	28 (0.71)	27 (0.68)
GI Celiac Disease	27 (0.68)	26 (0.65)
GI Autoimmune hepatitis	25 (0.63)	25 (0.63)
GI Primary biliary cholangitis (PBC)	22 (0.55)	23 (0.58)
Neuro Myasthenia gravis	22 (0.55)	21 (0.53)
Skin Alopecia areata	19 (0.48)	19 (0.48)
Arthritis Ankylosing spondylitis	17 (0.43)	18 (0.45)
Endocrine Graves Disease	17 (0.43)	17 (0.43)
Vasculitis Goodpastures syndrome	17 (0.43)	17 (0.43)
Neuro Optic neuritis	14 (0.35)	16 (0.40)
Arthritis Behcets disease	13 (0.33)	13 (0.32)
Endocrine T1D	13 (0.33)	12 (0.30)
Skin Vitiligo	12 (0.30)	11 (0.27)
Neuro Schilders disease	11 (0.27)	11 (0.27)
Arthritis Reiters syndrome	9 (0.22)	10 (0.25)
Neuro Guillain-Barre Syndrome	7 (0.17)	7 (0.17)
Vasculitis Takayasu's disease	7 (0.17)	6 (0.15)
Skin Pemphigoid	6 (0.15)	6 (0.15)
Vasculitis Cerebral Arteritis	6 (0.15)	6 (0.15)
Arthritis Palindromic rheumatism	4 (0.10)	5 (0.12)
Heme Evans syndrome	4 (0.10)	4 (0.10)
Muscle Inflammatory and immune myopathies	4 (0.10)	4 (0.10)
Neuro Myelitis transversa	4 (0.10)	4 (0.10)
Skin Pemphigus	3 (0.07)	3 (0.07)
Connective Sjogrens syndrome	2 (0.05)	1 (0.02)
Skin Dermatitis herpetiformis	1 (0.02)	1 (0.02)
Skin Ocular cicatricial pemphigoid	1 (0.02)	1 (0.02)

Table S4. GWAS for C3 and C4 levels pathway analysis.

Pathway	Genes (N)	Observed P value	Empirical P value	Genes
GWAS for C3 Levels				
484, ko04610, Complement and coagulation cascades	8	4.55E-14	0.0002	<i>F3, CFH, FGB, F2RL2, CFB, A2M, ITGAM, C3</i>
83073, hsa04610, Complement, and, coagulation, cascades	8	4.55E-14	0.0003	<i>F3, CFH, FGB, F2RL2, CFB, A2M, ITGAM, C3</i>
83122, hsa05322, Systemic, lupus, erythematosus	7	2.31E-12	0.0006	<i>FCGR3B, HIST3H2BB, C2, HLA-DPB1, H2AFV, H2AFJ, C3</i>
534, ko05322, Systemic, lupus, erythematosus	7	2.31E-12	0.001	<i>FCGR3B, HIST3H2BB, C2, HLA-DPB1, H2AFV, H2AFJ, C3</i>
144028, ko05140, Leishmaniasis	6	4.65E-11	0.001	<i>FCGR3B, STAT1, HLA-DPB1, ITGB1, ITGAM, C3</i>
144181, hsa05140, Leishmaniasis	6	4.65E-11	0.001	<i>FCGR3B, STAT1, HLA-DPB1, ITGB1, ITGAM, C3</i>
83095, hsa04940, Type, I, diabetes, mellitus	3	3.70E-07	0.005	<i>HSPD1, HLA-A, HLA-DPB1</i>
507, ko04940, Type, I, diabetes, mellitus	3	3.70E-07	0.006	<i>HSPD1, HLA-A, HLA-DPB1</i>
153910, hsa04145, Phagosome	13	2.49E-15	0.008	<i>FCGR3B, ATP6V1B1, HLA-A, HLA-DPB1, STX7, CD36, MSR1, ITGB1, SFTP, M6PR, ITGAM, C3, CALR</i>
153859, ko04145, Phagosome	13	2.49E-15	0.01	<i>FCGR3B, ATP6V1B1, HLA-A, HLA-DPB1, STX7, CD36, MSR1, ITGB1, SFTP, M6PR, ITGAM, C3, CALR</i>
459, ko04020, Calcium, signaling, pathway	11	5.02E-13	0.01	<i>CALML6, PTGER3, CACNA1S, CCKAR, SLC25A4, CACNA1B, VDAC2, HTR7, CHRM1, GRIN2D, MYLK2</i>
83050, hsa04020, Calcium, signaling, pathway	11	5.02E-13	0.02	<i>CALML6, PTGER3, CACNA1S, CCKAR, SLC25A4, CACNA1B, VDAC2, HTR7, CHRM1, GRIN2D, MYLK2</i>
83089, hsa04810, Regulation, of, actin, cytoskeleton	19	5.99E-18	0.04	<i>PIP5K1A, ROCK2, SOS1, ITGB6, AB2, FGF5, FGFR4, PTK2, ITGB1, FGFR2, HRAS, CHRM1, PAK1, ITGAM, MYH10, MYL12B, MAP2K2, MYLK2, MYL9</i>
GWAS for C4 Levels				
125138, hsa05416, Viral, myocarditis	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
536, ko05332, Graft-versus-host, disease	4	1.78E-12	0.01	<i>HLA-A, HLA-B, HLA-DOA, IL6</i>
83121, hsa05320, Autoimmune, thyroid, disease	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
83095, hsa04940, Type, I, diabetes, mellitus	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
535, ko05330, Allograft, rejection	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
507, ko04940, Type, I, diabetes, mellitus	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
533, ko05320, Autoimmune, thyroid, disease	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
83123, hsa05330, Allograft, rejection	3	1.77E-11	0.01	<i>HLA-A, HLA-B, HLA-DOA</i>
83124, hsa05332, Graft-versus-host, disease	4	1.78E-12	0.02	<i>HLA-A, HLA-B, HLA-DOA, IL6</i>
153910, hsa04145, Phagosome	8	6.34E-18	0.02	<i>FCGR2A, ATP6V1B1, MARCO, HLA-A, TUBB, ATP6V1G2, HLA-DOA, ITGB1</i>
153859, ko04145, Phagosome	8	6.34E-18	0.02	<i>FCGR2A, ATP6V1B1, MARCO, HLA-A, TUBB, ATP6V1G2, HLA-DOA, ITGB1</i>

Table S5. Genetic correlation of C3 levels with other complex traits.

