EXTENDED REPORT

Role of the *MHC2TA* gene in autoimmune diseases

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Objectives: Expression of major histocompatibility complex (MHC) class II genes is almost exclusively regulated by the class II transactivator. A promoter polymorphism (−168A/G, rs3087456) in the *MHC2TA* gene was associated with increased susceptibility to rheumatoid arthritis, multiple sclerosis and myocardial infarction in a northern European population. However, no evidence of association of this *MHC2TA* variant with the two autoimmune diseases could be subsequently detected in independent cohorts.

Aim: To test the aforementioned single nucleotide polymorphism and another G→C change (nt1614 from coding sequence, rs4774) to analyse the haplotype pattern in this *MHC2TA* gene.

Methods: A case–control study was performed with 350 patients with rheumatoid arthritis, 396 patients with multiple sclerosis, 663 patients with inflammatory bowel disease (IBD) and 519 healthy controls from Madrid. Genotyping was ascertained by using TaqMan assays-on-demand on a 7900HT analyser, following the manufacturer's suggestions (Applied Biosystems, Foster City, California, USA). Haplotypes were inferred with the expectation–maximisation algorithm implemented by the Arlequin software.

Results: No independent association with these autoimmune diseases was found for either polymorphism in the Spanish cohorts tested. However, when haplotypes were compared between patients with rheumatoid arthritis and controls, a significant difference in their overall frequency distribution was observed, evidencing a protective haplotype (−168A/1614C, p = 0.006; odds ratio (OR) 0.7) and a risk haplotype (−168G/1614C, p = 0.019; OR 1.6). Patients with multiple sclerosis mirrored these results, but no effect on IBD was identified.

Conclusions: The *MHC2TA* gene influences predisposition to rheumatoid arthritis and multiple sclerosis, but not to IBD. The −168G allele is not an aetiological variant in itself, but a genetic marker of susceptibility/protection haplotypes.

Major histocompatibility complex (MHC) molecules are involved in the induction and regulation of adaptive immune responses to invading pathogens, and they contribute to the maintenance of self-tolerance, as well as to the breakdown of tolerance in autoimmune diseases.[1] MHC class II molecules are cell-surface glycoproteins of critical importance to the adaptive immune response, as they present peptides to antigen receptors of CD4 T cells. MHC class II (*MHCII*) gene expression is regulated mainly at the level of transcription.[2] The enhanceosome proteins, which bind to the highly conserved SXY module in the promoter of *MHCII* genes, are expressed ubiquitously. The class II transactivator CIITA is the key element to exquisitely control the levels of *MHCII* expression.[3] The human CIITA gene, *MHC2TA*, is a 42-kb gene mapping to chromosome 16p13, which encodes the non-DNA-binding coactivator.[4] The activity of this *MHC2TA* gene is also regulated primarily at the transcriptional level, which is under the control of four different promoters in humans (pI–pIV), acting independently of one another without apparent cross talk.[4 5] Promoter I is responsible for the constitutive *MHC2TA* expression in dendritic cells, promoter III in B cells and promoter IV becomes activated by interferon γ in non-professional antigen-presenting cells. MHCII-mediated peptide presentation involves a complex gene expression and this is the only known system regulated by a single dedicated coactivator, rather than by the combination of several transcription factors.[2] The *MHC2TA* gene exhibits a strict cell type-specific, cytokine inducible and differentiation stage-specific pattern of expression that parallels that of *MHCII* genes.[6]

MHCII molecules are critical in T cell-dependent immunity and in inflammatory response, and they contribute to numerous diseases including rheumatoid arthritis and multiple sclerosis.[7] Rheumatoid arthritis is a chronic autoimmune disease affecting up to 1% of the Caucasian population. The multifactorial aetiology of rheumatoid arthritis is well established through linkage studies.[8–11] The role of the MHC locus on chromosome 6p21 as a rheumatoid arthritis susceptibility factor has been consistently replicated in different populations. The shared epitope-containing human leucocyte antigen (HLA)-DRB1 alleles represent the most important genetic rheumatoid arthritis risk factor. As mentioned, the class II transactivator, the *MHC2TA* gene, is essential for the expression of the genes encoding MHC class II.[6]

Multiple sclerosis is considered a chronic autoimmune disease of the central nervous system characterised by inflammation, demyelination and axonal injury.[12] Epidemiological and linkage analyses suggest that genetic factors play an important role in determining susceptibility to multiple sclerosis.[13–15] Although the aetiology of this neurodegenerative disorder is largely unknown, it is thought to result from failure to maintain tolerance against self-antigens.[16] Association with the MHC region has also been repeatedly reported in multiple populations.[17–19] The HLA-DRB1*1501 allele is a well-established susceptibility factor for multiple sclerosis.[20]

On the basis of sequence analysis, the *MHC2TA* gene belongs to the Caterpiller gene family, with more than 20 members.[21 22] Among them, the R proteins in plants constitute an ancient immune system critical for their survival.[23] Many of these genes

