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A novel and major association of *HLA-C* in Graves' disease that eclipses the classical *HLA-DRB1* effect

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Association of the major histocompatibility complex (MHC) class II-encoded *HLA-DRB1-DQA1-DQB1* haplotype with Graves' disease (GD) has been known for several years. Recent evidence from other autoimmune diseases has suggested that the HLA class I encoded HLA-B/-C molecules could be conferring *HLA-DRB1-DQA1-DQB1* independent effects on disease. The aim of this study was to determine the effect of *HLA-B* and *HLA-C* in GD in a white ethnic group of 806 patients with GD and 487 control subjects from the UK. Of the five loci (*HLA-B*, *-C*, *-DRB1*, *-DQA1*, *-DQB1*), *HLA-C* demonstrated the strongest association ($P = 1.20 \times 10^{-20}$) with HLA-C*07 predisposing [OR = 1.63, 95% CI (1.23–2.17)] and both HLA-C*03 [OR = 0.54, 95% CI (0.38–0.77)], HLA-C*16 [OR = 0.36, 95% CI (0.21–0.61)] protective. The other loci were then tested for *HLA-C*-independent associations. *HLA-B* was found to be associated independently of *HLA-C* ($P = 1.54 \times 10^{-6}$) with the other three loci, *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1*, also improving the model but with less confidence ($P > 10^{-5}$). This study has for the first time provided evidence of a primary association of *HLA-C*, and to a lesser extent *HLA-B*, with GD. Class II loci could still have effects on GD, but they appear smaller than the *HLA-C* association. A full investigation of the MHC region, including all class I and II loci is now required. Our results point to a primary role for class I-mediated responses in GD, a condition classically assumed to be a straightforward HLA-class II-restricted autoantibody response to the thyroid stimulating hormone receptor.

INTRODUCTION

Components of the major histocompatibility complex (MHC) region are attractive candidate loci for autoimmune disease (AID), with the DRB1–DQA1–DQB1 molecules extensively examined for association with a series of AIDs including Graves' disease (GD). The HLA class II region, including the DRB1*03 and DQA1*0501 alleles and the DRB1*03–DQA1*0501–DQB1*02 (DR3) haplotype, have been consistently associated with GD (1). We have previously reported that the individual contributions of *HLA-DQA1* and *HLA-DRB1*, to the association of the HLA class II-encoded *HLA-DRB1_-DQA1_-DQB1* susceptibility haplotypes with GD were indistinguishable (2). We, and others (2,3), have proposed that this association maybe attributable, in part, to *HLA-DRB1* exon 2-encoded position β74.

Recently, in the AIDs, type 1 diabetes and multiple sclerosis, evidence has arisen suggesting the existence of susceptibility loci within the HLA class I region, independent of known class II effects (4–7) (J.M.M. Howson and J.A. Todd, manuscript in preparation). Interestingly, upregulation of HLA class I molecules on thyroid cells, including HLA-B and HLA-C molecules, has been demonstrated in response to immune cell infiltration of the thyroid gland, which may be one of the earliest features of autoimmune attack in GD (8). Methimazole used in the treatment of GD has been shown to function, in part, by reducing HLA class I and class II expression on thyrocytes (8,9).

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Table 1. Association of *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1* in British Graves' disease cases and controls collected in the Midlands

Gene	Number of Graves' cases typed	Number of controls typed	*P*-value
HLA-C	673	492	1.20×10^{-20}
HLA-B	678	493	2.31×10^{-7}
HLA-DRB1	769	621	6.67×10^{-12}
HLA-DQA1	769	621	1.52×10^{-11}
HLA-DQB1	769	621	1.31×10^{-6}

Owing to the strong evidence for a role of HLA class I-encoded molecules in GD susceptibility, the aim of this study was to extend the typing from our original MHC class II study (2) to investigate the contribution of the MHC class I encoded HLA-B and HLA-C genes to GD.