Phenotype	With HLA				Without HLA			
	r _g	SE	Z-score	P	r _g	SE	Z-score	P
Albuminuria ¹	0.29	0.17	1.70	0.09	0.31	0.22	1.37	0.17
Allergy ²	-0.11	0.14	-0.80	0.43	-0.11	0.17	-0.66	0.51
Body mass index ³	0.23	0.13	1.82	0.07	0.23	0.13	1.79	0.07
Celiac disease ⁴	-0.04	0.16	-0.27	0.79	0.02	0.17	0.12	0.90
Chicken pox ⁵	0.54	0.34	1.61	0.11	0.78	0.47	1.67	0.10
Childhood ear infections ⁵	0.20	0.17	1.21	0.23	0.28	0.24	1.19	0.23
Chronic sinus infections ⁵	0.20	0.35	0.56	0.57	0.11	0.42	0.25	0.80
Cold sores ⁵	-0.20	0.28	-0.71	0.48	-0.09	0.48	-0.19	0.85
Colds ⁵	0.17	0.28	0.60	0.55	0.12	0.34	0.35	0.73
Coronary artery disease ⁶	0.30	0.16	1.85	0.06	0.31	0.20	1.56	0.12
Crohn's disease ⁷	-0.09	0.15	-0.60	0.55	-0.11	0.17	-0.66	0.51
eGFRcreat ⁸	-0.12	0.16	-0.76	0.45	-0.16	0.19	-0.84	0.40
eGFRcys ⁸	0.13	0.24	0.53	0.60	0.06	0.24	0.26	0.79
Essential hypertension ⁹	0.36	0.18	1.98	0.05	0.39	0.25	1.57	0.12
Height ¹⁰	-0.17	0.11	-1.52	0.13	-0.17	0.11	-1.52	0.13
Hepatitis A ⁵	-0.52	0.61	-0.85	0.40	-0.73	0.88	-0.83	0.41
Hepatitis B ⁵	0.06	0.34	0.18	0.86	0.12	0.50	0.23	0.82
Inflammatory bowel disease ¹¹	-0.07	0.14	-0.52	0.60	-0.08	0.16	-0.46	0.64
Measles ⁵	0.35	0.45	0.77	0.44	0.51	0.64	0.80	0.43
Membranous nephropathy ¹²	-0.11	0.16	-0.67	0.50	-0.18	0.32	-0.57	0.57
Mononucleosis ⁵	-0.19	0.33	-0.58	0.56	-0.25	0.52	-0.48	0.63
Mumps ⁵	0.29	0.41	0.70	0.48	0.55	0.46	1.19	0.24
Myringotomy ⁵	-0.27	0.33	-0.82	0.41	-0.36	0.38	-0.94	0.35
Plantar warts ⁵	0.10	0.25	0.38	0.70	0.01	0.41	0.02	0.99
Pneumonia ⁵	0.24	0.22	1.08	0.28	0.28	0.31	0.91	0.36
Positive tb ⁵	0.03	0.30	0.10	0.92	-0.48	0.75	-0.64	0.52
Rheumatoid arthritis ¹³	0.19	0.24	0.79	0.43	-0.10	0.19	-0.51	0.61
Rubella ⁵	0.32	0.30	1.05	0.29	0.38	0.37	1.02	0.31
Scarlet fever ⁵	0.22	0.30	0.74	0.46	0.39	0.42	0.94	0.35
Serum Thyroglobulin ¹⁴	-0.28	0.36	-0.78	0.44	-0.29	0.38	-0.76	0.45
Shingles ⁵	0.00	0.29	0.01	0.99	0.40	0.43	0.94	0.35
Strep throat ⁵	0.23	0.30	0.76	0.45	0.43	0.41	1.05	0.29
Systemic lupus erythematosus ¹⁵	-0.25	0.17	-1.46	0.14	-0.36	0.28	-1.30	0.19
Tonsillectomy ⁵	-0.07	0.18	-0.38	0.70	0.00	0.18	0.02	0.98
Type 1 diabetes ⁹	0.13	0.19	0.68	0.50	0.36	0.39	0.91	0.36
Type 2 diabetes ¹⁶	0.14	0.15	1.00	0.32	0.14	0.14	1.00	0.32
Ulcerative colitis	-0.05	0.14	-0.34	0.73	-0.03	0.19	-0.17	0.86
Urinary tract infection ⁵	0.02	0.20	0.12	0.90	0.04	0.24	0.16	0.88
Yeast infections ⁵	0.06	0.25	0.26	0.79	0.14	0.26	0.52	0.60

Table S10. Genetic correlation of C4 levels with other complex traits.

Phenotype	With HLA				Without HLA			
	r _g	SE	Z-score	P	r _g	SE	Z-score	P
Childhood ear infections ⁵	0.09	0.10	0.96	0.33	0.35	0.88	0.39	0.69
Chronic sinus infections ⁵	0.16	0.23	0.71	0.47	-0.10	0.77	-0.13	0.89
Mononucleosis ⁵	0.20	0.17	1.16	0.24	NA	NA	NA	NA
Strep throat ⁵	0.32	0.13	2.40	0.01	NA	NA	NA	NA
Albuminuria ¹	0.02	0.09	0.18	0.85	0.16	0.42	0.37	0.70
Allergy ²	0.01	0.12	0.10	0.91	-0.36	0.59	-0.60	0.54
Ankylosing	0.29	0.15	1.92	0.05	NA	NA	NA	NA
Body mass index ³	0.20	0.63	0.32	0.74	0.35	0.70	0.50	0.61
Celiac disease ⁴	-0.57	0.11	-5.07	4.08E-07	-0.36	1.97	-0.18	0.85
Chicken pox ⁵	0.07	0.11	0.67	0.49	0.04	0.58	0.08	0.94
Cold sores ⁵	-0.31	0.16	-1.93	0.05	0.09	1.22	0.07	0.94
Colds last year ⁵	0.09	0.23	0.42	0.67	-0.33	1.00	-0.33	0.74
Coronary artery disease ⁶	0.20	0.11	1.78	0.07	0.66	1.65	0.40	0.69
Crohn's disease ⁷	-0.27	0.11	-2.38	0.01	-0.14	0.33	-0.43	0.66
eGFRcys ⁸	0.24	0.62	0.38	0.70	NA	NA	NA	NA
Essential hypertension ⁹	0.20	0.15	1.37	0.17	0.68	1.38	0.49	0.62
Height ¹⁰	-0.23	0.38	-0.60	0.54	-0.34	0.53	-0.64	0.52
Hepatitis A ⁵	0.34	0.23	1.47	0.14	0.32	1.18	0.27	0.78
Hepatitis B ⁵	0.30	0.22	1.37	0.16	0.56	1.53	0.36	0.71
Inflammatory bowel disease ¹¹	-0.09	0.11	-0.82	0.41	0.11	0.33	0.33	0.73
Measles ⁵	0.19	0.22	0.87	0.38	0.58	1.79	0.32	0.74
Membranous nephropathy ¹²	-0.75	0.13	-5.89	3.89E-09	0.37	1.41	0.26	0.79
Mumps ⁵	0.08	0.22	0.37	0.70	0.91	1.87	0.49	0.62
Myringotomy ⁵	-0.26	0.22	-1.20	0.23	0.02	0.66	0.03	0.97
Plantar warts ⁵	-0.26	0.21	-1.27	0.20	-0.55	1.35	-0.41	0.68
Pneumonia ⁵	0.28	0.16	1.74	0.08	0.08	0.47	0.16	0.86
Positive TB ⁵	-0.45	0.22	-2.00	0.04	-0.43	1.43	-0.30	0.76
Rheumatic fever ⁵	0.07	0.68	0.11	0.91	NA	NA	NA	NA
Rheumatoid arthritis ¹³	0.03	0.31	0.10	0.91	-0.47	0.96	-0.49	0.62
Rubella ⁵	0.23	0.27	0.85	0.39	-0.24	0.65	-0.36	0.71
Scarlet fever ⁵	-0.28	0.16	-1.76	0.07	-0.63	1.19	-0.53	0.59
Serum Thyroglobulin ¹⁴	0.21	0.75	0.28	0.78	0.40	1.23	0.33	0.74
Shingles ⁵	-0.11	0.17	-0.62	0.53	0.18	1.01	0.18	0.85
Systemic lupus erythematosus ¹⁵	-0.74	0.11	-6.87	6.38E-12	-1.00	1.27	-0.79	0.42
Tonsillectomy ⁵	0.19	0.07	2.56	0.01	0.27	0.57	0.47	0.63
Type 1 diabetes	-0.51	0.11	-4.66	3.17E-06	-0.13	1.14	-0.12	0.90
Type 2 diabetes ¹⁶	0.05	0.19	0.27	0.78	0.09	0.24	0.37	0.70
Ulcerative colitis ¹⁷	0.08	0.09	0.86	0.38	0.27	0.54	0.51	0.61
Urinary tract infection ⁵	0.27	0.19	1.42	0.15	-0.07	0.67	-0.10	0.92
Yeast infections ⁵	-0.07	0.15	-0.46	0.64	-0.41	0.87	-0.47	0.63

