ERAP1, ERAP2, and two copies of HLA-Aw19 alleles increase the risk for Birdshot Chorioretinopathy in HLA-A29 carriers

Supplementary Material

Supplementary Figure and Table Legend

Supplementary Figure 1. Main differences between risk Aw19 alleles and A32. A) Sequence differences between risk Aw19 alleles (red) and protective A32 allele (green). A32 exhibits F at position 9 as is the reference A:01:01 allele, while risk alleles are either T or S at that position. The Bw4 epitope sequence is apparent at positions 79-83 or A32 only. B+C)Protein structure calculated using PyMol v2.0.4[1] exhibit position 9 (pink) in the peptide binding groove and positions 79-83 (bright blue) on the alpha-1 helix.

Supplementary Table 1. HLA-A 2nd allele frequencies in the French cohort compared to UKB and GHS EUR A29 carriers. Alleles belonging to the Aw19 broad antigen group that increase risk are A29, A30, A31 and A33 (red) and A32 exhibits protection (green). A logistic regression test with covariates included for sex and six principal components, calculated based on genetic array data for each analytic set. Results are presented for all HLA-A alleles that have three or more case carriers. Alleles are sorted as in Table 1. *Three principal components.

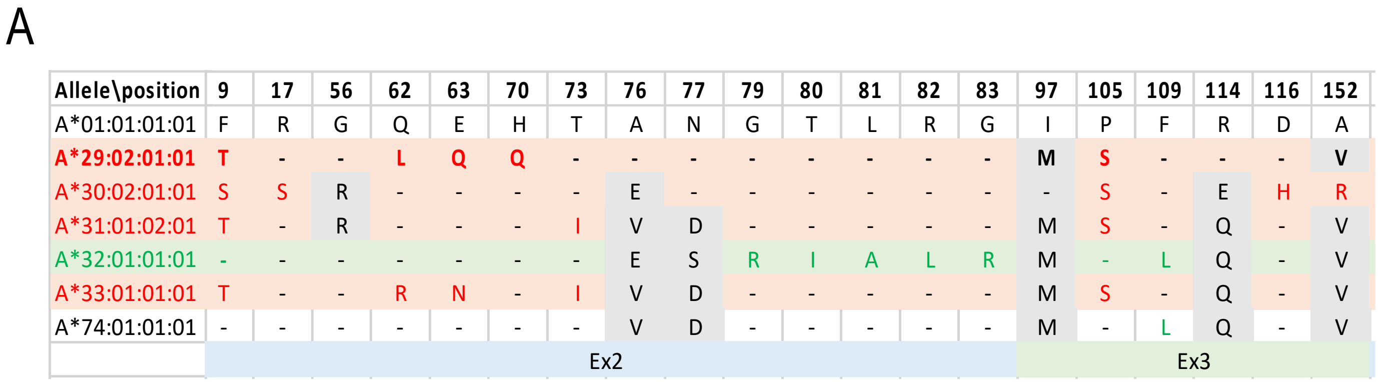
Supplementary Table 2: Haplotype analysis of *ERAP1*. Haplotype analysis examining the association of all eight *ERAP1* haplotypes with the case-control status, showing that Hap1 and Hap2 are strongly associated with protection from BSCR.

Supplementary Table 3: The combined risk of ERAP2 and Aw19. Utilizing 286 Birdshot cases and 4,014 controls from GHS cohort #1 to calculate additive risk while combining risk factors in *ERAP2* and Aw19. An additive genotype model of *ERAP2* risk signal tagged by rs10044354 and single (A29/-) or double (A29/Aw19) Aw19 copies relative to lowest risk combination of rs10044354-CC and one copy of Aw19 allele (A29).

