Supplementary information

Geography

At each locus we examined the geographical variation in allele frequency by multinomial logistic regression, to check if we were justified in pooling all three case groups. We detected a significant variation in allele frequency between the case cohorts at *HLA-C*, $P = 0.0008$, supplementary Tables 1 and 2. We also tested whether the Midlands were different to the pooled South and Southwest case groups, again HLA-C was different, $P = 0.002$, Supplementary Table 1. The difference in allele frequency in our collection is attributable to *HLA-C*03*, which is less frequent in the southern regions than in the Midlands.

Supplementary Table 1: Tests of geographical variation in allele frequency at the five MHC loci typed.

Gene	*P* value for all 3 regions	*P* value for 2 regions
HLA-C	0.0008	0.002
HLA-B	0.39	0.29
HLA-DRB1	0.74	0.56
HLA-DQA1	0.91	0.73
HLA-DQB1	0.47	0.31

Supplementary Table 2: HLA-C allele frequencies by region; n = number of chromosomes.

HLA-C allele	Frequency in Midlands, n (%)	Frequency in Southwest, n (%)	Frequency in the South, n (%)	South + Southwest, n (%)
*01	35 (2.6)	3 (2.6)	10 (5.8)	13 (4.5)
*02	52 (3.9)	4 (3.4)	7 (4.1)	11 (3.8)
*03	103 (7.7)	1 (0.9)	4 (2.3)	5 (1.7)
*04	123 (9.1)	11 (9.5)	24 (14.0)	35 (12.2)
*05	125 (9.3)	10 (8.6)	20 (11.6)	30 (10.4)
*06	98 (7.3)	8 (6.9)	13 (7.6)	21 (7.3)
*07	685 (50.9)	73 (62.9)	70 (41.0)	143 (49.7)
*08	34 (2.5)	3 (2.6)	2 (1.2)	5 (1.7)
*12	28 (2.1)	2 (1.7)	11 (6.4)	13 (4.5)
*14	4 (0.3)		2 (1.2)	2 (0.7)
*15	21 (1.6)	1(0.9)	6 (3.5)	7 (2.4)
*16	26 (1.9)		3 (1.7)	3 (1.0)
*17	12 (0.9)			
Total number of chromosomes	1346	116	172	288

Consequently, we analysed *HLA-C* in the Midlands as we did not have geographically matched controls from the South and South Western regions. For the other loci there was no evidence to suggest that allele frequency varied between centres of collection therefore we report here the results in the full dataset of 1,571 individuals.

Association with Graves' disease of the MHC loci in the full 1,571 subjects

Supplementary Table 3: Association of *HLA-C, HLA-B, HLA-DRB1, HLA-DQA1* and *HLA-DQB1* in the full 1,571 Graves' disease case control cohort. *P*-values are for multiplicative effects of alleles.

Gene	Number of Graves cases typed	Number of controls typed	*P*
HLA-C	817	492	1.40×10^{-24}
HLA-B	822	493	1.07×10^{-7}
HLA-DRB1	946	621	5.85×10^{-11}
HLA-DQA1	946	621	4.27×10^{-13}
HLA-DQB1	946	621	4.82×10^{-6}

Supplementary Table 4: Two locus association results, adding the alleles of the test locus, to the alleles and genotypes of *HLA-C*.

Test locus	Addition of test locus to *HLA-C* alleles*, *P*	Addition of test locus to *HLA-C* genotypes**, *P*
HLA-B	2.64×10^{-7}	3.83×10^{-6}
HLA-DRB1	0.0013	1.07×10^{-4}
HLA-DQA1	0.0013	7.71×10^{-5}
HLA-DQB1	9.86×10^{-5}	1.61×10^{-4}

* Assumes a multiplicative model at *HLA-C*.
** Does not assume a specific mode of inheritance at *HLA-C*.

Supplementary Table 5: Alleles of *HLA-C*; ORs with 95% confidence intervals are reported in all cases using the most common HLA-C*07 allele as reference and also the neutral allele, HLA-C*05. Both unconditional ORs and ORs conditioned on *HLA-B* alleles are reported.