Supplementary Figures

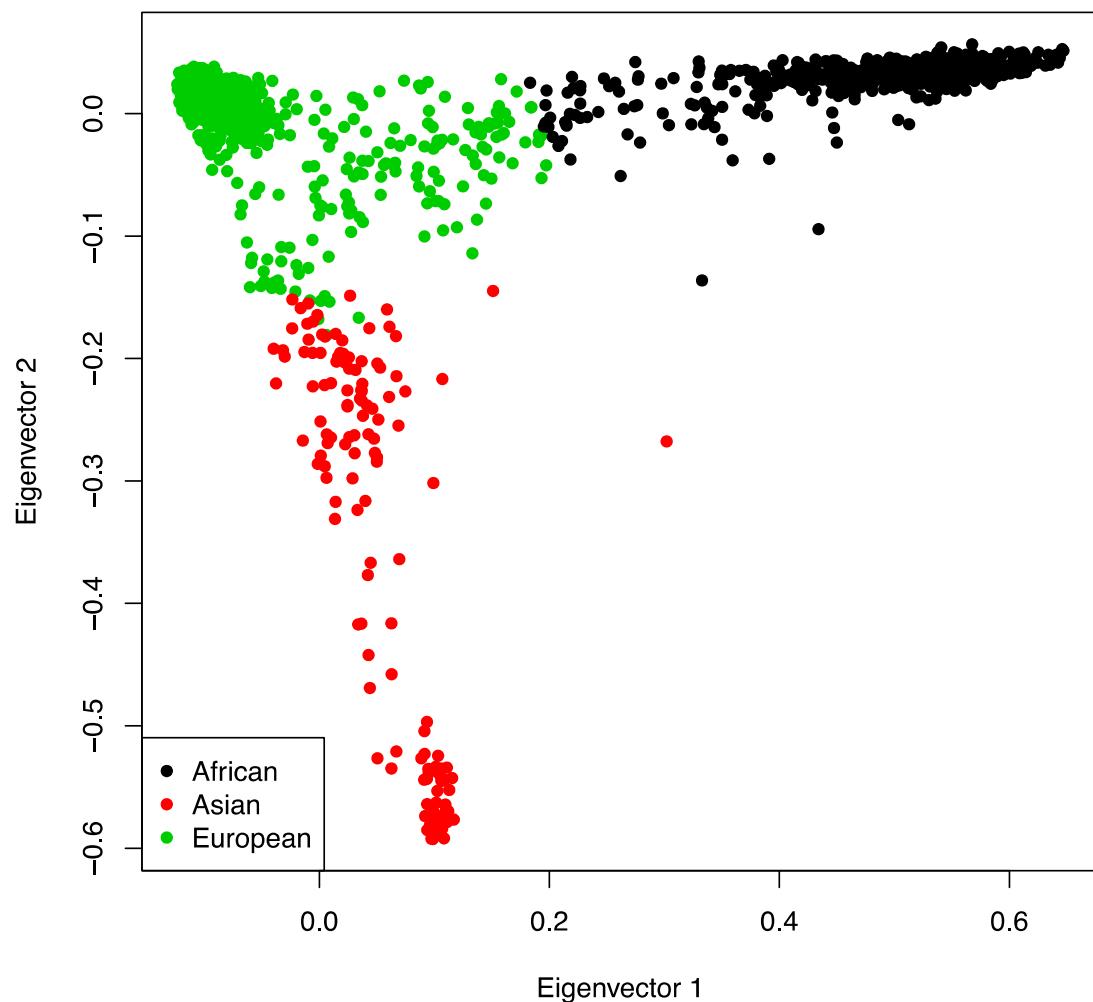


Figure S1: Principal component analysis plot of the eMERGE-III participants with available C3 and C4 levels. The three colors indicate the three separate continental ancestral groups as defined agnostically by the k-means clustering algorithm with three predefined number of groups (k=3).

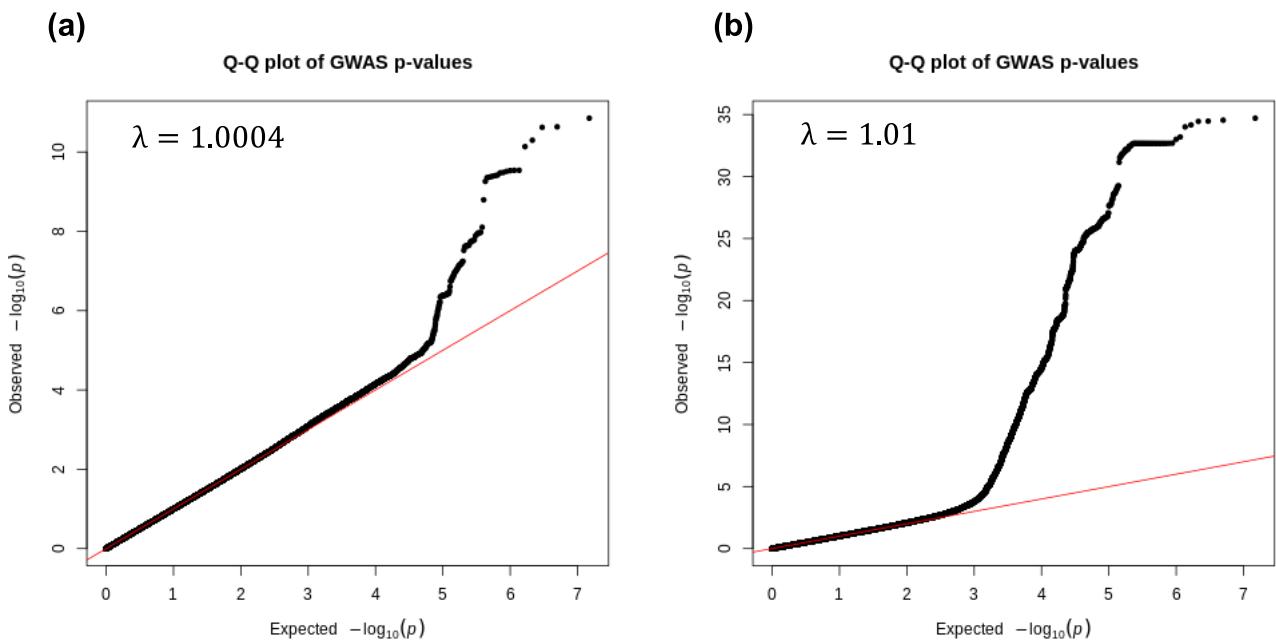


Figure S2: The Quantile-Quantile (QQ) plots for (a) GWAS results for C3 levels, (b) GWAS results for C4 levels; λ = genomic inflation factor.

