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HLA-B62 and HLA-DQ8 are associated with Complex Regional Pain Syndrome with fixed dystonia

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ABSTRACT

Complex Regional Pain Syndrome (CRPS) is clinically characterized by pain in combination with sensory, autonomic, and motor symptoms that may include weakness, tremor, myoclonus and dystonia of the affected limb(s). The syndrome is multifactorial in origin and mostly attributed to tissue injury. There is some evidence that the human leukocyte antigen (HLA) system plays a role in the pathophysiology of CRPS, but previous studies lacked power. Here we performed the most extensive study investigating the contribution of HLA alleles (i.e. HLA-A, HLA-B, HLA-DRB1, and HLA-DQB1) in 150 CRPS patients who also had fixed dystonia. HLA-B62 (OR = 2.05 [95% CI 1.41–2.99], $P = 0.0005$) and HLA-DQ8 (OR = 1.75 [95% CI 1.20–2.57], $P = 0.005$) were found significantly associated with CRPS and dystonia. The association remained significant after correction (HLA-B62 $P_{corrected}$ [P_c] = 0.02 and HLA-DQ8 $P_c = 0.04$). The involvement of HLA-B62 and HLA-DQ8 in CRPS with dystonia may indicate that these HLA loci are implicated in the susceptibility or expression of the disease.

1. Introduction

Complex Regional Pain Syndrome type I (CRPS) is characterized by various combinations of pain, edema, skin discoloration, altered temperature, hyperhidrosis, and various movement disorders [16,34]. Dystonia, which is characterized by sustained muscle contractions in the affected limb causing fixed posturing at rest, is the most frequently reported movement disorder in CRPS, affecting about 25% of the patients [31,32]. CRPS is more common in women and usually preceded by tissue injury [6]. The pathophysiology of CRPS is only partly understood, but compelling evidence indicates that aberrant inflammation in which C sensory nerve fibers (neurogenic inflammation) and the immune system of the skin are involved [15], plays an important role in the acute phase of the syndrome [1,26]. Further evidence to support the role of inflammatory mechanisms in CRPS came from epidemiological data showing higher co-occurrence of asthma in the medical history of CRPS patients [7].

For many diseases with an inflammatory component (i.e. multiple sclerosis and celiac disease), genetic associations have been found with the major histocompatibility complex (MHC), including the human leukocyte antigen (HLA) system [4,24,36]. The MHC region consists of a complex of genes located on chromosome 6p21 and contains the six transplantation HLA genes and other genes that have important roles in the regulation of the immune system (for a recent review see [27]). Genes are grouped into three classes, class I genes include the HLA antigens A, B, and C, class II genes include the heterodimeric HLA-DR, DP, and DQ genes, and class III genes include complement components, tumor necrosis factor alpha, and other genes. Although for decades serological methods were used to type HLA alleles, this is nowadays performed using DNA-based methods.

Also for CRPS a link with the HLA system has been suggested [20,19]. Significant associations have been found between CRPS and HLA-DQ1 [17,33], and HLA-DR6 [33] and CRPS-related dystonia and HLA-DR13 [28,30]. However, these studies had drawbacks, as for instance, small numbers of patients and broad inclusion criteria resulting in clinically heterogeneous phenotypes.

To reduce clinical heterogeneity, we selected only CRPS patients with fixed dystonia. As the age at onset of this more severely affected subtype of CRPS is, on average, 11 years younger as compared to CRPS patients without dystonia [32], we envisage that genetic factors may play a more prominent role in CRPS patients with this particular subtype.

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Table 1
Criteria for Complex Regional Pain Syndrome type I.

a.	CRPS is a syndrome that develops after an initiating noxious event
b.	Spontaneous pain, allodynia or hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event.
c.	There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event
d.	This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

For the diagnosis of CRPS-1, criteria b–d must be fulfilled [19].