HLA-C allele	Frequency in cases n (%)	Frequency in controls n (%)	Unconditional		Conditioned on *HLA-B*	
			OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
C*17	12 (0.7)	2 (0.20)	1.91 [0.46-7.97]	3.08 [0.72-13.07]	1.19 [0.25-5.65]	1.79 [0.37-8.58]
C*07	**828 (50.7)**	**328 (33.3)**	**1.00 [reference]**	**1.61 [1.22-2.11]**	**1.00 [reference]**	**1.50 [0.97-2.32]**
C*02	63 (3.9)	32 (3.3)	0.89 [0.57-1.39]	1.43 [0.86-2.36]	0.59 [0.32-1.10]	0.89 [0.47-1.69]
C*01	48 (2.9)	26 (2.6)	0.79 [0.48-1.28]	1.26 [0.75-2.14]	0.55 [0.29-1.06]	0.83 [0.42-1.62]
C*04	158 (9.7)	81 (8.2)	0.79 [0.60-1.04]	1.27 [0.89-1.80]	0.51 [0.32-0.82]	0.76 [0.47-1.23]
C*05	155 (9.5)	101 (10.3)	0.62 [0.47-0.82]	1.00 [reference]	0.67 [0.43-1.03]	1.00 [reference]
C*06	119 (7.3)	84 (8.5)	0.56 [0.42-0.75]	0.91 [0.63-1.29]	0.60 [0.34-1.07]	0.90 [0.50-1.64]
C*15	28 (1.7)	20 (2.0)	0.56 [0.32-0.97]	0.90 [0.50-1.62]	0.36 [0.17-0.75]	0.53 [0.25-1.15]
C*12	41 (2.5)	39 (4.0)	0.44 [0.43-1.17]	0.71 [0.43-1.17]	0.26 [0.14-0.49]	0.39 [0.20-0.75]
C*08	39 (2.4)	40 (4.1)	0.42 [0.27-0.65]	0.67 [0.41-1.09]	0.15 [0.06-0.37]	0.22 [0.09-0.57]
C*03	**108 (6.6)**	**156 (15.9)**	**0.29 [0.22-0.38]**	**0.47 [0.33-0.66]**	**0.13 [0.08-0.21]**	**0.19 [0.12-0.33]**
C*16	**29 (1.8)**	**59 (6.0)**	**0.21 [0.13-0.33]**	**0.33 [0.20-0.55]**	**0.21 [0.12-0.37]**	**0.31 [0.19-0.52]**
C*14	6 (0.4)	16 (1.6)	0.15 [0.06-0.40]	0.24 [0.09-0.66]	0.09 [0.03-0.29]	0.14 [0.04-0.44]

Supplementary Table 6: Alleles of *HLA-B*; ORs with 95% confidence intervals are reported, for all cases and controls, using the most common HLA-B*08 and the neutral HLA-B*07 allele as reference. Both unconditional ORs and ORs conditioned on *HLA-C* alleles are reported.

HLA-B allele	Frequency in all cases n (%)	Frequency in controls n (%)	Unconditional		Conditioned on *HLA-C*	
			OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
B*39	46 (2.8)	13 (1.3)	1.79 [0.94-3.41]	1.20 [0.64-2.26]	2.28 [1.37-6.03]	1.91 [0.92-3.94]
B*08	**404 (24.6)**	**154 (15.6)**	**1.49 [1.11-1.99]**	**1.00 [reference]**	**1.51 [1.11-2.04]**	**1.00 [reference]**
B*35	136 (8.3)	68 (6.9)	1.11 [0.77-1.60]	0.75 [0.53-1.05]	2.20 [1.25-3.89]	1.46 [0.83-2.56]
B*38	17 (1.0)	8 (0.8)	1.07 [0.46-2.50]	0.72 [0.31-1.67]	3.34 [1.12-9.92]	2.21 [0.75-6.56]
B*55	34 (2.1)	18 (1.8)	1.02 [0.56-1.85]	0.68 [0.38-1.23]	4.53 [2.12-9.69]	3.00 [1.42-6.36]
B*07	221 (13.4)	122 (12.4)	1.00 [reference]	0.67 [0.50-0.90]	1.00 [reference]	0.66 [0.49-0.90]
B*50	12 (0.7)	7 (0.7)	0.93 [0.38-2.24]	0.62 [0.26-1.51]	1.53 [0.54-4.35]	1.02 [0.36-2.89]
B*37	21 (1.3)	13 (1.3)	0.91 [0.43-1.92]	0.61 [0.30-1.27]	1.55 [0.58-4.09]	1.03 [0.39-2.68]
B*15	103 (6.3)	67 (6.8)	0.88 [0.61-1.28]	0.59 [0.41-0.84]	2.89 [1.70-4.92]	1.92 [1.14-3.21]
B*27	46 (2.8)	30 (3.0)	0.85 [0.52-1.40]	0.57 [0.35-0.93]	1.60 [0.78-3.29]	1.06 [0.52-2.17]
B*14	56 (3.4)	40 (4.1)	0.81 [0.51-1.28]	0.55 [0.35-0.85]	4.63 [1.78-12.04]	3.07 [1.19-7.92]
B*18	48 (2.9)	31 (3.1)	0.81 [0.49-1.35]	0.55 [0.33-0.90]	1.31 [0.71-2.39]	0.87 [0.48-1.57]
B*40	116 (7.1)	78 (7.9)	0.80 [0.55-1.15]	0.53 [0.38-0.76]	3.31 [1.89-5.80]	2.20 [1.27-3.79]
B*57	50 (3.0)	41 (4.2)	0.69 [0.44-1.09]	0.46 [0.30-0.72]	1.16 [0.58-2.33]	0.77 [0.39-1.54]
B*51	56 (3.4)	48 (4.9)	0.62 [0.40-0.97]	0.42 [0.27-0.64]	2.16 [1.07-4.35]	1.43 [0.71-2.87]
B*44	**196 (11.9)**	**176 (17.9)**	**0.62 [0.46-0.83]**	**0.41 [0.31-0.55]**	**1.13 [0.71-1.79]**	**0.75 [0.47-1.18]**
B*58	7 (0.4)	8 (0.8)	0.51 [0.18-1.50]	0.34 [0.12-0.98]	0.91 [0.27-3.07]	0.60 [0.18-2.01]
B*49	11 (0.7)	15 (1.5)	0.46 [0.20-1.05]	0.31 [0.14-0.70]	0.44 [0.18-1.08]	0.29 [0.12-0.71]
B*13	11 (0.7)	20 (2.0)	0.31 [0.14-0.66]	0.20 [0.10-0.44]	0.52 [0.20-1.34]	0.34 [0.13-0.88]
rares	53 (3.2)	29 (2.9)	0.97 [0.59-1.58]	0.65 [0.40-1.06]	1.94 [1.01-3.25]	1.29 [0.67-2.48]