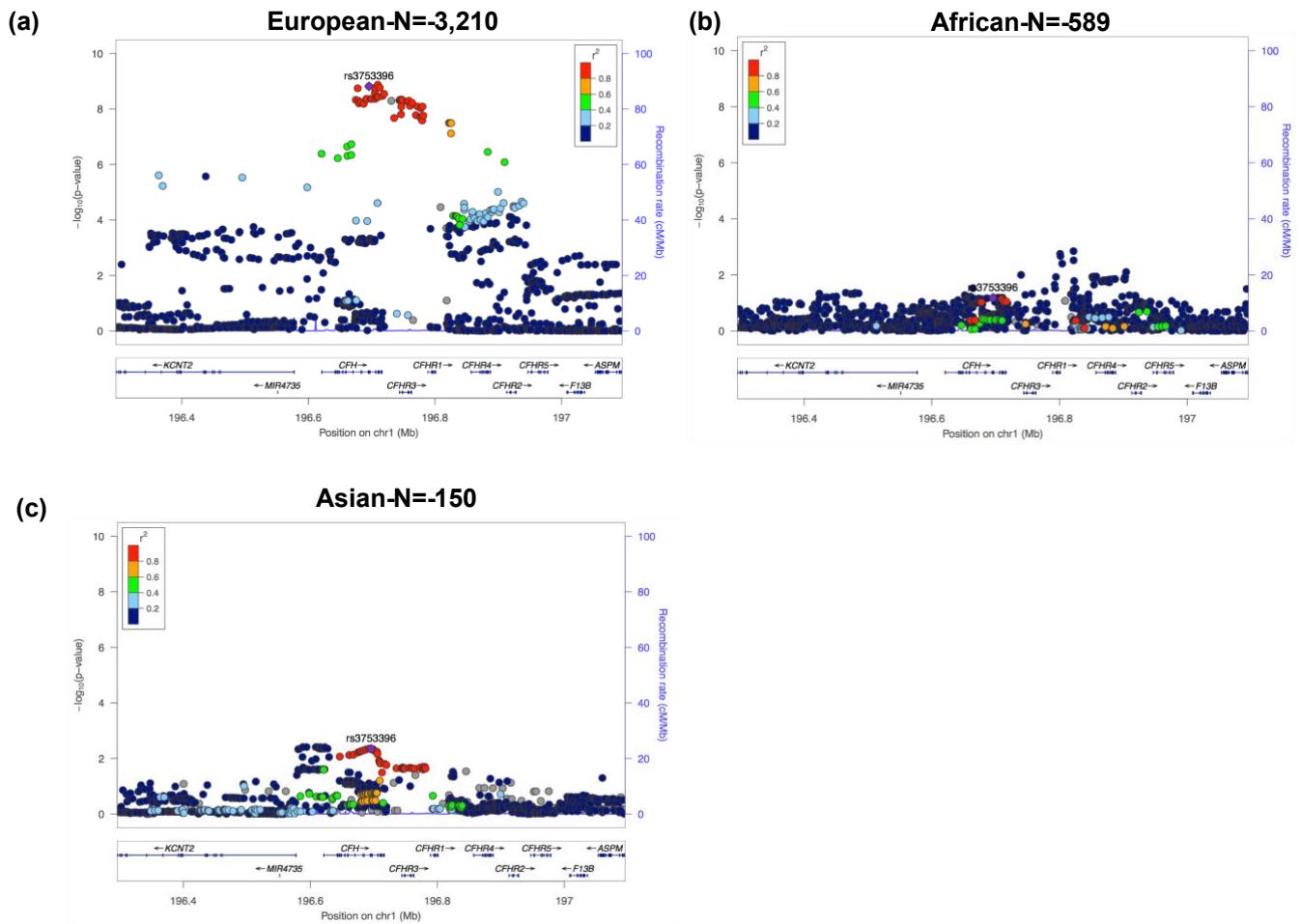


Figure S3: Regional plots of the *CFH* locus: **(a)** European **(b)** African and **(c)** Asian ancestry depicted with LocusZoom using 1000 Genomes European, African and Asian LD reference panels, respectively.

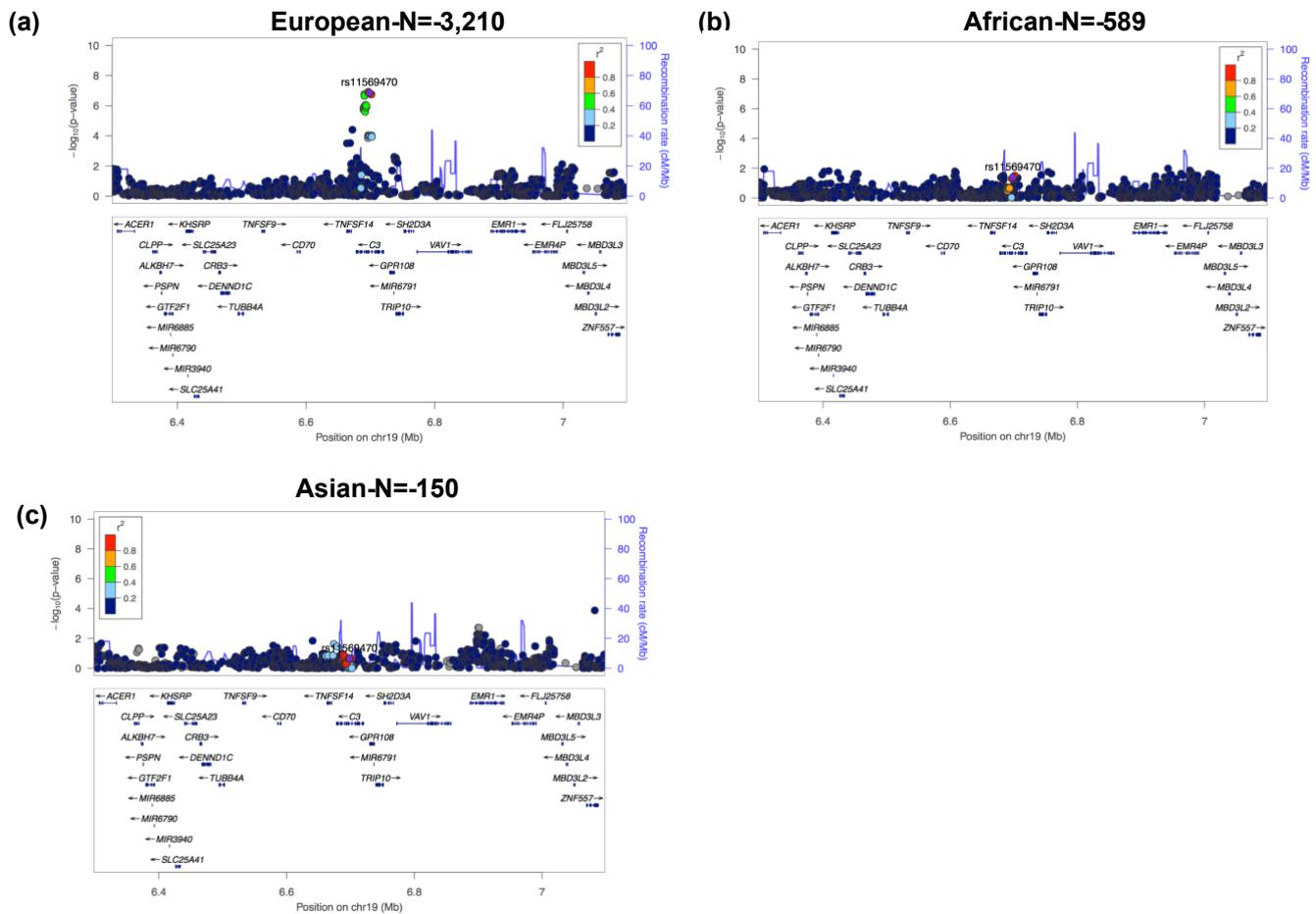


Figure S4: Regional plots of the C3 locus by **(a)** European **(b)** African and **(c)** Asian ancestry depicted with LocusZoom using 1000 Genomes European, African and Asian LD reference panels, respectively.

