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Supplemental Data

Family Clustering of Autoimmune Vitiligo Results Principally from Polygenic Inheritance of Common Risk Alleles

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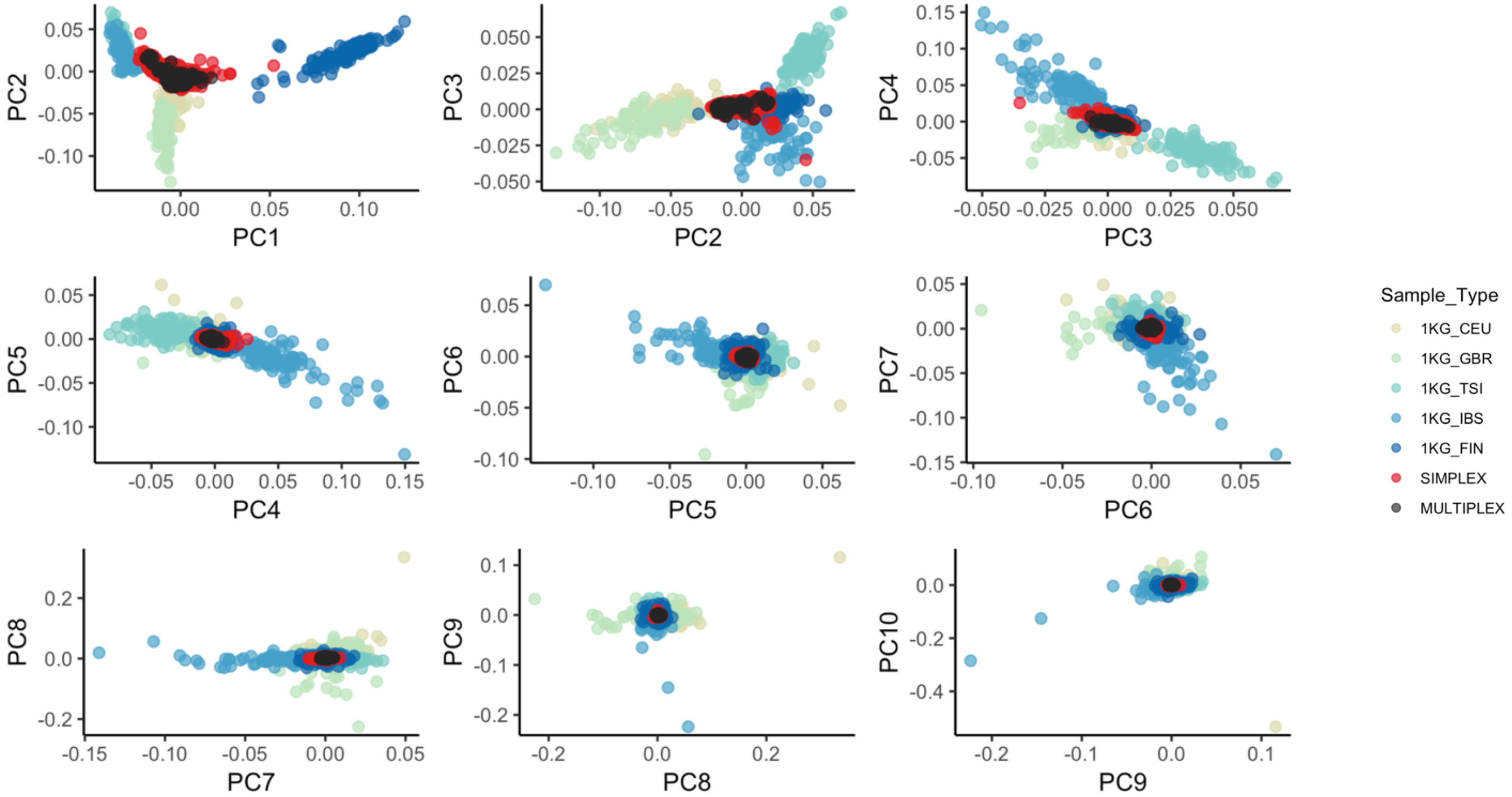
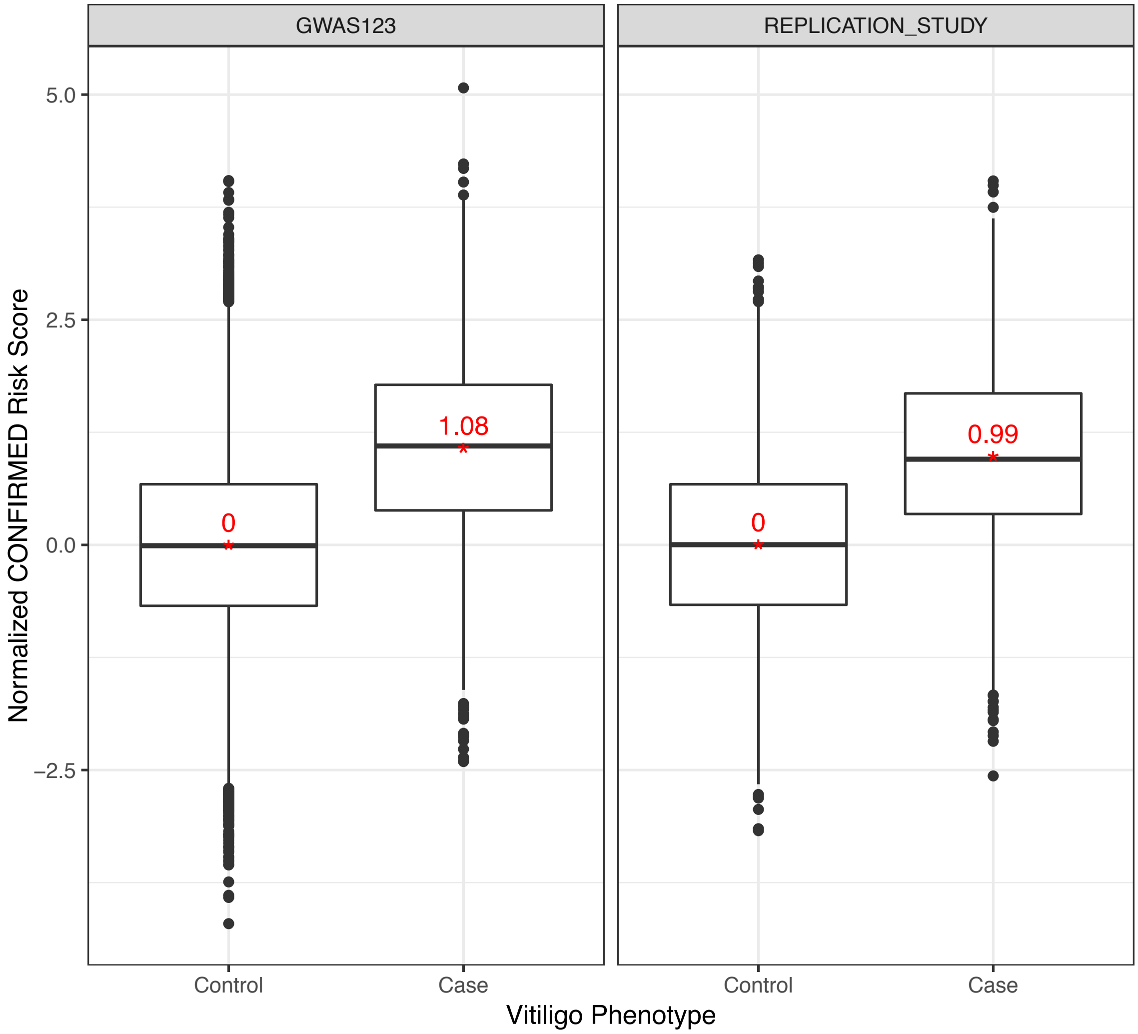
Figure S1: Multiplex and Simplex Probands from GWAS123 are Homogeneous with Respect to European Ancestry



