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*J. Clin. Pathol.* 2005;58;860-863  
doi:10.1136/jcp.2004.022681

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## ORIGINAL ARTICLE

## Association of chronic fatigue syndrome with human leucocyte antigen class II alleles

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Accepted for publication  
23 February 2005

**Background:** A genetic component to the development of chronic fatigue syndrome (CFS) has been proposed, and a possible association between human leucocyte antigen (HLA) class II antigens and chronic fatigue immune dysfunction has been shown in some, but not all, studies.

**Aims:** To investigate the role of HLA class II antigens in CFS.

**Methods:** Forty nine patients with CFS were genotyped for the HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles and the frequency of these alleles was compared with a control group comprising 102 normal individuals from the UK. All patients and controls were from the same region of England and, apart from two patients, were white.

**Results:** Analysis by  $2 \times 2$  contingency tables revealed an increased frequency of HLA-DQA1\*01 alleles in patients with CFS (51.0% v 35%; odds ratio (OR), 1.93;  $p = 0.008$ ). HLA-DQB1\*06 was also increased in the patients with CFS (30.2% v 20.0%; OR, 1.73,  $p = 0.052$ ). Only the association between HLA-DQA1\*01 and CFS was significant in logistic regression models containing HLA-DQA1\*01 and HLA-DRB1\*06, and this was independent of HLA-DRB1 alleles. There was a decreased expression of HLA-DRB1\*11 in CFS, although this association disappeared after correction for multiple comparisons.

**Conclusions:** CFS may be associated with HLA-DQA1\*01, although a role for other genes in linkage disequilibrium cannot be ruled out.

Chronic fatigue syndrome (CFS) is a complex illness that affects approximately 0.2–0.7% of people in the West. It affects more women than men with an onset usually between 30 and 40 years of age.<sup>1, 2</sup> The disease manifests as severe incapacitating fatigue that persists for six months or longer, which is not the result of exertion and is not improved by bed rest. Other symptoms include: lack of concentration and/or impaired memory, recurrent sore throats, tender cervical or axillary lymph nodes, muscle pain, new headaches, unrefreshing sleep, and post-exertion malaise.<sup>3</sup> Diagnosis is made according to the symptom based CFS case definition of the Centers for Disease Control (CDC).<sup>4</sup>

"Lymphocyte proliferation and the production of cytokines and high affinity antibodies is mediated by the HLA system"

The cause of CFS remains largely unknown. Current research using molecular biological techniques has improved our knowledge of the disease. It has been shown that certain viruses—for example, Epstein-Barr virus, cytomegalovirus,<sup>5</sup> and parvovirus B19<sup>6</sup>—may play an important role in some cases of CFS. Other studies<sup>7–11</sup> suggest that host immune dysfunction may influence the course of the disease, although one study failed to find evidence of immune dysfunction or immune activation in CFS.<sup>12</sup> Such differences may depend on which immunological parameters are measured. The immunology of CFS has recently been reviewed by Lyall and colleagues.<sup>13</sup> Studies on twins<sup>14–17</sup> and an association with HLA-DR4<sup>7</sup> indicate a possible genetic predisposition to the disease. However, some studies have failed to find an association between HLA class II alleles and CFS,<sup>18, 19</sup> and one study has suggested a negative association with HLA-DR4.<sup>20</sup>

HLA genes are located in a highly polymorphic locus on chromosome 6p21, where they encode a family of cell surface

glycoproteins responsible for specific antigen presentation and immune activation of other cells.<sup>21</sup> Lymphocyte proliferation and the production of cytokines and high affinity antibodies is mediated by the HLA system, and various HLA alleles have been associated with both infectious disease and autoimmune dysfunction.<sup>22</sup> A role for the HLA system in CFS is suggested by the finding of increased concentrations of some cytokines in CFS.<sup>6, 23, 24</sup> The possibility of an infective agent in this disease would also indicate involvement of the HLA system. In a recent study<sup>25</sup> investigating the association between HLA and symptomatic parvovirus B19 infection, we reported that some of the patients fulfilled the criteria for CFS.

The genetic component to the development of CFS is the subject of ongoing research in various laboratories, including our own. This research includes studies on differential gene expression, which may highlight specific genes that are crucial in the disease process. For an improved understanding of the pathophysiology of CFS, in our present study we have further investigated the association between specific HLA class II alleles and the disease. We HLA typed patients who fulfilled the CDC criteria for CFS and compared the results with those for healthy controls.