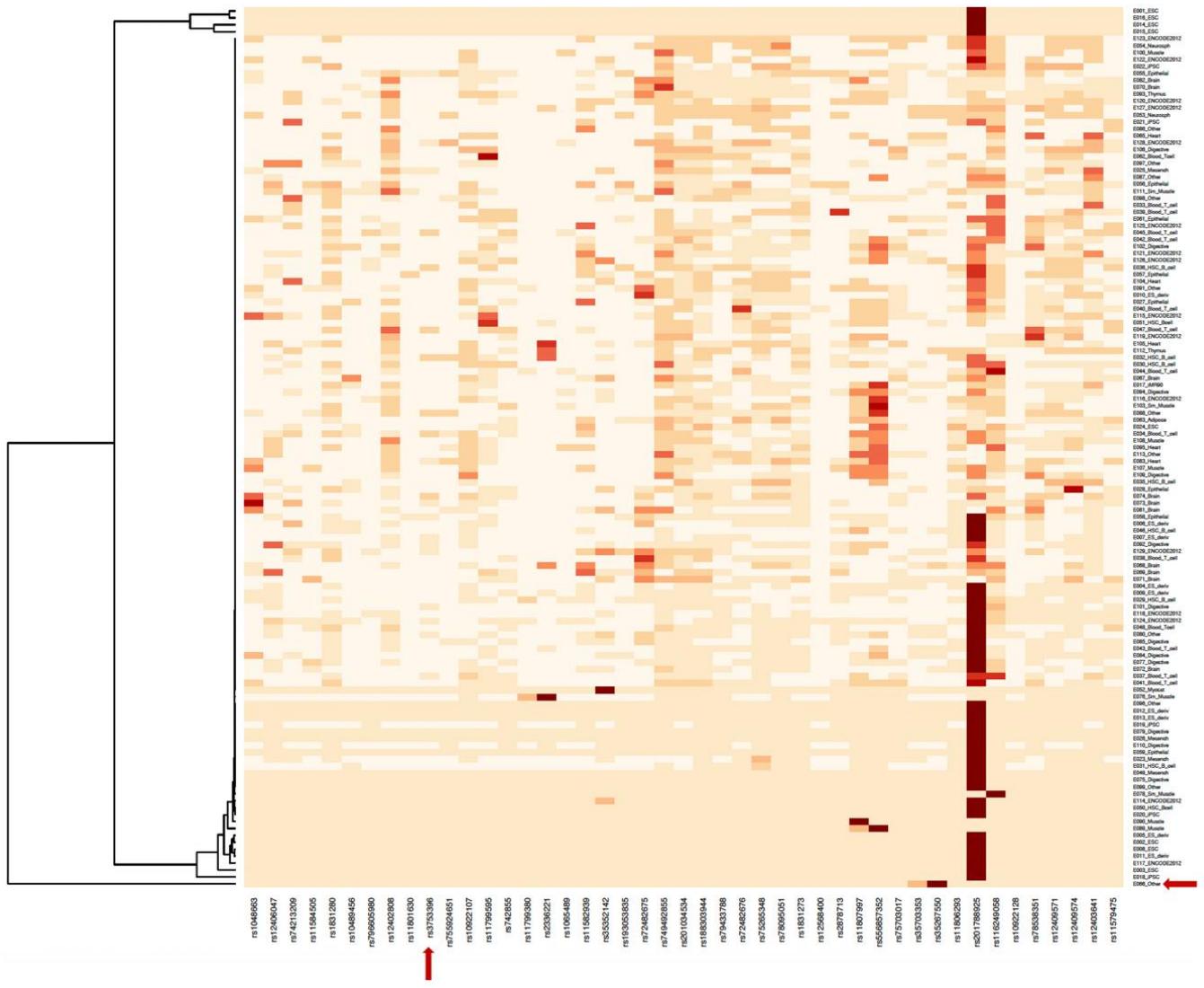


Figure S5: Tissue-specific functional predictions for variants at the *CFH* locus. The arrow points to the index SNP (rs3753396), additional X-axis columns correspond to all of its SNP proxies defined by $r^2 \geq 0.8$. The SNPs were ordered by genomic location and the 127 tissues/cell types from Roadmap Epigenomics were clustered along the Y-axis using hierarchical clustering approach based on the pattern of their functional latent Dirichlet allocation (FUN-LDA) scores across the locus. Higher FUN-LDA scores are indicated in darker color. The Y-axis arrow indicates liver tissue.

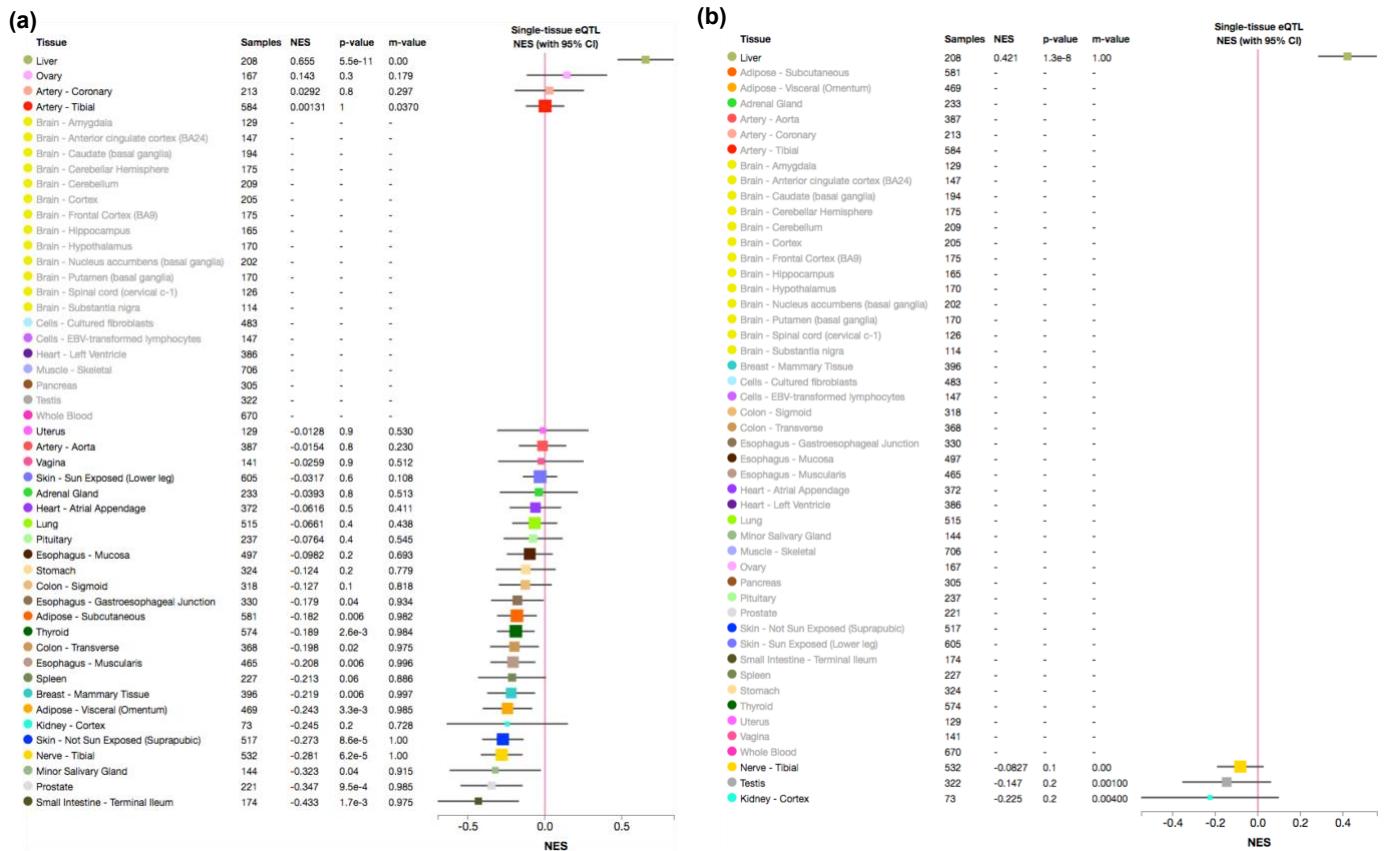


Figure S6: Expression QTL effects for rs3753396-G, the top signal on chr.1q31.3 (based GTEx version 8) demonstrating a strong and highly specific liver eQTL effect on (a) *CFHR3* and (b) *CFHR4* transcripts.