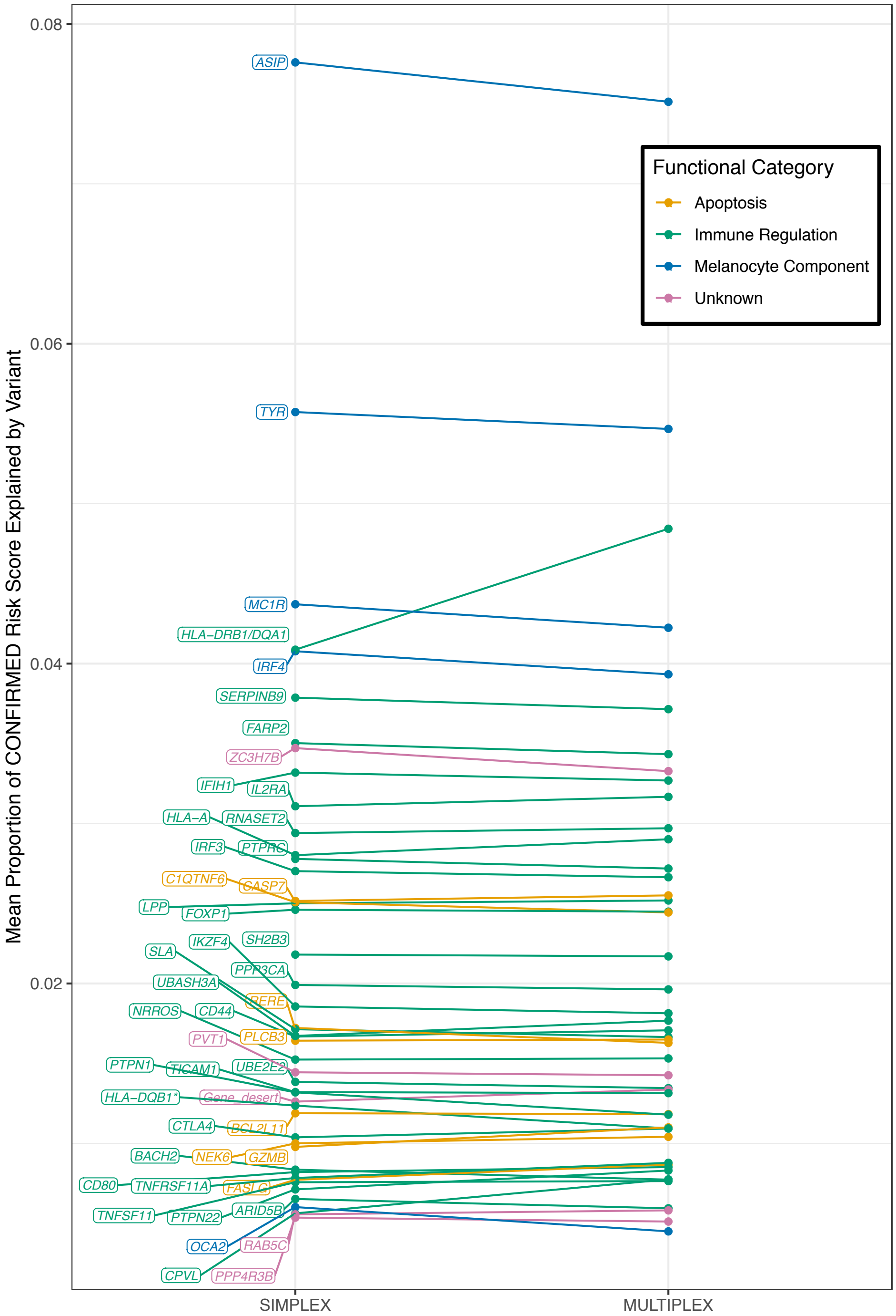
Vitiligo GWAS123 Multiplex and Simplex probands and 1000 Genomes Project European-derived (1KGP EUR) subjects plotted by ancestry-derived principal components analysis (PCA). Nine outlying 1KGP subjects were removed from plots to improve visualization of GWAS123 vitiligo cases. Each dot represents a subject and the color of each dot represents the subject's population: 1KG_CEU, 1KG Utah Resident; 1KG_GBR, 1KG British in England and Scotland; 1KG_TSI, 1KG Toscani in Italia; 1KG_IBS, 1KG Iberian Population in Spain; 1KG_FIN, 1KG Finnish in Finland; SIMPLEX, simplex cases from vitiligo GWAS123; MULTIPLEX, multiplex cases (unrelated) from vitiligo GWAS123.