## MATERIALS AND METHODS

Forty nine patients were diagnosed according to the CDC criteria for chronic fatigue syndrome.<sup>4</sup> These were referrals to the King's College Hospital CFS Service and came from the South East of England. The ages of the patients ranged from 21 to 63 years, with a mean of 42 years. The female to male ratio was approximately 3 : 1. All patients were white except for two Afro-Caribbeans. Twenty four were depressed and 25 were not depressed, according to an interview by a

**Abbreviations:** CFS, chronic fatigue syndrome; CI, confidence interval; HLA, human leucocyte antigen; CDC, Centers for Disease Control; OR, odds ratio

**Table 1** Allele frequencies of HLA-DRB1, HLA-DQA1, and HLA-DQB1 in patients with CFS and controls

	CFS (2n = 98)	Allele frequency	Controls (2n = 200)	Allele frequency
<b>HLA-DRB1</b>				
01	16	0.163	18	0.090
15	14	0.143	20	0.100
16	1	0.010	4	0.020
03	12	0.122	31	0.155
04	13	0.133	41	0.205
11	5	0.051*	25	0.125
12	1	0.010	0	0.000
13	16	0.163	22	0.110
14	4	0.041	5	0.025
07	12	0.122	26	0.130
08	3	0.031	3	0.015
09	1	0.010	2	0.015
10	0	0.010	2	0.010
<b>HLA-DQA1</b>				
01	50	0.510†	70	0.350
02	12	0.122	29	0.145
03	15	0.153	43	0.215
04	2	0.020	3	0.015
05	19	0.194	55	0.275
<b>HLA-DQB1</b>				
02	20	0.208	50	0.250
0301	11	0.115	43	0.215
0302	8	0.083	24	0.120
0303	5	0.052	10	0.050
04	2	0.021	3	0.015
05	21	0.219	30	0.150
06	29	0.302‡	40	0.200

The frequency distribution of the alleles for each of the HLA class II markers in the CFS group was compared with that of controls by  $\chi^2$  tests for homogeneity. No overall difference was found in the frequency distribution of the HLA-DRB1, HLA-DQA1, or HLA-DQB1 alleles in the CFS group compared with controls.

Individual alleles in the CFS group that showed significant differences compared with the controls (by examination of adjusted residuals) were examined further by  $\chi^2$  tests using 2x2 contingency tables.

All comparisons versus controls: \*OR, 0.40; 95% CI, 0.12 to 1.08; p=0.046; †OR, 1.93; 95% CI, 1.2 to 3.3; p=0.008; ‡OR, 1.73; 95% CI, 0.96 to 3.1; p=0.052.

CFS, chronic fatigue syndrome; CI, confidence interval; HLA, human leucocyte antigen; OR, odds ratio.

psychiatrist using a semi-structured interview format and DSM-IV.<sup>26</sup>

### Controls

The controls were a group of 102 white cadaveric donors whose cause of death was trauma based and who had no reported symptoms of either fatigue or CFS.

### HLA typing

Patients and controls were typed for HLA class II alleles: HLA-DRB1, HLA-DQA1, and HLA-DQB1 by polymerase chain reaction using sequence specific primers, with DNA extracted from whole blood.

### Statistical analysis

The frequency distribution of alleles for HLA-DRB1, HLA-DQA1, and HLA-DQB1 in patients with CFS was initially compared with that of controls by  $\chi^2$  tests for homogeneity. The alleles that contributed most to the  $\chi^2$  were determined by examining the adjusted residuals (deviations from expected values). Each allele in the disease group that showed a significant difference compared with the controls was then examined further by either  $\chi^2$  or Fisher exact analysis of 2 x 2 contingency tables. The strength of the association between CFS and the HLA alleles and phenotypes was estimated using odds ratios (OR) and 95% confidence intervals (CI). To examine whether any association of HLA class II alleles was independent of other alleles in linkage

disequilibrium we carried out multivariate logistic regression analyses with different combinations of HLA-DRB1, HLA-DQA1, and HLA-DQB1 phenotypes as independent (explanatory) variables, and the presence or absence of CFS as the dependent (outcome) variable. Analyses were carried out using the Number Cruncher Statistical Package for Windows (NCSS 2000), or the PEPI software package (v 2.0) for epidemiological analysis.

## RESULTS

### HLA-DRB1 associations in patients with CFS

Table 1 shows the allele frequencies of HLA-DRB1 in the patient group and controls. Initial  $\chi^2$  analysis revealed that the frequency distribution of HLA-DRB1 alleles was not significantly different between the CFS group and the controls (likelihood ratio:  $\chi^2 = 17.5$ ; degrees of freedom, 10; p = 0.1). However, examination of the adjusted residuals indicated that the frequency of the HLA-DRB1\*11 allele was significantly different to controls and made the largest contribution to the  $\chi^2$  value. Further analysis by 2 x 2 contingency tables revealed a decreased frequency of HLA-DRB1\*11 alleles in patients with CFS compared with controls, although this was only weakly significant (5.1% v 12.5%; OR, 0.4; 95% CI, 0.12 to 1.08; p = 0.046).