To better establish the role of the HLA system in CRPS, we performed a comprehensive analysis testing HLA alleles in 150 CRPS patients with fixed dystonia.

2. Methods

2.1. Patients

Between May 2005 and June 2007, 150 Dutch Caucasian CRPS patients with CRPS-related fixed dystonia of at least one extremity were recruited at the Movement Disorders Clinic of the Department of Neurology of the Leiden University Medical Center. CRPS was diagnosed according to the criteria of the International Association for the Study of Pain (IASP) (Table 1) [21]. Dystonia was diagnosed by a neurologist with expertise in movement disorders (JJvH). Characteristics of the patients are shown in Table 2. The study protocol was approved by the Ethics Committee of the Leiden University Medical Center. All subjects gave written informed consent before entering the study.

2.2. Controls

Frequencies of HLA alleles were compared with those of a previously published group of 2440 healthy Caucasian Dutch blood donors [25].

2.3. HLA genotyping

HLA typing was performed for HLA-A (17 alleles) and HLA-B (32 alleles) by using a commercially available reverse line hybridization strip assay (RELI™ SSO, Invitrogen, Washington, DC, USA). PCR amplification and hybridizations were done according to manufacturers recommendations. HLA-DRB1 (14 alleles) and HLA-DQB1 (7 alleles) were typed with sequence-specific oligonucleotide probe (PCR/SSOP) technique described elsewhere [35]. The interpretation of the raw data was carried out with computer-assisted analysis software [14].

Table 2
Characteristics of Complex Regional Pain Syndrome (CRPS) patients.

Number of patients	150
Percentage (*N*) of females	88% (132)
Mean (SD) age at onset of CRPS -years	31.5 (12.0)
Median disease duration (IQR)-years	8.7 (4.0–14.0)
Percentage (*N*) patients with > 1 affected extremity	73% (110)
First affected extremity – percentage (*N*)	
Arm	48% (72)
Leg	45% (67)
Both	7% (11)
Sign and symptoms calculated from non-missing data* – percentage (*N*)	
Allodynia, hyperesthesia or hyperalgesia	75% (102)
Hypoesthesia or hypoalgesia	79% (108)
Edema	90% (132)
Temperature difference	97% (140)
Color differences	97% (146)

N, number; SD, standard deviation; IQR, interquartile range.
* Variables were considered present if a sign, a symptom or both were reported or observed.

2.4. Statistical analysis

Genetic associations for HLA alleles were assessed by chi-square tests based on a 2×2 contingency table. *P* values were obtained by the two-sided Fisher's exact test. A corrected *P* value (P_c), that is, the raw *P* value multiplied by the estimated number of HLA alleles present within the loci examined (17 for HLA-A, 32 for HLA-B, 14 for HLA-DRB1, and seven for HLA-DQB1), was calculated to evaluate the inflation of type I error due to multiple testing for multi-alleles [8]. A P_c less than 0.05 was considered to indicate a significant difference. Odds ratios (OR) with 95% confidence interval (CI) were calculated according to the Woolf–Haldane test [12].

3. Results

3.1. HLA marker analysis

We typed 70 HLA alleles (of the HLA-A, HLA-B, HLA-DR, and HLA-DQ loci) in 150 CRPS patients with fixed dystonia. Frequencies of HLA alleles were compared with those of 2440 healthy Caucasian Dutch blood donors. Genetic associations of HLA-A, HLA-B, HLA-DR, and HLA-DQ alleles with CRPS patients with fixed dystonia were determined (see tables 3, 4, 5 and 6). Initial uncorrected association analyses revealed four HLA alleles that appeared associated with disease: HLA-A23 (OR = 2.63 [95% CI 1.29–5.31], $P = 0.017$), HLA-B62 (OR = 2.05 [95% CI 1.41–2.99] $P = 0.001$), HLA-DR4 (1.55 [95% CI 1.11–2.18] $P = 0.016$), and HLA-DQ8 (1.75 [95% CI 1.20–2.57] $P = 0.005$). After correction for comparisons of multiple HLA alleles (P_c), HLA-B62 ($P_c = 0.02$), and HLA-DQ8 ($P_c = 0.04$) remained significantly associated (see Tables 4 and 6).