Figure S2: The CONFIRMED Risk Score Distribution in GWAS123 and Independent Replication Study Subjects



*The normalized CONFIRMED risk score is plotted for vitiligo cases (n=2,841) and controls (n=37,255) in GWAS123 (left) and for cases (n=1,827) and controls (n=2,181) in the independent replication study (right). The mean and SD used for normalization were derived from GWAS123 controls; thus, the Y-axis units represent standard deviations (SD) difference from the mean risk score in GWAS123 controls. Horizontal lines denote the median, red * denotes the mean, and the value of the mean is shown in red text. Boxes denote first through third quartiles. Each vertical bar extends from the box to the largest or smallest value, no more than 1.5 times the inter-quartile range. Data beyond the vertical bars are considered outliers and are plotted individually.*

Figure S3: Comparison of single-variant contributions to the CONFIRMED risk score in simplex and multiplex probands from GWAS123 + replication study



*Each point represents the mean proportion contributed to the CONFIRMED risk score by each of the 48 loci. Higher vertical position represents increased contribution to the risk score on average, with more common, high-effect-size loci generally contributing the most. Dots for the same variant are connected by a horizontal line and a larger slope represents a larger difference between mean contribution of the variant in simplex probands versus in multiplex probands. Dot and label colors represent the likely functional category of the locus, as in Figure 1. * denotes a HLA-DQB1 locus specifically associated in early-onset vitiligo cases[2]; the effect size used for the HLA-DQB1 variant here was derived from all vitiligo cases, regardless of age-of-onset. Association results for each locus are presented in Table S3.*

Table S1: Variants Used in Constructing 48-Variant CONFIRMED Risk Score

Chr.	Index variant	Position (hg19)	Locus	RA/OA	GWAS123[b] OR	Risk Score Weight[c]
1	rs301807	8484823	*RERE*	A/G	1.22	0.199
1	rs2476601	114377568	*PTPN22*	A/G	1.39	0.329
1	rs78037977	172715702	*FASLG*	G/A	1.33	0.285
1	rs16843742	198672299	*PTPRC*	T/C	1.22	0.198
2	rs10200159	55845109	*PPP4R3B*	C/T	1.48	0.392
2	rs4308124	112010486	*BCL2L11-MIR4435-2HG*	C/T	1.17	0.157
2	rs2111485	163110536	*IFIH1*	G/A	1.33	0.288
2	rs231725	204740675	*CTLA4*	A/G	1.18	0.166
2	rs41342147	242407588	*FARP2-STK25*	G/A	1.25	0.223
3	rs34080387[a]	23505187	*UBE2E2*	C/G	1.15	0.139
3	rs34346645	71557945	*FOXP1*	C/A	1.25	0.223
3	rs59374417[a]	119288414	*CD80-ADPRH*	C/A	1.37	0.315
3	rs13076312	188089254	*LPP*	T/C	1.32	0.278
3	rs6583331	196347253	*FBXO45-NRROS*	T/A	1.16	0.151
4	rs1031034	102223386	*PPP3CA*	C/A	1.16	0.151
6	rs12203592	396321	*IRF4*	C/T	1.30	0.261
6	rs78521699	2908591	*SERPINB9*	A/G	1.27	0.236
6	rs60131261	29937335	*HLA-A*	D/I	1.53	0.425
6	rs145954018[d,e]	32440321	*HLA-DQB1* & Early Vitiligo Onset[d]	D/I	2.42	0.884
6	rs9271597[e]	32591291	*HLA-DRB1/DQA1*[e]	A/T	1.77	0.571
6	rs72928038	90976768	*BACH2*	A/G	1.28	0.247
6	rs4710154[a]	167394634	*RNASET2-FGFR1OP-CCR6*	A/T	1.27	0.236
7	rs117744081	29132279	*CPVL*	G/A	1.95	0.668
8	rs10087240[f]	129012574	*PVT1*[f]	T/C	1.18	0.166
8	rs2687812	133931055	*TG-SLA-WISP1*	A/T	1.21	0.191
9	rs10986311	127071493	*NEK6*	C/T	1.16	0.148
10	rs706779	6098824	*IL2RA*	T/C	1.35	0.301
10	rs71508903	63779871	*ARID5B*	T/C	1.18	0.166