RESULTS

The newly typed *HLA-B* and *HLA-C* loci were combined with the previously typed *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1* data. The strongest association signal came from *HLA-C* ($P = 1.20 \times 10^{-20}$; Table 1) with the most common allele, HLA-C*07 being the most predisposing (OR = 1.63, 95% CI = 1.23–2.17; Table 2). Protective effects were observed for HLA-C*03 and HLA-C*16: OR = 0.54, 95% CI = 0.38–0.77 and OR = 0.36, 95% CI = 0.21–0.61, respectively, using the approximately neutral HLA-C*05 allele as a reference (Table 2). *HLA-B* was also strongly associated ($P = 2.31 \times 10^{-7}$; Table 1). The allele, HLA-B*08 (OR = 1.62, 95% CI = 1.19–2.19; Table 3) was the most predisposing (using the neutral B*07 allele as reference), with a protective association for B*44 (OR = 0.64, 95% CI = 0.47–0.88; Table 3).

Next, we tested if *HLA-B*, *HLA-DRB1*, *HLA-DQA1* or *HLA-DQB1*, had an association with GD that was independent of *HLA-C*. Each locus in turn was added to the alleles or genotypes of *HLA-C* in a logistic model and a likelihood ratio test used to evaluate whether a given locus improved the model (10). *HLA-B* improved a model containing *HLA-C* whether the alleles or the genotypes of *HLA-C* were used as the null model ($P = 1.54 \times 10^{-6}$ and $P = 1.51 \times 10^{-5}$, respectively; Table 4). All three MHC class II loci, *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1*, also improved *HLA-C*. Conversely, *HLA-C* significantly improved all models when added to *HLA-B*, *HLA-DRB1*, *HLA-DQA1* or *HLA-DQB1* ($P = 8.68 \times 10^{-13} - 3.26 \times 10^{-19}$).

As *HLA-B* may be contributing to the association of the MHC with GD, we examined the allelic ORs of both *HLA-C* and *HLA-B* having conditioned on the effects of the other MHC class I locus. Conditioning on *HLA-B* had little effect on the *HLA-C* allelic ORs (except the C*07 allele whose 95% CI crossed 1; Table 2). However, conditioning on *HLA-C* had a greater effect on the *HLA-B* ORs, with B*44 no longer showing a protective association (Table 3).

We found there was linkage disequilibrium (LD) between the previously associated HLA-DRB1*03, *07 and the HLA-C*07, *03 alleles. HLA-C*03 has $D' = 0.88$ with HLA-DRB1*03 and $D' = 0.75$ with HLA-DRB1*07, and HLA-C*07 has $D' = 0.66$ and 0.65 with HLA-DRB1*03 and HLA-DRB1*07, respectively. The most common *HLA-C_-B_-DRB1* haplotype was HLA-C*07_HLA-B*08_HLA-DRB1*03 in both cases and controls. When LD was investigated between HLA-C*07 and the HLA-B*08-HLA-DRB1*03 haplotype, it was shown that the HLA-B*08-HLA-DRB1*03 haplotype did not add to HLA-C*07 ($P = 0.167$), suggesting that the results seen at HLA-C*07 were not attributed to LD with the HLA-B*08-HLA-DRB1*03 haplotype.

DISCUSSION

Strong LD confounds determination of the exact location(s) of aetiological variant(s) in the MHC region. This study has for the first time provided evidence in support of a primary association of *HLA-C* with GD, which appears to eclipse the classical association of *HLA-DRB1* in GD. Furthermore, a second class I locus, *HLA-B*, may also be associated with GD. This work therefore calls into doubt a primary contribution of position β74 to GD. However, we cannot rule out independent effects for components of the class II-encoded *HLA-DRB1*/*HLA-DQA1*/*HLA-DQB1* haplotypes in disease susceptibility in the British population but they do appear, unexpectedly, to be smaller than the MHC class I gene, *HLA-C*.

Early studies investigating the HLA region and GD over 30 years ago reported association of the class I-encoded HLA-B*08 (11–15) and HLA-A*08 (16) alleles. However, owing to strong LD and an inability of statistical methodology at the time to split these effects, association between class I loci and disease was presumed to be secondary to the class II region which appeared to be exerting a larger effect (17). Consequently, most subsequent studies focused on the class II loci. Interestingly, a more recent study investigated the HLA class I region, reported an association of the class I encoded HLA-A*02 in a small Taiwanese population, although conditional analyses to exclude a primary class II effect was not performed (18).