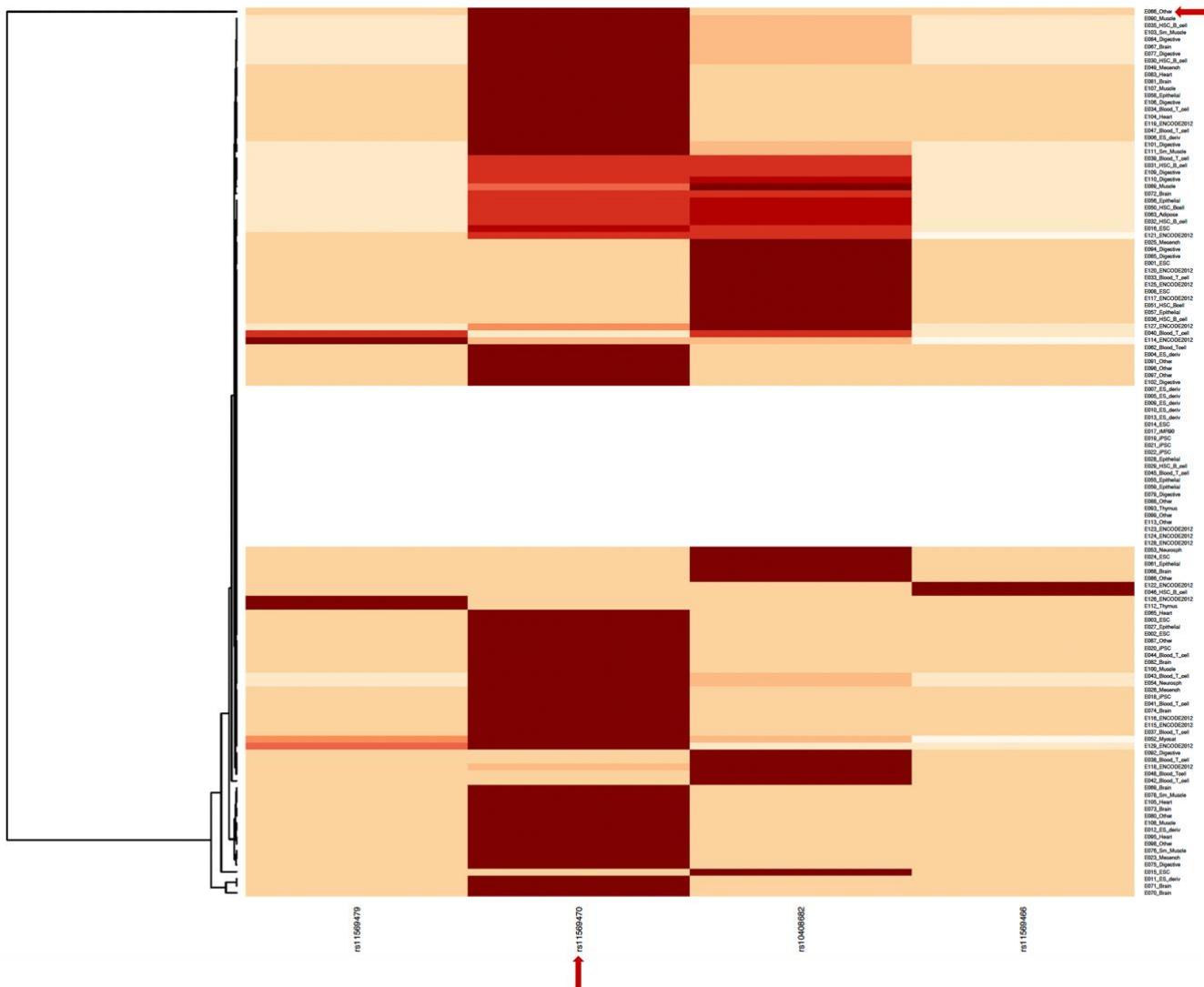


Figure S7: Tissue-specific functional predictions for the C3 locus variants. The index SNP rs1156470 (arrow), its three proxies defined by $r^2 > 0.8$ along the X-axis, and Y-axis arrow indicating liver tissue. The SNPs were ordered by genomic location and the 127 tissues/cell types from Roadmap Epigenomics were clustered using hierarchical clustering approach based on the pattern of functional latent Dirichlet allocation (FUN-LDA) scores along the Y-axis. Higher FUN-LDA scores indicated in darker color.

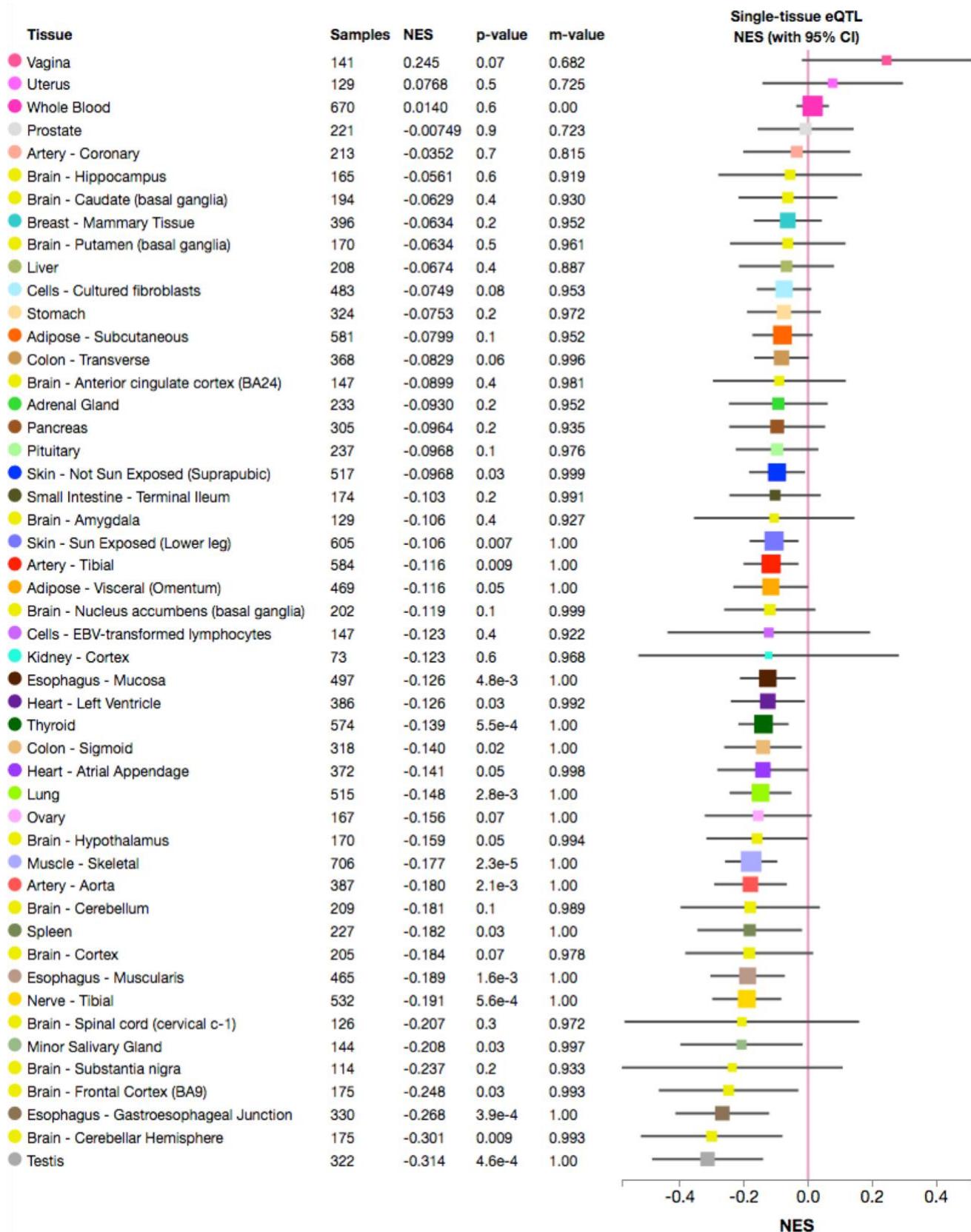


Figure S8: The top rs11569470-A on chr.19p13.3 demonstrating significant eQTLs for *GPR108* transcript in several tissues based on data from GTEx version 8.