### HLA-DQA1 and HLA-DQB1 associations in patients with CFS

The overall frequency distribution of the HLA-DQA1 and HLA-DQB1 alleles in the CFS group was not significantly different from the controls (table 1). However, examination of adjusted residuals indicated that there were differences in the frequency of the HLA-DQA1\*01 and HLA-DQB1\*06 alleles between the patients and controls. Analysis by 2 x 2 contingency tables revealed an increased frequency of HLA-DQA1\*01 in patients with CFS (51.0% v 35%; OR, 1.93; 95% CI, 1.2 to 3.3; p = 0.008). HLA-DQB1\*06 was also increased in the patients with CFS (30.2% v 20.0%; OR, 1.73; 95% CI, 0.96 to 3.1), although this was on the borderline of significance (p = 0.052).

The HLA-DRB1, HLA-DQA1, and HLA-DQB1 associations need to be treated with caution because they have not been corrected for multiple comparisons. If corrected for all 22 possible comparisons then significance was lost. However, a less conservative approach of correcting for multiple comparisons at each multiallelic locus (at HLA-DRB1, HLA-DQA1, and HLA-DQB1 separately), suggests a possible association of HLA-DQA1\*01 (p = 0.04) with CFS.

### Primary HLA class II association with CFS

HLA-DQA1\*0101 alleles are in strong linkage disequilibrium with HLA-DQB1\*05 and HLA-DRB1\*01 alleles, whereas HLA-DQA1\*0102/0103 alleles are in linkage disequilibrium with HLA-DQB1\*06 and HLA-DRB1\*15/16 alleles. Therefore, we

**Table 2** Multivariate logistic regression analysis to demonstrate the association of HLA-DQA1\*01 with CFS, independent of HLA-DRB1\*01 and HLA-DQB1\*05

	Regression coefficient	SE	OR (95% CI)	p Value
Constant	-1.435	0.352		
DQA1*01	0.914	0.456	2.49 (1.02 to 6.1)	0.04
DQB1*05	0.234	0.613	1.26 (0.4 to 4.2)	0.7
DRB1*01	0.036	0.647	1.04 (0.3 to 3.7)	0.9

Multivariate logistic regression analysis with presence or absence of CFS as the dependent variable. All independent variables were adjusted for each other in the model. The p values represent the significance of each variable compared with individuals negative for that variable. CFS, chronic fatigue syndrome; CI, confidence interval; OR, odds ratio.

**Table 3** Multivariate logistic regression analysis to demonstrate the association of HLA-DQA1\*01 with CFS, independent of HLA-DRB1\*15/16 and HLA-DQB1\*06

	Regression coefficient	SE	OR (95% CI)	p Value
Constant	-1.435	0.352		
DQA1*01	1.004	0.492	2.73 (1.04 to 7.2)	0.04
DQB1*06	0.208	0.486	1.23 (0.5 to 3.2)	0.7
DRB1*15/16	-0.257	0.485	0.77 (0.3 to 2.0)	0.6

Multivariate logistic regression analysis with presence or absence of CFS as the dependent variable. All independent variables were adjusted for each other in the model. The p values represent the significance of each variable compared with individuals negative for that variable. CFS, chronic fatigue syndrome; CI, confidence interval; OR, odds ratio.

investigated whether HLA-DQA1\*01 might form part of an extended haplotype with other class II HLA alleles, thereby explaining the association with CFS. In the absence of family data we could not assign definitive haplotypes to individual patients. Instead, we carried out logistic regression analyses in which combinations of phenotypes were included together as one variable (for example, HLA-DRB1\*01, HLA-DQA1\*01, and HLA-DQB1\*05) for comparison between patients with CFS and controls. Any individual not carrying this combination was considered negative. No significant differences were found between patients and controls for any combination of HLA-DRB1, HLA-DQA1, and HLA-DQB1 phenotypes.

We next carried out multivariate logistic regression analyses to investigate whether the HLA-DQA1\*01 association was independent of HLA-DQB1 and HLA-DRB1. Individual HLA-DRB1, HLA-DQA1, and HLA-DQB1 phenotypes were included as separate independent variables in the same model. Inclusion of all these variables suggested that the primary association with CFS was with HLA-DQA1\*01, and that this was independent of the HLA-DRB1 and HLA-DQB1 alleles. Table 2 shows that HLA-DQA1\*01 is associated with CFS independent of HLA-DRB1\*01 and HLA-DQB1\*05. A similar result was found in a regression model containing HLA-DQA1\*01, HLA-DRB1\*15/16, and HLA-DQB1\*06 (table 3).

Twenty five of the patients with CFS suffered from depression. Within the CFS group, there were no HLA class II associations with depression versus non-depression.