HLA class I molecules could be playing a greater role than class II molecules in GD for a number of reasons. HLA class I molecules bind and present internally derived peptides including viral or bacterial antigens which may be linked to disease initiation through molecular mimicry (19). The most postulated bacterial trigger for GD is *Yersinia enterocolitica*. Antibodies raised against *Y. enterocolitica* have been shown to displace the thyroid stimulating hormone (TSH) from binding to its receptor (TSHR) (20,21), suggesting immune cross-reactivity between *Y. enterocolitica* and the TSHR. Several other viral triggers including human intracisternal type A retroviral particle (HIAP) (22) and gag protein from the human foamy virus (HPV) (23,24) have also been proposed, although further work is needed to determine a pathogenic role for these in GD. It has been suggested that viral or bacterial peptides could act as superantigens, causing a series of non-specific T cells to bind to the bacterial peptide/class I complex and become activated, some of which could cross-react, causing autoimmune attack of the thyroid gland (25).

Cytotoxic T cells, including natural killer (NK) cells, specific for TSHR peptides could have an early regulatory

Table 2. Alleles of *HLA-C*

HLA-C allele	Frequency in cases, $n = 1346$ (%)	Frequency in controls, $n = 984$ (%)	Unconditional OR(7) (95% CI)	OR(5) (95% CI)	Conditional OR(7) (95% CI)	OR(5) (95% CI)
*17	12 (0.9)	2 (0.20)	2.23 (0.53–9.42)	3.66 (0.85–15.72)	1.39 (0.28–6.76)	2.00 (0.41–9.87)
***07**	**685 (50.9)**	**328 (33.3)**	**1.00 (reference)**	**1.63 (1.23–2.17)**	**1.00 (reference)**	**1.44 (0.91–2.86)**
*02	52 (3.9)	32 (3.3)	0.89 (0.56–1.40)	1.45 (0.86–2.43)	0.58 (0.31–1.11)	0.84 (0.43–1.64)
*04	123 (9.1)	81 (8.2)	0.75 (0.56–1.01)	1.23 (0.85–1.78)	0.52 (0.31–0.86)	0.75 (0.45–1.24)
*01	35 (2.6)	26 (2.6)	0.71 (0.42–1.19)	1.15 (0.65–2.03)	0.47 (0.23–0.97)	0.68 (0.33–1.42)
*05	125 (9.3)	101 (10.3)	0.61 (0.46–0.81)	1.00 (reference)	0.69 (0.44–1.10)	1.00 (reference)
*06	98 (7.3)	84 (8.5)	0.56 (0.41–0.76)	0.91 (0.63–1.32)	0.57 (0.32–1.03)	0.82 (0.44–1.52)
*15	21 (1.6)	20 (2.0)	0.51 (0.28–0.92)	0.83 (0.44–1.55)	0.32 (0.14–0.74)	0.46 (0.20–1.07)
*08	34 (2.5)	40 (4.1)	0.44 (0.28–0.69)	0.71 (0.43–1.18)	0.18 (0.07–0.45)	0.26 (0.10–0.67)
*12	28 (2.1)	39 (4.0)	0.38 (0.24–0.63)	0.63 (0.37–1.07)	0.17 (0.8–0.35)	0.24 (0.11–0.52)
***03**	**103 (7.7)**	**156 (15.9)**	**0.33 (0.25–0.44)**	**0.54 (0.38–0.77)**	**0.16 (0.10–2.64)**	**0.24 (0.14–0.40)**
***16**	**26 (1.9)**	**59 (6.0)**	**0.22 (0.14–0.36)**	**0.36 (0.21–0.61)**	**0.24 (0.13–0.43)**	**0.34 (0.20–0.59)**
*14	4 (0.3)	16 (1.6)	0.12 (0.04–0.38)	0.20 (0.06–0.64)	0.07 (0.02–0.26)	0.11 (0.03–0.39)

ORs with 95% CI are reported for cases and controls from the Midlands, using the most common HLA-C*07 [OR(7)] and the approximately neutral HLA-C*05 allele [OR(5)] as reference. Both unconditional ORs and ORs conditioned on *HLA-B* alleles are reported. The most associated common alleles are in bold font.