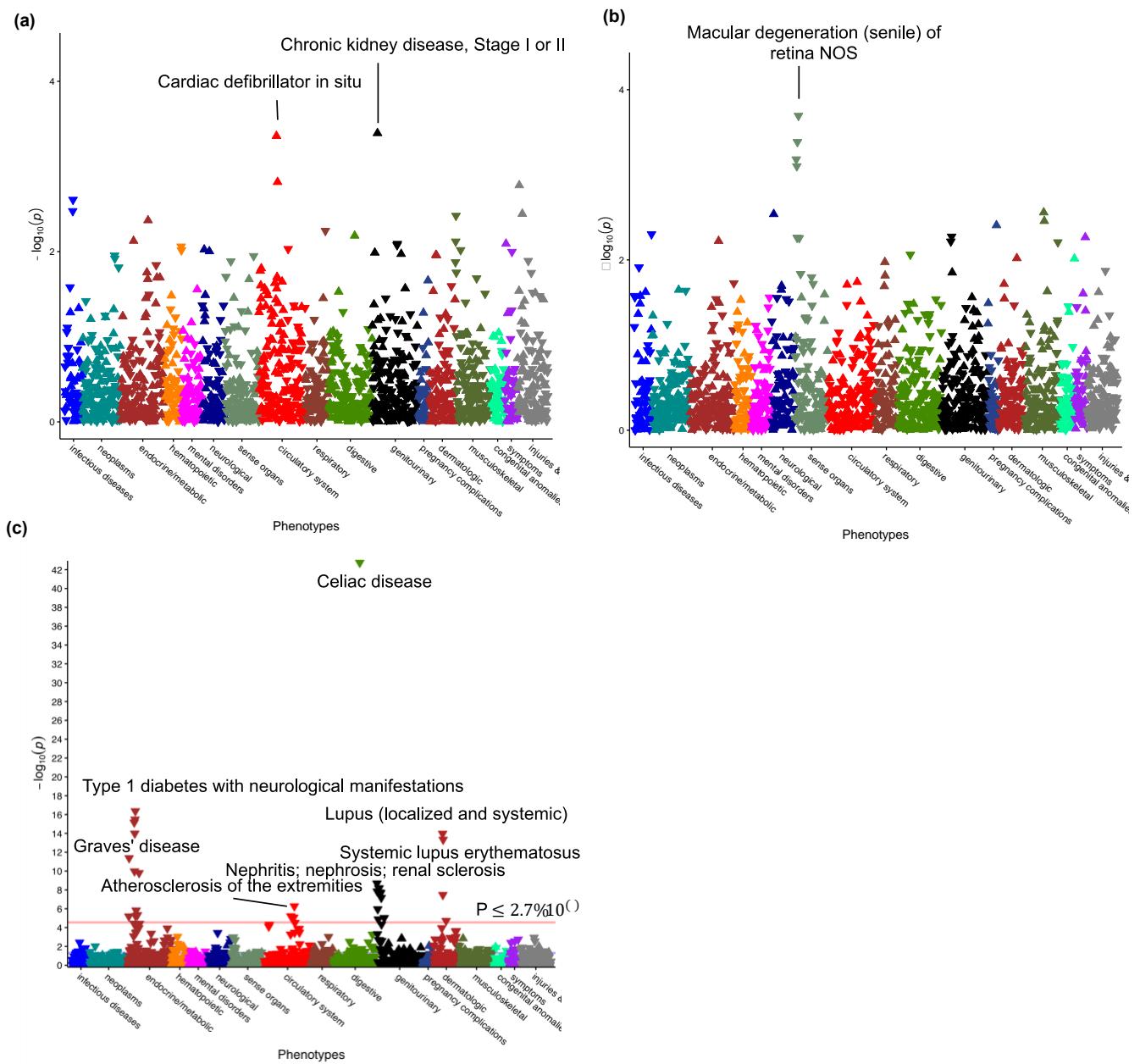


Figure S9: PheWAS plots for the top SNPs at the following loci: **(a)** *CFH*, **(b)** *C3*, **(c)** *C4*. Top associations are labeled across various organ systems. Red horizontal line corresponds to the Bonferroni-corrected significance threshold. Blue horizontal line represents a nominal significance level ($P=0.05$). The association analysis includes $N=102,138$ eMERGE participants.