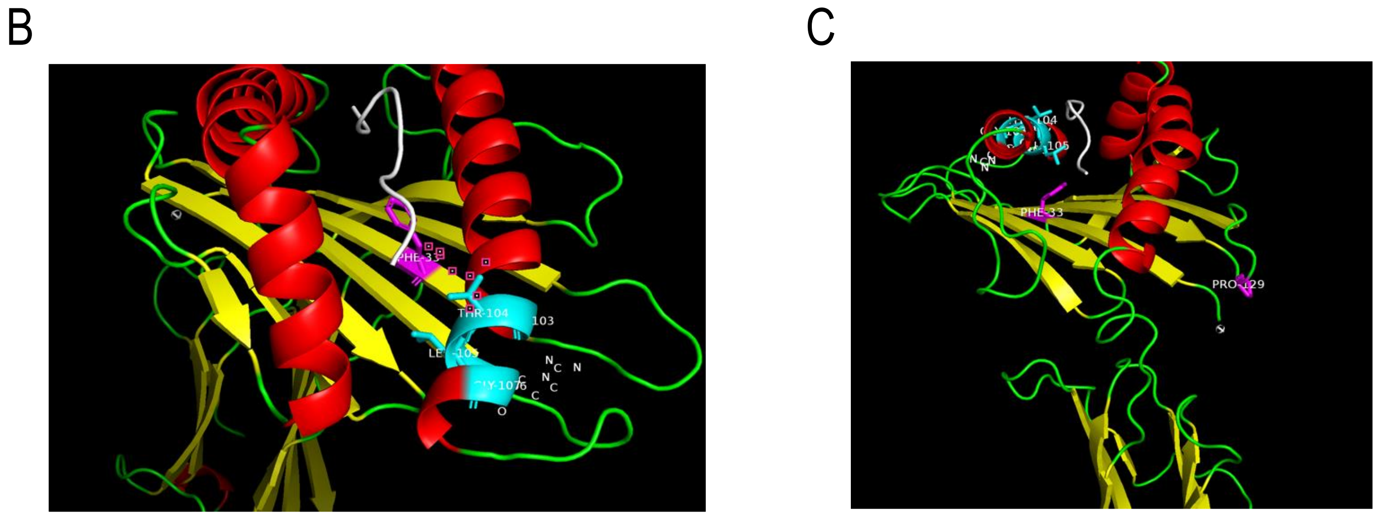
Supplementary Table 4: The combined risk of ERAP1 and Aw19. Utilizing 286 Birdshot cases and 4,014 controls from GHS cohort #1 to calculate additive risk while combining risk factors in *ERAP1* and Aw19. An additive genotype model of *ERAP1* risk signal tagged by rs27432 and single (A29/-) or double (A29/Aw19) Aw19 copies relative to lowest risk combination of rs27432-AA and one copy of Aw19 allele (A29).

Supplementary Table 5: The combined risk of ERAP1 and ERAP2. Utilizing 286 Birdshot cases and 4,014 controls from GHS cohort #1 to calculate additive risk while combining risk factors in *ERAP1* and *ERAP2*. An additive genotype model of *ERAP1* risk signal tagged by rs27432 and *ERAP2* signal tagged by rs10044354 relative to lowest risk combination of rs27432-AA and rs10044354-CC.

Supplementary Table 6: The combined risk of ERAP1, ERAP2 and Aw19. Utilizing 286 Birdshot cases and 4,014 controls from GHS cohort #1 to calculate additive risk while combining risk factors in *ERAP1*, *ERAP2* and Aw19. An additive genotype model of *ERAP1* and *ERAP2* risk signals and single (A29/-) or double (A29/Aw19) Aw19 copies relative to lowest risk combination. The genotypes are combined as following: 0 = *ERAP1* and *ERAP2* homozygous for protective allele. 1/[01],[01]/1 = either homozygous protective or heterozygous genotypes of both *ERAP1* and *ERAP2*. 2/.,./2 = homozygous risk allele of either *ERAP1* or *ERAP2*. 2/2 = homozygous risk allele of both *ERAP1* and *ERAP2*.



Allele\position	9	17	56	62	63	70	73	76	77	79	80	81	82	83	97	105	109	114	116	152
A*01:01:01:01	F	R	G	Q	E	H	T	A	N	G	T	L	R	G	I	P	F	R	D	A
A*29:02:01:01	**T**	**-**	**-**	**L**	**Q**	**Q**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**M**	**S**	**-**	**-**	**-**	**V**
A*30:02:01:01	S	S	R	-	-	-	-	E	-	-	-	-	-	-	-	S	-	E	H	R
A*31:01:02:01	T	-	R	-	-	-	I	V	D	-	-	-	-	-	M	S	-	Q	-	V
A*32:01:01:01	-	-	-	-	-	-	-	E	S	R	I	A	L	R	M	-	L	Q	-	V
A*33:01:01:01	T	-	-	R	N	-	I	V	D	-	-	-	-	-	M	S	-	Q	-	V
A*74:01:01:01	-	-	-	-	-	-	-	V	D	-	-	-	-	-	M	-	L	Q	-	V
	Ex2														Ex3					



Supplementary Figure 1. Main differences between risk Aw19 alleles and A32.