Table 3. Alleles of *HLA-B*

HLA-B allele	Frequency in cases, $n = 1356$ (%)	Frequency in controls, $n = 986$ (%)	OR(8) (95% CI)	Unconditional OR(7) (95% CI)	Conditioned on *HLA-C* OR(8) (95% CI)	OR(7) (95% CI)
*39	42 (3.1)	13 (1.3)	1.27 (0.67–2.39)	2.05 (1.07–3.94)	2.33 (1.08–5.03)	3.64 (1.66–7.98)
***08**	**341 (25.2)**	**154 (15.6)**	**1.00 (reference)**	**1.62 (1.19–2.19)**	**1.00 (reference)**	**1.56 (1.14–2.14)**
*38	16 (1.2)	8 (0.8)	0.79 (0.33–1.85)	1.27 (0.54–3.01)	3.80 (1.17–12.31)	5.92 (1.81–19.31)
*55	30 (2.2)	18 (1.8)	0.70 (0.39–1.27)	1.13 (0.61–2.10)	2.85 (1.33–6.12)	4.44 (2.05–9.65)
*27	39 (2.9)	30 (3.0)	0.70 (0.41–1.19)	1.13 (0.66–1.95)	1.14 (0.54–2.42)	1.78 (0.84–3.80)
*35	106 (7.8)	68 (6.9)	0.70 (0.48–1.00)	1.12 (0.77–1.65)	1.38 (0.76–2.50)	2.15 (1.17–3.92)
*37	18 (1.3)	13 (1.3)	0.64 (0.30–1.35)	1.03 (0.48–2.23)	1.12 (0.42–3.00)	1.75 (0.65–4.74)
***07**	**181 (13.4)**	**122 (12.4)**	**0.62 (0.46–0.84)**	**1.00 (reference)**	**0.64 (0.47–0.88)**	**1.00 (reference)**
*15	84 (6.2)	67 (6.8)	0.57 (0.39–0.83)	0.92 (0.62–1.37)	1.74 (1.01–2.97)	2.71 (1.56–4.70)
*14	48 (3.5)	40 (4.1)	0.56 (0.35–0.88)	0.90 (0.56–1.45)	2.65 (1.02–6.92)	4.13 (1.57–10.92)
*50	9 (0.7)	7 (0.7)	0.55 (0.22–1.37)	0.89 (0.35–2.23)	0.96 (0.32–2.83)	1.49 (0.51–4.40)
*18	40 (3.0)	31 (3.1)	0.55 (0.33–0.91)	0.88 (0.52–1.50)	0.90 (0.48–1.67)	1.40 (0.75–2.62)
*40	89 (6.6)	78 (7.9)	0.49 (0.34–0.71)	0.79 (0.54–1.17)	1.87 (1.06–3.31)	2.92 (1.63–5.23)
*57	44 (3.2)	41 (4.2)	0.49 (0.31–0.76)	0.78 (0.49–1.25)	0.84 (0.41–1.70)	1.31 (0.64–2.66)
*58	7 (0.5)	8 (0.8)	0.42 (0.15–1.20)	0.67 (0.23–1.96)	0.69 (0.21–2.28)	1.07 (0.32–3.60)
***44**	**152 (11.2)**	**176 (17.9)**	**0.40 (0.30–0.54)**	**0.64 (0.47–0.88)**	**0.69 (0.42–1.11)**	**1.07 (0.66–1.74)**
*51	43 (3.2)	48 (4.9)	0.38 (0.24–0.61)	0.62 (0.39–1.00)	1.49 (0.70–3.18)	2.32 (1.09–4.96)
*49	10 (0.7)	15 (1.5)	0.32 (0.14–0.75)	0.52 (0.22–1.23)	0.32 (0.13–0.79)	0.50 (0.20–1.25)
*13	10 (0.7)	20 (2.0)	0.22 (0.10–0.49)	0.36 (0.16–0.80)	0.38 (0.14–1.02)	0.60 (0.22–1.61)
Rares	47 (3.5)	29 (2.9)	0.57 (0.34–0.95)	0.92 (0.55–1.53)	1.41 (0.72–2.76)	2.19 (1.11–4.32)

ORs with 95% CI are reported for cases and controls from the Midlands, using the most common HLA-B*08 [OR(8)] and the neutral HLA-B*07 alleles [OR(7)] as reference. Both unconditional ORs and ORs conditioned on *HLA-C* alleles are reported. The most associated common alleles are in bold font.