Supplementary Table 7: Association of HLA-DRB1, using all subjects typed. All non-DRB1*03 and DRB1*07 alleles are coded X.

HLA-DRB1 genotype	OR [95% CI]	OR [95% CI]
03	1.00 [reference]	1.87 [1.53-2.29]
07	0.33 [0.25-0.44]	0.64 [0.50-0.81]
X	0.54 [0.45-0.66]	1.00 [reference]
03/03	3.08 [1.39-6.79]	3.17 [1.62-6.18]
03/07	1.00 [reference]	0.90 [0.52-1.55]
03/X	1.92 [1.15-3.20]	2.09 [1.62-2.69]
07/07	0.35 [0.14-0.87]	0.40 [0.17-0.92]
07/X	0.66 [0.38-1.13]	0.74 [0.54-1.03]
X/X	0.98 [0.59-1.61]	1.00 [reference]

Supplementary Table 8: Association of *HLA-C*, using all subjects typed. All non-HLA-C*03, *07 and *16 alleles are coded X.

HLA-C genotype	Cases, n (%)	Controls, n (%)	OR [95% CI]	OR [95% CI]
03	103 (7.7)	156 (15.9)	0.30 [0.22-0.39]	0.55 [0.42-0.73]
07	685 (50.9)	328 (33.3)	1.00 [reference]	1.64 [1.38-1.95]
16	26 (1.9)	59 (6.0)	0.21 [0.13-0.34]	0.37 [0.23-0.60]
X	532 (39.5)	441 (44.8)	0.63 [0.53-0.74]	1.00 [reference]
16/16	2 (0.2)	3 (0.6)	0.16 [0.03-1.00]	0.39 [0.06-2.36]
03/16	2 (0.2)	9 (1.8)	0.03 [0.00-0.22]	0.13 [0.03-0.61]
03/03	7 (0.9)	17 (3.5)	0.10 [0.04-0.26]	0.24 [0.10-0.60]
03/07	53 (6.5)	54 (11.0)	0.23 [0.14-0.37]	0.57 [0.36-0.89]
03/X	39 (4.8)	59 (12.0)	0.16 [0.09-0.26]	0.38 [0.24-0.61]
07/16	14 (1.7)	23 (4.7)	0.13 [0.06-0.27]	0.35 [0.17-0.72]
07/07	254 (31.1)	52 (10.6)	1.00 [reference]	2.84 [1.94-4.16]
07/X	253 (31.0)	147 (30.0)	0.33 [0.23-0.47]	1.00 [0.73-1.37]
X/16	9 (1.1)	21 (4.3)	0.10 [0.05-0.24]	0.25 [0.11-0.56]
X/X	184 (22.5)	107 (21.8)	0.33 [0.22-0.49]	1.00 [reference]