	UParis (A29 EUR Carriers)				GHS cohort #1 (A29 EUR)			GHS cohort #2 (A29 EUR)			UKB* (A29 EUR)		
Second HLA-A Allele	**Cases n=286**	**Ctrls n=108**	**OR (LCI-UCI)**	**p-val**	**Carriers n=4014**	**OR (LCI-UCI)**	**p-val**	**Carriers n=2829**	**OR (LCI-UCI)**	**p-val**	**Carriers n=38,543**	**OR (LCI-UCI)**	**p-val**
A19 co-susceptible (29,30,31,33)	**41**	**4**	**4.05 (1.40-11.77)**	**0.01**	**247**	**2.21 (1.47-3.33)**	**1.55E-04**	**164**	**2.49 (1.63-3.81)**	**2.34E-05**	**2416**	**2.24 (1.52-3.30)**	**4.57E-05**
A3002	**13**	**1**	**4.32 (0.55-33.79)**	**0.16**	**45**	**2.78 (1.31-5.88)**	**7.66E-03**	**20**	**4.26 (1.83-9.92)**	**7.68E-04**	**396**	**4.01 (2.05-7.84)**	**4.99E-05**
A3301	**9**	**0**	**6204540.00 (0.00-Inf)**	**0.98**	**39**	**3.12 (1.29-7.58)**	**0.01**	**32**	**2.69 (1.15-6.28)**	**0.02**	**255**	**2.00 (0.80-5.01)**	**0.14**
A0301	26	15	0.71 (0.35-1.45)	0.35	592	0.69 (0.45-1.08)	0.11	380	0.72 (0.46-1.14)	0.16	5497	0.65 (0.43-1.01)	0.05
A0101	71	17	1.84 (1.01-3.35)	0.05	662	1.57 (1.15-2.16)	0.00	448	1.59 (1.15-2.19)	0.01	7411	1.82 (1.35-2.45)	0.00
A3201	**3**	**4**	**0.22 (0.05-1.04)**	**0.06**	**152**	**0.30 (0.09-0.97)**	**4.38E-02**	**105**	**0.22 (0.06-0.83)**	**2.52E-02**	**1323**	**0.28 (0.08-0.90)**	**3.33E-02**
A0201	64	24	0.97 (0.56-1.68)	0.92	1085	0.87 (0.64-1.20)	0.41	756	0.87 (0.63-1.20)	0.41	10680	0.82 (0.61-1.11)	0.20
A2902	**10**	**1**	**3.26 (0.40-26.32)**	**0.27**	**48**	**1.83 (0.80-4.20)**	**0.15**	**37**	**1.94 (0.84-4.46)**	**0.12**	**750**	**2.10 (1.05-4.23)**	**0.04**
A2601	8	3	1.09 (0.28-4.26)	0.90	115	0.87 (0.39-1.91)	0.72	91	0.91 (0.40-2.09)	0.82	834	0.73 (0.33-1.61)	0.44
A2501	3	2	0.55 (0.08-3.61)	0.54	101	0.57 (0.16-2.01)	0.38	47	0.69 (0.18-2.62)	0.59	673	0.66 (0.20-2.15)	0.49
A2402	23	11	0.85 (0.39-1.85)	0.67	356	0.99 (0.61-1.61)	0.97	249	1.06 (0.65-1.74)	0.81	2801	1.00 (0.63-1.59)	0.99
A3101	**9**	**2**	**1.75 (0.37-8.33)**	**0.48**	**115**	**1.42 (0.68-2.97)**	**0.35**	**75**	**1.57 (0.72-3.41)**	**0.25**	**1015**	**1.24 (0.58-2.64)**	**0.57**
A1101	14	10	0.55 (0.23-1.34)	0.19	255	0.81 (0.45-1.48)	0.50	177	0.83 (0.45-1.53)	0.54	2278	0.82 (0.46-1.45)	0.49
A2301	6	2	1.06 (0.21-5.47)	0.94	94	0.85 (0.34-2.17)	0.74	61	0.73 (0.28-1.95)	0.53	672	0.85 (0.35-2.10)	0.73
A6801	9	8	0.42 (0.16-1.15)	0.09	128	0.95 (0.45-2.04)	0.90	100	0.76 (0.35-1.67)	0.50	1142	1.43 (0.70-2.91)	0.33
A19 all (29,30,31,32,33)	**44**	**8**	**2.07 (0.92-4.64)**	**0.08**	**399**	**1.49 (1.02-2.18)**	**0.04**	**269**	**1.58 (1.07-2.34)**	**0.02**	**3739**	**1.51 (1.04-2.18)**	**0.03**

Supplementary Table 1. HLA-A 2nd allele frequencies in the French cohort compared to UKB and GHS EUR A29 carriers.