10	rs12771452	115488331	*CASP7*	G/A	1.20	0.186
11	rs1043101	35274829	*CD44-SLC1A2*	G/A	1.24	0.215
11	rs12421615	64021605	*PPP1R14B-PLCB3-BAD-GPR137-KCNK4-TEX40-ESRRA-TRMT112-PRDX5*	G/A	1.15	0.139
11	rs1126809	89017961	*TYR*	G/A	1.49	0.400
11	rs11021232	95320808	Gene desert	C/T	1.38	0.322
12	rs772921[a]	56403577	*IKZF4*	T/C	1.31	0.270
12	rs10774625[a]	111910219	*SH2B3-ATXN2*	A/G	1.25	0.223
13	rs35860234	43070206	*TNFSF11*	G/T	1.16	0.148
14	rs8192917	25102160	*GZMB*	C/T	1.23	0.207
15	rs1635168	28535266	*OCA2-HERC2*	A/C	1.43	0.358
16	rs4268748	90026512	*MC1R*	T/C	1.37	0.315
17	rs11079035	40289012	*KAT2A-HSPB9-RAB5C*	A/G	1.18	0.166
18	rs8083511	60028655	*TNFRSF11A*	C/A	1.24	0.215
19	rs4807000	4831878	*TICAM1*	A/G	1.19	0.174
19	rs2304206	50168871	*SCAF1-IRF3-BCL2L12*	G/A	1.22	0.198
20	rs6059655	32665748	*RALY-EIF252-ASIP-AHCY-ITCH*	G/A	1.59	0.462
20	rs6012953	49123043	*PTPN1*	G/A	1.16	0.148
21	rs12482904	43851828	*UBASH3A*	A/T	1.43	0.358
22	rs229527	37581485	*C1QTNF6*	A/C	1.34	0.293
22	rs9611565	41767486	*ZC3H7B-TEF*	T/C	1.28	0.248

Chr., Chromosome; RA, Risk Allele; OA, Other Allele; OR, Odds Ratio.

[a] *Tag SNP used for risk score calculation in place of index variant reported in GWAS123: rs34080387 in place of rs35161626 (D'= 0.997, r^2=0.993); rs59374417 in place of rs148136154 (D'=0.999 r^2=0.984); rs4710154 in place of rs2247314 (D'=0.995 r^2=0.985); rs772921 in place of rs2017445 (D'=1 r^2=0.998); rs10774625 in place of rs10774624 (D'=0.975 r^2=0.919).*

[b] *Published GWAS123 OR[1]*

[c] *Risk score weight ($\widehat{\boldsymbol{\beta}}$) is the ln(GWAS123 OR)*

[d] *Association between rs145954018 and early-onset vitiligo[2]; OR reported is from GWAS123 meta-analysis in all cases and controls without accounting for vitiligo age-of-onset.*

[e] *Special coding is used in risk score calculation to account for LD between rs145954018 and rs9271597, see Methods for details.*