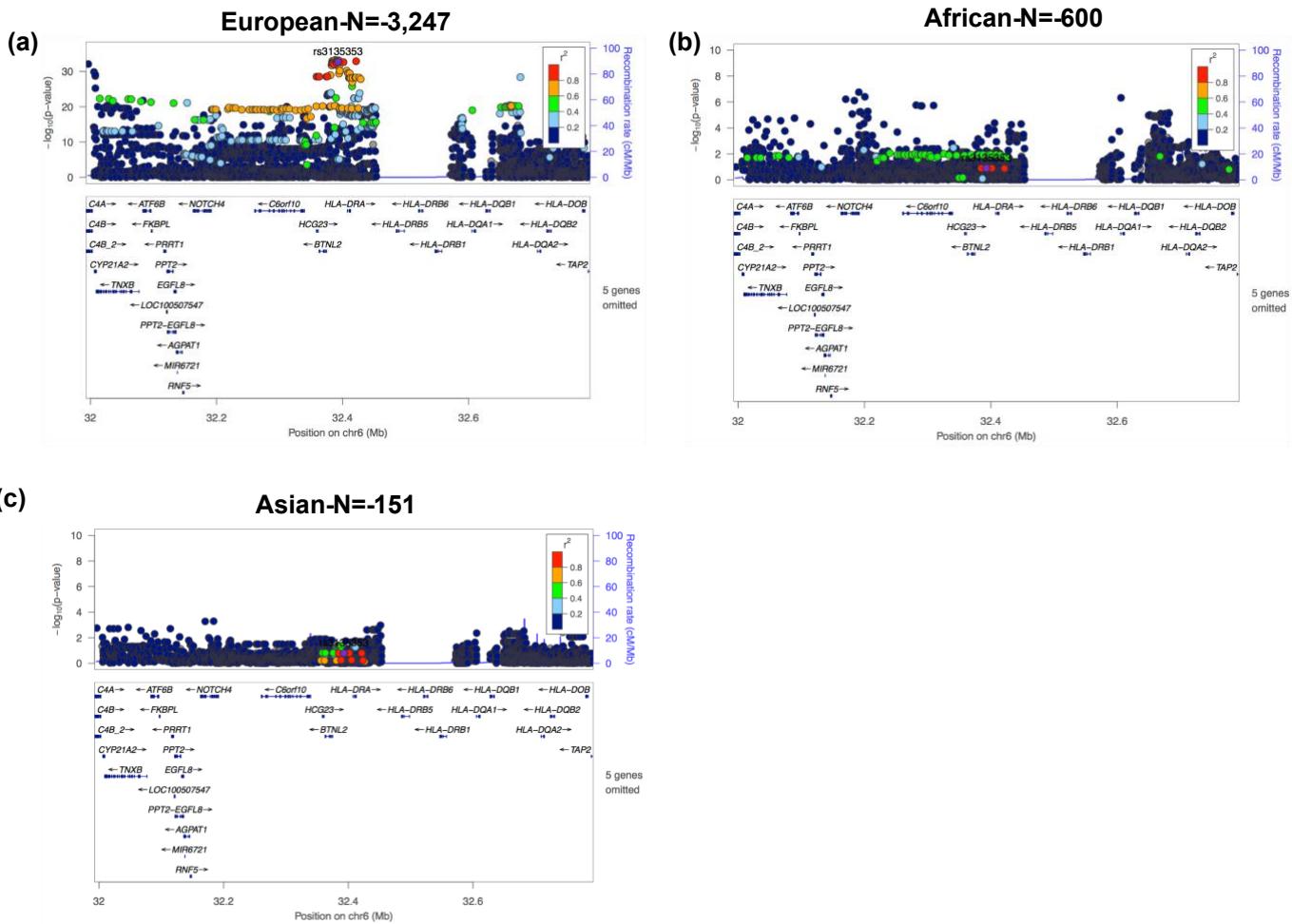


Figure S10: Regional plots of the C4 locus: **(a)** European **(b)** African and **(c)** Asian ancestry depicted with LocusZoom using 1000 Genomes European, African and Asian LD reference panels, respectively.

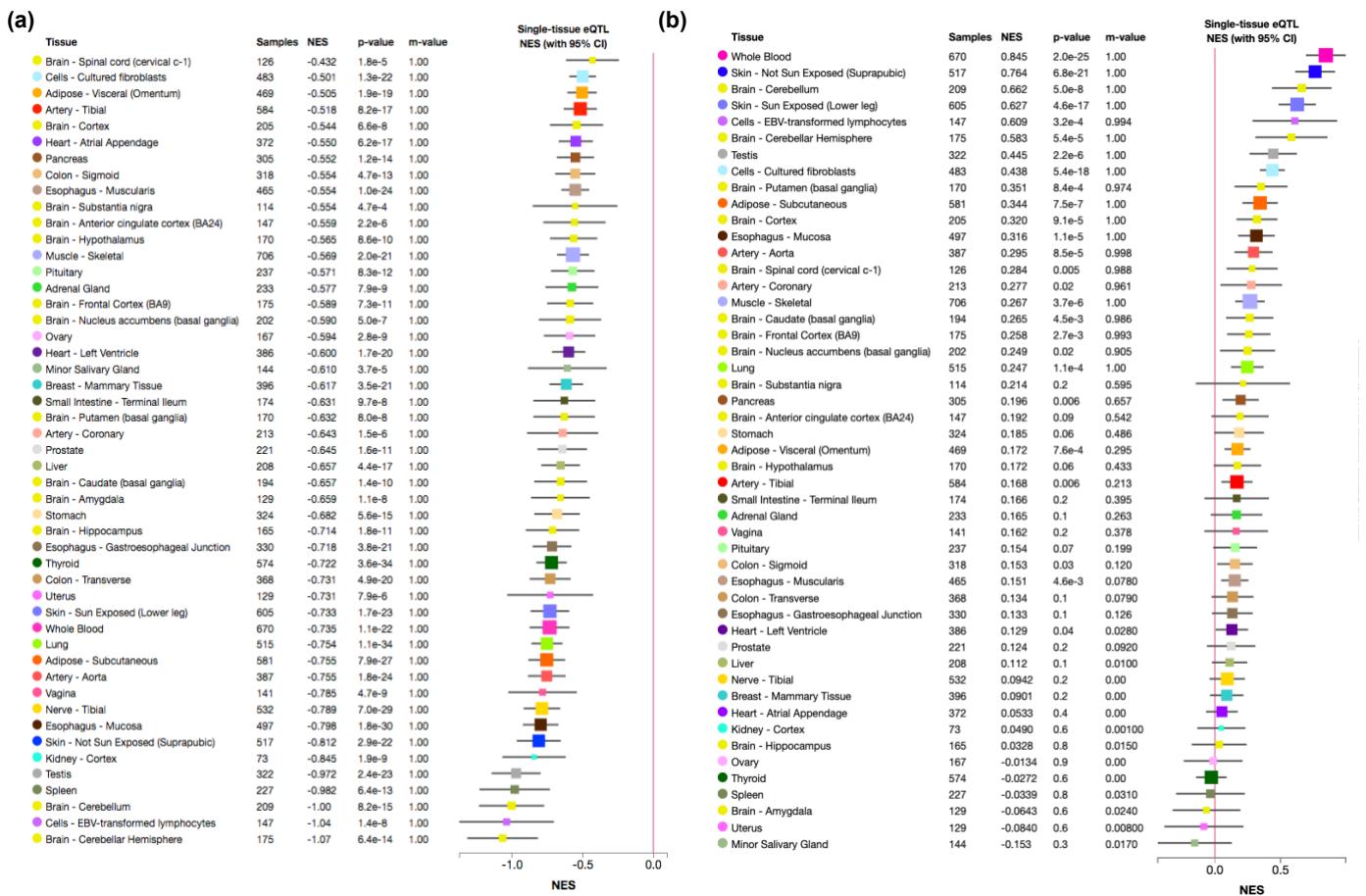
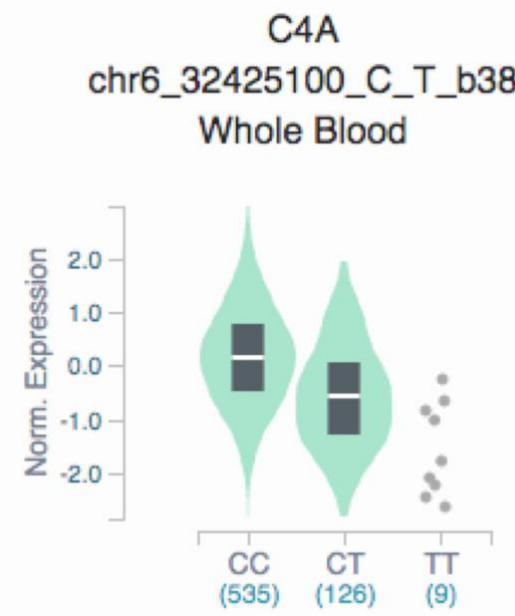


Figure S11: The top rs3135353-T on chr.6p21.32 demonstrating highly significant eQTLs for (a) *C4A* and (b) *C4B* transcripts in multiple tissues based on GTEx version 8.

(a)



(b)

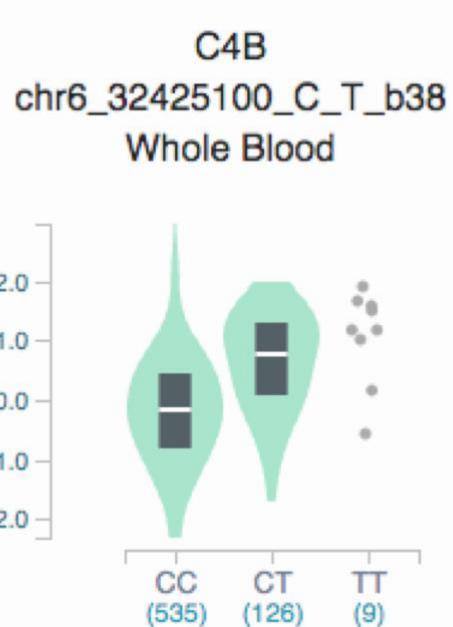


Figure S12: The opposed cis-eQTL effects of rs3135353 on: (a) C4A and (b) C4B transcript level in whole blood (based on GTEx version 8). Y-axis corresponds to normalized expression levels of a transcript; X-axis corresponds to rs3135353 genotype.

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