ERAP1	rs72773968 5:96803892:G:A	rs3734016 5:96803761:C:T	rs26618 5:96795133:T:C	rs27895 5:96793840:C:T	rs2287987 5:96793832:T:C	rs30187 5:96788627:T:C	rs10050860 5:96786506:C:T	Rs17482078 5:96783162:C:G	rs27044 5:96783148:C:G	**UParis**			
										F cases	*F* controls	OR	P
Function	**I12T**	**E56K**	**I276M**	**G346D**	**M349V**	**K528R**	**D575N**	**R725Q**	**Q730E**				
Hap 1	I	E	I	G	M	K	D	R	Q	0.17	0.35	0.41	**6.7E-6**
Hap 2	T	E	I	G	M	K	D	R	Q				
Hap 3	T	E	I	G	M	K	D	R	E	0.55	0.48	1.32	0.11
Hap 5	T	E	I	D	M	R	D	R	E				
Hap 6	T	E	I	G	M	R	D	R	E				
Hap 7	T	K	I	G	M	R	D	R	E				
Hap 8	T	E	M	G	M	R	D	R	E				
Hap 10	**T**	**E**	**I**	**G**	**V**	**R**	**N**	**Q**	**E**	**0.28**	**0.17**	**1.78**	**8.0E-3**

Supplementary Table 2: Haplotype analysis of *ERAP1*. Haplotype analysis examining the association of all eight *ERAP1* haplotypes with the case-control status.

Aw19	ERAP2-rs10044354	case_n	contr_n	case_F	controlF	OR	OR CI_low	OR CI_high	P
A29/-	CC	46	1296	0.167	0.319	1.000	NA	NA	NA
A29/-	CT	132	1842	0.478	0.453	2.019	1.421	2.911	3.95E-05
A29/-	TT	56	681	0.203	0.167	2.316	1.522	3.539	4.51E-05
A29/Aw19	CC	13	94	0.047	0.023	3.891	1.861	7.644	2.13E-04
A29/Aw19	CT	17	119	0.062	0.029	4.019	2.092	7.413	2.32E-05
A29/Aw19	TT	12	34	0.043	0.008	9.902	4.378	21.197	1.16E-07

Supplementary Table 3: The combined risk of ERAP2 and Aw19.

Aw19	ERAP1-rs27432	cases number	controls number	cases freq.	controls freq.	OR	OR CI_low	OR CI_high	P
A29/-	AA	9	298	0.033	0.073	1.000	NA	NA	NA
A29/-	AG	58	1550	0.212	0.378	1.239	0.601	2.876	0.734
A29/-	GG	164	2001	0.601	0.488	2.713	1.374	6.105	1.72E-03
A29/Aw19	AA	2	24	0.007	0.006	2.747	0.274	14.391	0.209
A29/Aw19	AG	15	91	0.055	0.022	5.430	2.144	14.579	9.32E-05
A29/Aw19	GG	25	133	0.092	0.032	6.196	2.708	15.515	1.54E-06

Supplementary Table 4: The combined risk of ERAP1 and Aw19.

ERAP1-rs27432	ERAP2-rs10044354	cases number	controls number	cases freq.	controls freq.	OR	OR_CIlo	OR_CIhi	P
AA	CC	7	255	0.026	0.063	1.000	NA	NA	NA
AA	CT	4	60	0.015	0.015	2.420	0.503	9.885	0.236
AA	TT	0	2	0.000	0.000	0.000	0.000	208.116	1.000
AG	CC	19	687	0.070	0.170	1.007	0.400	2.871	1.000
AG	CT	49	856	0.180	0.212	2.084	0.924	5.521	0.072
AG	TT	5	86	0.018	0.021	2.113	0.515	7.964	0.197
GG	CC	32	443	0.118	0.109	2.628	1.118	7.160	0.024
GG	CT	94	1030	0.346	0.255	3.323	1.525	8.594	8.29E-04
GG	TT	62	627	0.228	0.155	3.598	1.617	9.446	4.03E-04

Supplementary Table 5: The combined risk of ERAP1 and ERAP2.

Aw19	ERAP1-rs27432	ERAP2-rs10044354	cases number	controls number	cases freq.	controls freq.	OR	OR_CIlo	OR_CIhi	P	Absolute risk
A29/-	0	0	5	237	0.018	0.059	NA	NA	NA	NA	3.43E-05
A29/-	0/1	0/1	60	1510	0.220	0.373	1.883	0.752	6.071	0.197	6.45E-05
A29/-	2_either	2_either	113	1457	0.414	0.360	3.674	1.506	11.653	1.16E-03	1.26E-04
A29/-	2_both	2_both	53	596	0.194	0.147	4.211	1.666	13.665	6.26E-04	1.44E-04
A29/Aw19	0	0	2	18	0.007	0.004	5.204	0.465	34.701	0.092	1.78E-04
A29/Aw19	0/1	0/1	12	93	0.044	0.023	6.079	1.929	22.651	5.23E-04	2.08E-04
A29/Aw19	2_either	2_either	19	104	0.070	0.026	8.604	3.002	30.314	3.09E-06	2.95E-04
A29/Aw19	2_both	2_both	9	31	0.033	0.008	13.527	3.791	54.766	1.17E-05	4.63E-04

Supplementary Table 6: The combined risk of ERAP1, ERAP2 and Aw19.

1 Schrodinger, LLC. *The PyMOL Molecular Graphics System, Version 2.0.4* (2015).

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