4. Discussion

CRPS is commonly preceded by tissue injury, which induces a series of specific reactions aiming to repair damage, promote

Table 3
Odd ratios and *P*-values estimated for HLA-A alleles typed among CRPS cases with fixed dystonia and control subjects.

	% Cases	% Controls	OR	95% CI	*P*	P_c
A1	26	31	0.80	[0.55–1.16]	0.272	0.996
A2	55	53	1.08	[0.78–1.50]	0.674	1.000
A3	29	29	1.00	[0.70–1.44]	1.000	1.000
A11	13	12	1.20	[0.74–1.95]	0.512	1.000
A23	6	2	2.63	[1.29–5.31]	0.017	0.253
A24	16	17	0.97	[0.62–1.51]	0.910	1.000
A25	2	2	1.22	[0.41–3.67]	0.760	1.000
A26	2	4	0.51	[0.18–1.51]	0.209	0.982
A28	8	10	0.81	[0.45–1.46]	0.483	1.000
A29	7	5	1.60	[0.85–3.00]	0.177	1.000
A30	3	3	1.04	[0.43–2.50]	1.000	0.964
A31	6	6	1.05	[0.53–2.07]	1.000	1.000
A32	7	6	1.15	[0.60–2.19]	0.726	1.000
A33	3	1	2.27	[0.84–6.18]	0.153	0.940
A34	0	0	NA	NA	NA	NA
A36	0	0	NA	NA	NA	NA
A66	0	0	NA	NA	NA	NA

CRPS, Complex Regional Pain Syndrome; OR, Woolf–Haldane odds ratio; 95% CI, 95% confidence interval; NA, not applicable because of low numbers. P_c, *P* values corrected for multiple testing using the method of Edwards for 17 HLA-A alleles.

Table 4
Odd ratios and *P*-values estimated for HLA-B alleles typed among CRPS cases with fixed dystonia and control subjects.

	% Cases	% Controls	OR	95% CI	*P*	P_c
B7	26	27	0.94	[0.65–1.36]	0.777	1.000
B8	23	23	1.01	[0.68–1.49]	1.000	1.000
B13	3	4	0.80	[0.34–1.93]	0.681	1.000
B14	3	3	1.27	[0.52–3.07]	0.621	1.000
B18	3	6	0.44	[0.17–1.15]	0.079	0.929
B27	10	6	1.66	[0.96–2.87]	0.092	0.954
B35	18	18	1.04	[0.68–1.60]	0.912	1.000
B37	4	4	1.06	[0.47–2.38]	1.000	1.000
B38	1	4	0.40	[0.11–1.42]	0.123	0.985
B39	5	3	1.55	[0.72–3.34]	0.343	1.000
B41	0	1	0.28	[0.02–4.63]	0.405	1.000
B42	0	0	NA	NA	NA	NA
B44	25	24	1.04	[0.71–1.53]	0.844	1.000
B45	1	1	0.66	[0.13–3.41]	0.721	1.000
B46	0	0	NA	NA	NA	NA
B47	0	0	NA	NA	NA	NA
B48	0	0	NA	NA	NA	NA
B49	2	1	2.25	[0.73–6.96]	0.219	1.000
B50	1	1	0.82	[0.16–4.26]	1.000	1.000
B51	12	11	1.10	[0.66–1.81]	0.790	1.000
B52	1	1	1.56	[0.29–8.41]	0.618	1.000
B53	1	1	1.25	[0.23–6.61]	1.000	1.000
B54	0	0	NA	NA	NA	NA
B55	4	4	0.99	[0.44–2.23]	1.000	1.000
B56	1	1	0.72	[0.14–3.72]	0.719	1.000
B57	6	6	1.15	[0.58–2.27]	0.714	1.000
B58	1	1	1.52	[0.41–5.60]	0.678	1.000
B60	15	15	1.00	[0.63–1.59]	1.000	1.000
B61	2	3	0.75	[0.25–2.23]	0.624	1.000
B62	**27**	**15**	**2.05**	**[1.41–2.99]**	**0.001**	**0.015**
B63	0	0	NA	NA	NA	NA
B70	0	0	NA	NA	NA	NA