[f] *Association with rs10087240 published[3] separately from GWAS123*

Table S2: Variants Used in Constructing 14-Variant FAMILY Risk Score

Chr.	Locus	Position (hg19)	FAMILY Risk Score Variant	GWAS123 Top Variant (If Different from FAMILY Variant)	r^2	*D'*	RA/OA	Risk Score Weight[a]
1	*RERE*	8501786	rs301819	rs301807	0.97	1	A/G	0.199
1	*PTPN22*	114377568	rs2476601				A/G	0.329
2	*CTLA4*	204763882	rs3096851	rs231725	0.88	0.96	C/A	0.166
3	*FOXP1*	71573135	rs17008723	rs34346645	0.16	0.99	G/T	0.223
3	*LPP*	188089254	rs13076312				T/C	0.278
6	*HLA-A*	29942639	rs35066870	rs60131261	0.97	1.00	G/A	0.425
6	*HLA-DRB1/DQA1*	32578052	rs532098	rs9271597	0.81	0.95	A/G	0.571
10	*IL2RA*	6098824	rs706779				T/C	0.301
11	*CD44-SLC1A2*	35289819	rs1570214	rs1043101	0.99	0.99	G/A	0.215
11	*TYR*	89011046	rs1393350	rs1126809	0.93	1.00	G/A	0.400
11	Gene Desert	95311422	rs4409785	rs11021232	0.92	0.99	C/T	0.322
14	*GZMB*	25102160	rs8192917				C/T	0.207
21	*UBASH3A*	43848521	rs2839511	rs12482904	0.96	0.99	A/G	0.358
22	*C1QTNF6*	37581485	rs229527				A/C	0.293

Chr., Chromosome; r^2, SNP correlation between FAMILY and GWAS123 Top SNP; D', linkage disequilibrium between FAMILY and GWAS123 Top SNP; RA, Risk Allele; OA, Other Allele.

[a] *Risk Score Weight ($\hat{\boldsymbol{\beta}}$) is the ln(GWAS123 OR) of the most-associated GWAS123[1] (the same weight used in Table S1).*

Table S3: CONFIRMED Risk Score Explained by Individual Variants in Multiplex and Simplex Vitiligo Cases

Variant	Locus	Mean Proportion CONFIRMED Explained in Simplex Cases	Mean Proportion CONFIRMED Explained in Multiplex Cases	$\hat{\beta}_{multiplex}$	SE($\hat{\beta}_{multiplex}$)	p value	FDR-Adjusted p value
rs301807	*RERE*	1.72E-02	1.63E-02	-9.40E-04	6.60E-04	0.15	0.54
rs2476601	*PTPN22*	7.12E-03	8.31E-03	1.20E-03	7.10E-04	0.09	0.41
rs78037977	*FASLG*	7.72E-03	8.68E-03	9.40E-04	6.80E-04	0.17	0.54
rs16843742	*PTPRC*	2.78E-02	2.72E-02	-6.00E-04	5.30E-04	0.26	0.73
rs10200159	*PPP4R3B*	5.36E-03	5.12E-03	-2.30E-04	6.90E-04	0.74	0.89
rs4308124	*BCL2L11-MIR4435-2HG*	1.19E-02	1.18E-02	-5.40E-05	5.20E-04	0.92	0.92
rs2111485	*IFIH1*	3.32E-02	3.27E-02	-5.10E-04	8.90E-04	0.57	0.78
rs231725	*CTLA4*	1.04E-02	1.09E-02	5.60E-04	5.20E-04	0.28	0.75
rs41342147	*FARP2-STK25*	3.50E-02	3.43E-02	-6.80E-04	4.80E-04	0.16	0.54
rs34080387	*UBE2E2*	1.38E-02	1.35E-02	-3.90E-04	4.60E-04	0.39	0.75
rs34346645	*FOXP1*	2.46E-02	2.45E-02	-1.20E-04	7.10E-04	0.87	0.92
rs59374417	*CD80-ADPRH*	8.21E-03	8.52E-03	2.90E-04	7.30E-04	0.69	0.87
rs13076312	*LPP*	2.50E-02	2.52E-02	1.70E-04	8.90E-04	0.85	0.92
rs6583331	*FBXO45-NRROS*	1.52E-02	1.53E-02	7.60E-05	4.90E-04	0.88	0.92
rs1031034	*PPP3CA*	1.99E-02	1.96E-02	-2.80E-04	4.40E-04	0.52	0.78
rs12203592	*IRF4*	4.08E-02	3.93E-02	-1.40E-03	5.70E-04	0.01	0.13
rs78521699	*SERPINB9*	3.79E-02	3.72E-02	-7.20E-04	4.80E-04	0.13	0.52
rs60131261	*HLA-A*	2.80E-02	2.90E-02	1.00E-03	1.30E-03	0.46	0.78
rs145954018	*HLA-DQB1* & Early Vitiligo Onset	1.24E-02	1.09E-02	-1.40E-03	1.50E-03	0.34	0.75
rs9271597	*HLA-DRB1/DQA1*	4.09E-02	4.84E-02	7.60E-03	1.90E-03	9.6E-05	4.6E-03
rs72928038	*BACH2*	8.36E-03	7.74E-03	-6.30E-04	6.30E-04	0.32	0.75
rs4710154	*RNASET2-FGFR1OP-CCR6*	2.94E-02	2.97E-02	3.10E-04	7.10E-04	0.66	0.86
rs117744081	*CPVL*	5.63E-03	7.75E-03	2.10E-03	9.10E-04	0.02	0.18
rs10087240	*PVT1*	1.44E-02	1.43E-02	-1.90E-04	5.40E-04	0.72	0.89
rs2687812	*TG-SLA-WISP1*	1.71E-02	1.66E-02	-5.00E-04	6.30E-04	0.43	0.78