## DISCUSSION

A genetic component to the development of CFS has been suggested by various twin studies.<sup>14-16</sup> Immune dysfunction studies<sup>9-10, 22</sup> highlighted cytokine deregulation and immune cell disruption<sup>27</sup> as important features in the pathophysiology of the disease. In our current study, we show an increase in the expression of HLA DQA1\*01 in patients with CFS. There was also a marginal increase in the expression of HLA-DQB1\*06, although the association with CFS disappeared after inclusion of HLA-DQB1\*06 as an independent variable in the same logistic regression model as HLA-DQA1\*01. This suggests that HLA-DQA1\*01 may be the primary association with CFS. We also found decreased expression of HLA-DRB1\*11 in CFS, although this association was weak and disappeared after correction for all possible comparisons of HLA-DRB1 alleles between patients and controls.

Specific HLA-DQ polymorphisms have been associated with various diseases including diabetes and coeliac disease.<sup>28-29</sup> In previous work, Keller *et al* found a possible association of HLA-DQ3 with chronic fatigue syndrome,<sup>7</sup> but HLA-DQ3 is a broad definition based on serological typing, so any association with disease could not be assigned to specific HLA-DQ alleles. The HLA-DQA1\*01 allele has been associated with few disease conditions, although associations have been

found with tubulointerstitial nephritis and uveitis syndrome,<sup>30</sup> and hyper-response to measles vaccine.<sup>31</sup>

“Although our results will need independent replication, they do provide possible target HLA alleles to investigate further for association with chronic fatigue syndrome”

Underhill *et al* found no association between HLA alleles and CFS.<sup>19</sup> However, they did not examine the frequency of the HLA-DQA1 alleles, so it is not possible to make a direct comparison of results. Interestingly, in their study the combined frequency of the HLA-DQB1\*0601 and HLA-DQB1\*0602 phenotypes was significantly higher in the patients than in the controls (35% v 21%; p = 0.045), if correction for multiple comparisons was omitted. Although not commented upon in the Underhill study, these data are consistent with the marginal increase in HLA-DQB1\*06 allele frequency seen in our study, and may be indicative of an increased frequency of HLA-DQA1\*01 alleles in linkage disequilibrium. The patients studied by Underhill *et al* came from the same clinical service as in our present study, although they were different patients.<sup>19</sup> Therefore, any differences between the two studies are unlikely to be explained by selection bias.

HLA-DQB1\*06 forms the largest group of HLA-DQB1 molecules,<sup>32</sup> and has been associated with several diseases, including narcolepsy<sup>33</sup> and multiple sclerosis.<sup>34</sup> Interestingly, it has been suggested that narcolepsy, which is strongly associated with HLA-DQB1\*0602, may need to be excluded in the differential diagnosis of CFS.<sup>35</sup> The marginal increase in HLA-DQB1\*06 seen in our study will need to be investigated further. The same is true for the decreased expression of HLA-DRB1\*11.

There may be several reasons for the inconsistency seen in studies of HLA molecules and CFS. Early studies used serological typing, which is unable to discriminate between many of the alleles identified by the sequence specific primer/polymerase chain reaction technique used here. Even so, additional subtyping of HLA-DQA1\*01 and HLA-DQB1\*06 alleles will be necessary to identify which particular subtypes are important. A second major problem is that the few studies that have been carried out have used relatively small numbers of patients with CFS, and may lack sufficient power to show significant differences. Our current study also suffers from this caveat and, although differences between patients and controls were detected, the results need to be treated with caution. In particular, the need for multiple testing at multiallelic loci is a major problem in this type of study, especially when the number of available cases is low. Although our results will need independent replication, they do provide possible target HLA alleles to investigate further for association with CFS.

In conclusion, the current available data on immune cell and cytokine deregulation in CFS are consistent with an immunomodulatory role for the HLA system in this disease.

## Take home messages

- Our results suggest an association between chronic fatigue syndrome (CFS) and the HLA class II region, primarily the HLA-DQA1\*01 allele
- However, because of the strong linkage disequilibrium between genes in this region, an association with other genes within the HLA locus cannot be ruled out
- Further studies are needed to clarify the situation

The results of our study provide provisional evidence for an association of CFS with the HLA class II region, and suggest that this may be primarily with the HLA-DQA1\*01 allele. However, because of the strong linkage disequilibrium between genes in this region, an association with other genes within the HLA locus cannot be ruled out.

## ACKNOWLEDGEMENTS

This research was funded by the CFS Research Foundation, Hertfordshire, UK and the Royal Brompton and Harefield NHS Trust. We also thank D Blair, who was funded by the Joint Research Council of King's College Hospital and GKT School of Medicine, for help in subject recruitment and sample collection.

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