CRPS, Complex Regional Pain Syndrome; OR, Woolf–Haldane odds ratio; 95% CI, 95% confidence interval; NA, not applicable because of low numbers. P_c, *P* values corrected for multiple testing using the method of Edwards for 32 HLA-B alleles.
Bold, significant after Edwards correction.

wound healing and recruit host defense mechanisms. The perturbed immune response to traumatized tissue in CRPS shares several characteristics with common inflammatory diseases in which the pathogenic role of MHC gene polymorphisms is well established [39]. The MHC comprises a gene family that has important immunologic functions. MHC gene variations confer susceptibility to a variety of inflammatory disorders such as celiac disease and multiple sclerosis [22,36]. Attempts to identify MHC loci increasing the risk for CRPS have revealed several HLA susceptibility alleles (HLA-DQ1, HLA-DR6, and HLA-DR13) [17,30,33]. However, clinical heterogeneity, statistical analysis of unplanned post hoc evaluations, and underpowering of these studies that included about 80 patients or less, are important drawbacks and most likely explain the apparent inconsistent data [17,20,28,30,33].

In view of the methodological problems associated with the previous HLA association studies conducted in CRPS, we recruited a larger sample of patients. In addition, we applied an enrichment strategy by focusing on a severe distinct phenotype of the syndrome that is characterized by a generally much younger age at onset, which may indicate a larger role of genetic factors [32]. We observed significant associations between CRPS with dystonia and HLA-B62 and HLA-DQ8 alleles, which remained significant after correction for multiple comparisons. We also observed significant associations with alleles HLA-A23 and HLA-DR4, but these associations failed to maintain significance after correction for multiple comparisons (see Tables 3 and 5).

In considering potential biological mechanisms for disease, associations with HLA alleles should be interpreted in the context of the phenotype under study. All of our CRPS patients had long-standing chronic disease with sensory and motor manifestations of the central nervous system. Notably, the initial inflammatory response of the syndrome may induce profound changes in the processing of sensory input in the spinal cord, a process known as central sensitization. Neuroplasticity is a process whereby neurons reorganize their connectivity in response to altered experiences like injury [37,38]. In central sensitization, neuroplasticity is maladaptive and clinically associated with chronification of pain, and the occurrence of positive sensory phenomena like allodynia and hyperalgesia. Because central sensitization corrupts spinal sensorimotor networks this may also lead to dystonia in CRPS [9,29]. Interestingly, HLA class I molecules have also been implicated in non-immune roles including synaptic development and plasticity in the central nervous system [5,10]. Consequently, our findings of an association with HLA-B62 (MHC class I) may also point at a role of HLA class I in maladaptive neuroplasticity in CRPS.

Regarding HLA class II counterparts, their potential non-immunological role remains unknown. However, it is interesting to note that HLA-DQ8 (MHC class II) that we found associated with CRPS and dystonia, is also associated with susceptibility for developing celiac disease (CD) in about 4–5% of the CD population (for a review see Louka and Sollid [2003]) [18]. CD may lead to neurological manifestations including cerebellar ataxia, myoclonus, chorea, and peripheral neuropathy [11]. Notwithstanding a single case of paroxysmal non-kinesiogenic dystonia has been reported in CD so far, however this phenotype is substantially different from fixed dystonia encountered in CRPS [13]. Although the mechanisms behind the neurological manifestations of CD have not been elucidated, molecular mimicry and intermolecular help have been suggested to play a role [11]. Whereas the link of a cellular

Table 5
Odd ratios and *P*-values estimated for HLA-DR alleles typed among CRPS cases with fixed dystonia and control subjects.