rs10986311	*NEK6*	1.00E-02	1.04E-02	4.20E-04	4.70E-04	0.37	0.75
rs706779	*IL2RA*	3.11E-02	3.17E-02	5.90E-04	9.50E-04	0.54	0.78
rs71508903	*ARID5B*	6.53E-03	5.94E-03	-5.90E-04	4.50E-04	0.19	0.57
rs12771452	*CASP7*	2.52E-02	2.55E-02	3.50E-04	5.20E-04	0.50	0.78
rs1043101	*CD44-SLC1A2*	1.67E-02	1.71E-02	3.90E-04	6.90E-04	0.57	0.78
rs12421615	*PPP1R14B-PLCB3-BAD-GPR137-KCNK4-TEX40-ESRRA-TRMT112-PRDX5*	1.64E-02	1.65E-02	7.20E-05	4.30E-04	0.87	0.92
rs1126809	*TYR*	5.57E-02	5.47E-02	-1.10E-03	1.10E-03	0.31	0.75
rs11021232	*Gene desert*	1.26E-02	1.34E-02	7.50E-04	8.80E-04	0.39	0.75
rs772921	*IKZF4*	1.86E-02	1.81E-02	-4.00E-04	8.60E-04	0.64	0.85
rs10774625	*SH2B3-ATXN2*	2.18E-02	2.17E-02	-1.30E-04	7.20E-04	0.86	0.92
rs35860234	*TNFSF11*	7.57E-03	7.64E-03	6.30E-05	4.30E-04	0.88	0.92
rs8192917	*GZMB*	9.78E-03	1.10E-02	1.20E-03	6.00E-04	0.04	0.26
rs1635168	*OCA2-HERC2*	6.02E-03	4.50E-03	-1.50E-03	6.90E-04	0.03	0.20
rs4268748	*MC1R*	4.37E-02	4.22E-02	-1.50E-03	8.40E-04	0.08	0.41
rs11079035	*KAT2A-HSPB9-RAB5C*	5.56E-03	5.81E-03	2.50E-04	4.30E-04	0.56	0.78
rs8083511	*TNFRSF11A*	7.84E-03	8.79E-03	9.50E-04	5.70E-04	0.09	0.41
rs4807000	*TICAM1*	1.32E-02	1.31E-02	-6.70E-05	5.70E-04	0.91	0.92
rs2304206	*SCAF1-IRF3-BCL2L12*	2.70E-02	2.66E-02	-3.80E-04	5.50E-04	0.49	0.78
rs6059655	*RALY-EIF252-ASIP-AHCY-ITCH*	7.76E-02	7.51E-02	-2.50E-03	7.40E-04	8.2E-04	0.02
rs6012953	*PTPN1*	1.32E-02	1.18E-02	-1.40E-03	4.90E-04	4.2E-03	0.07
rs12482904	*UBASH3A*	1.67E-02	1.77E-02	9.50E-04	1.00E-03	0.36	0.75
rs229527	*C1QTNF6*	2.51E-02	2.44E-02	-6.30E-04	9.60E-04	0.51	0.78
rs9611565	*ZC3H7B-TEF*	3.47E-02	3.33E-02	-1.40E-03	6.80E-04	0.04	0.24

SE, Standard Error

SUPPLEMENTAL REFERENCES

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