or pathogenic role in GD, as has been proposed in type 1 diabetes. Killer immunoglobulin-like receptors (KIR) on the surface of NK cells interact with specific HLA molecules and play a key role in inhibiting NK cell-mediated destruction. For HLA-C there are two sets of KIRs, 2DL1 and 2DL2/2DL3 which recognize specific sets of HLA-C molecules, group C1 molecules (containing C*02, *04, *05 and *06) and group C2 molecules (containing C*01, *03, *07 and *08), respectively (26). Groups C1 and C2 are distinguished by the presence of serine at position 77 and asparagine at position 80 of the α1 helix or asparagine at position 77 and a lysine at position 80, respectively. KIR/HLA-C interactions can be altered by peptide loading and presentation by HLA-C (27,28), which could suggest that interaction of the associated HLA-C molecules with a given autoantigen/s such as TSHR could be affecting KIR binding and that this could play a role in the onset of autoimmunity. Finally, specific class I molecules may be prone to misfolding or when they are themselves presented to the immune system by HLA class II molecules an autoimmune response could be triggered (29). These mechanisms are neither mutually exclusive nor exhaustive but represent hypotheses warranting further study.

Given these findings, a full investigation of the MHC region is now justified and required in larger, more statistically

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	1.54×10^{-6}	1.51×10^{-5}
HLA-DRB1	0.0030	0.0005
HLA-DQA1	0.0049	0.0005
HLA-DQB1	9.73×10^{-5}	0.0002

powerful and independent datasets, including those of differing ethnic origin, using the dense SNP maps now available. This should include, for example, the third class I locus, *HLA-A*, as well as *MICA* and *MICB* and the *HLA-DPB1* locus, in order to localize all the primary GD variants and establish whether *HLA-C* is causative or simply in LD with the aetiological variant(s).

MATERIALS AND METHODS

Subjects

Unrelated white patients of UK origin with GD were recruited from thyroid clinics in Birmingham, Walsall, Bournemouth and Exeter, UK, as previously described (2,30). Patients were defined as having GD by the presence of biochemical hyperthyroidism together with either the presence of dysthyroid eye disease (NOPPSECS score >2) or two of the following criteria: diffuse goiter, a significant titer of microsomal, thyroglobulin or thyrotropin (TSH) receptor autoantibodies as described in detail previously (2,30). Control subjects were recruited from Birmingham, UK. All patients and subjects gave informed written consent and the project approved by the Local Research Ethics Committee.

In total, DNA was obtained from 950 unrelated white British GD patients and 621 British, age- and gender-matched controls. The cases were collected from three locations in Great Britain: 773 cases were from Birmingham in the Midlands; 100 cases were from Exeter in the Southwest; and 77 cases were from Bournemouth in the South. All 621 controls were collected from the Birmingham area. We found that *HLA-C* allele frequencies were geographically variable ($P = 0.0008$) and therefore, we only report analyses for the 1394 subjects from the Midlands. Geographical information and analyses for the full collection are reported in the Supplementary information (Supplementary Material, Tables S1–S8).

Materials and methods

DNA was prepared from whole blood using the Nucleon Bacc II kit (Tepnel Life Sciences PLC, UK). Genotyping was performed at the University of Birmingham, UK using the primer sequences and methods published by Bunce *et al.* (31) with primers obtained from Sigma Genosys (Poole, UK).

The *HLA-DRB1*, *-DQB1* and *-DQA1* regions were typed previously (2), however, 79 additional cases were typed for this study using the same method.

Statistical analysis

We were well powered to find the primary effects of the MHC loci in GD. With 800 cases and 500 controls assuming a multiplicative model and a minor allele frequency of 0.10, we had 98% power to find an effect size of 2.0 at a type 1 error rate, $\alpha = 0.0001$. Logistic regression in STATA (http://www.stata.com) with software written by David Clayton for use within that package (http://www.gene.cimr.cam.ac.uk/clayton/software/stata) was used to test for association and calculate odds ratios (ORs) at all loci (10). No evidence was obtained for non-multiplicative inheritance at any locus studied ($P > 0.3$); hence, only allelic models, which assume a multiplicative model are reported. Analyses stratified by sex were performed; however, they were not qualitatively different to the unstratified analyses; hence, unstratified results are reported. Haplotypes were reconstructed in PHASE version 2.1.1 (32,33). All loci were in Hardy–Weinberg equilibrium in the controls ($P > 0.06$).

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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Conflict of Interest statement. None of the authors have any conflicts of interest.

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