	% Cases	% Controls	OR	95% CI	*P*	P_c
DR1	25	20	1.34	[0.92–1.97]	0.142	0.883
DR4	38	28	1.55	[1.11–2.18]	0.016	0.196
DR7	25	19	1.39	[0.95–2.04]	0.110	0.806
DR8	5	5	0.92	[0.43–1.96]	0.852	1.000
DR9	1	2	0.67	[0.19–2.40]	0.580	1.000
DR10	2	4	0.54	[0.18–1.59]	0.281	0.990
DR11	9	14	0.64	[0.37–1.11]	0.123	0.813
DR12	3	5	0.79	[0.33–1.89]	0.682	1.000
DR13	24	28	0.80	[0.55–1.18]	0.262	0.986
DR14	5	5	1.03	[0.51–2.11]	1.000	1.000
DR15	29	26	1.22	[0.84–1.76]	0.330	0.996
DR16	4	2	2.37	[1.02–5.49]	0.118	0.826
DR17	23	25	0.90	[0.53–1.50]	0.693	1.000
DR18	0	0	NA	NA	NA	NA

CRPS, Complex Regional Pain Syndrome; OR, Woolf–Haldane odds ratio; 95% CI, 95% confidence interval; NA, not applicable because of low numbers. P_c, *P* values corrected for multiple testing using the method of Edwards for 14 HLA-DR alleles.

Table 6
Odd ratios and *P*-values estimated for HLA-DQ alleles typed among CRPS cases with fixed dystonia and control subjects.

	% Cases	% Controls	OR	95% CI	*P*	P_c
DQ2	39	37	1.09	[0.78–1.53]	0.664	1.000
DQ4	5	3	1.57	[0.69–3.57]	0.331	0.940
DQ5	33	35	0.95	[0.66–1.37]	0.781	1.000
DQ6	48	50	0.92	[0.65–1.30]	0.660	1.000
DQ7	23	28	0.77	[0.52–1.13]	0.187	0.765
DQ8	**31**	**20**	**1.75**	**[1.20–2.57]**	**0.005**	**0.037**
DQ9	8	8	1.07	[0.57–2.00]	0.870	1.000

CRPS, Complex Regional Pain Syndrome; OR, Woolf–Haldane odds ratio; 95% CI, 95% confidence interval. P_c, *P* values corrected for multiple testing using the method of Edwards for 7 HLA-DQ alleles.
Bold, significant after Edwards correction.

immune response with CD is well established, this type of response likely plays a minor role in conferring CRPS susceptibility. In fact, further studies are needed to answer the question whether – given the findings of HLA-DQ8 as a possible genetic factor in CD and CRPS – both diseases, perhaps in part, share similar underlying pathophysiological mechanisms. Notably, a role of autoantibodies has been suggested in CRPS [2,3] and it has been reported that most associations of a variety of diseases with autoantibodies were with HLA class II [23].

Since the present study only included patients with CRPS-related dystonia, it is not possible to assess the contribution of the HLA system in specific subtypes of CRPS, with, for instance, a restricted inflammatory phenotype or chronic CRPS without dystonia, and it is not possible to indicate if our findings relate more to the susceptibility to respond with a perturbed inflammatory response, susceptibility for chronification of the syndrome or susceptibility to develop dystonia.

Although previous associations of the HLA locus with CRPS with or without dystonia have been reported, we would still consider our study hypothesis-generating, and because association studies carry the risk of being false positive findings our findings need replication. Our results encourage future studies to evaluate the role of HLA-B62 and HLA-DQ8 in different subtypes of CRPS.

Conflict of interest

All authors declare that they have no conflict of interest with respect to the subject of this study.

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