Abbreviations: CIITA, class II transactivator; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; MHC, major histocompatibility complex

have been associated with a variety of immunological diseases: the *CIAS1* gene predisposes to chronic infantile neurological cutaneous articular syndrome,[24] mutations in *NOD2/CARD15* determine increased susceptibility to Crohn's disease[25 26] and genetic changes in the *MHC2TA* gene lead to type II bare lymphocyte syndrome.[27] Moreover, the −168A/G promoter polymorphism in the *MHC2TA* gene, shown to control expression in cultured leucocytes after interferon γ stimulation, has been recently associated with increased predisposition to two complex diseases, rheumatoid arthritis and multiple sclerosis, in Nordic countries.[28] However, this positive association could not be reproduced in Germany[29] or in Austria.[30] To clarify these seemingly contradictory data, we aimed at replicating the aforementioned association with rheumatoid arthritis and multiple sclerosis in our southern European population. We extended this study to another autoimmune disease, inflammatory bowel disease (IBD). The MHC region has been repeatedly involved in IBD risk.[31–34]

MATERIALS AND METHODS

A total of 350 white Spanish patients with rheumatoid arthritis (53% women), 396 patients with multiple sclerosis (65% women), 329 patients with Crohn's disease and 361 patients with ulcerative colitis (57% women) consecutively recruited from a single centre (Hospital Clínico, Madrid, Spain), and 519 ethnically matched healthy controls (61% women), mainly blood donors and staff, were included in a case–control study. The diagnosis of rheumatoid arthritis was established on the basis of the American College of Rheumatology criteria.[35] The mean age at onset was 53 years; 59% patients carried the shared epitope; 75% were positive for rheumatoid factor and 32% presented nodular disease. The diagnosis of multiple sclerosis conformed to the Poser criteria.[36] The mean age at onset was 28 years; 79% of patients had relapsing remitting disease, 11% secondary progressive disease and 9% primary progressive disease. In all, 36% patients with multiple sclerosis carried HLA-DRB1 1501^{+}. Diagnosis of patients with IBD was based on standard clinical, radiological, endoscopic and histological criteria.[37] The mean age at onset for patients with ulcerative colitis was 38 years; 41% had pancolitis, 47% presented extraintestinal manifestations and 13% had colectomy. Patients with Crohn's disease were classified on the basis of the location of the lesions in ileal (48%), colonic (16%), ileocolonic (32%) and upper gastrointestinal tract (3%), and on the basis of the disease behaviour in inflammation (43%), structuring (15%) and perforation (42%). Only 20% of the patients with Crohn's disease had onset after the age of 40 years. Our population was homogeneous, and no problems of substructure have been detected in the past. All patients were included in the study after informed consent was obtained, and the study was approved by the hospital ethics committee.

MHC2TA genotyping of the samples was performed by using TaqMan Assays-on-Demand (Applied Biosystems C__15793789_10 and C___381733_10 corresponding to rs3087456 and rs4774, respectively). The 5 µl polymerase chain reaction with 1× TaqMan Universal Master Mix, 1× probe and primers assay mix and 20 ng of genomic DNA, was performed in 384-well plates in a 7900HT Fast Real-Time Polymerase Chain Reaction System (Applied Biosystems, Foster City, California, USA) under the conditions recommended by the manufacturer.

Statistical analysis was performed with a standard statistical package (Epi Info V.6.02; World Health Organization, Geneva, Switzerland). Phenotype and genotype frequencies in patients and controls were compared by the χ^2 test or Fisher's exact test, when necessary. The strength of association was given as an odds ratio (OR) with a 95% confidence interval (CI), and p values <0.05 were considered significant. Haplotypic frequencies were estimated using the expectation–maximisation algorithm implemented in the Arlequin V.2.000 software,[38] with the number of iterations set at 5000 and initial conditions at 50, with an epsilon value of 10^{-7}.

RESULTS

The −168A→G polymorphism located in the *MHC2TA* B cell specific promoter was analysed in Spanish patients and ethnically matched in controls. This polymorphism was previously studied, and the minor allele frequency described in the Japanese healthy cohort was 12%,[39] whereas it reached 22% in Nordic countries,[28] 26% in Germany,[29] 31% in Austria,[30] 29% in Italy[40] and 37% in white North Americans.[41] We found a frequency of 24% in the Spanish controls. Genotypes were concordant with those expected with the Hardy–Weinberg equilibrium.

No significant difference was detected between patients and controls for single-marker comparisons in any of the autoimmune diseases analysed (table 1). To analyse haplotypes present in this region, we additionally studied another variant conveniently located in exon 11 (rs4774), which does not show an association in the Swedish population or in ours. The haplotypes defined by the two markers tested could be assigned by direct counting, with the only uncertainty of double heterozygotic individuals. When the four observed haplotypes were compared between patients with rheumatoid arthritis and controls, the omnibus comparison yielded a significant difference ($p = 0.04$; $\chi^2 = 8.3$). The rs3087456/rs4774 A/C haplotype conferred protection ($p = 0.024$; OR 0.72 (95% CI 0.54 to 0.97))

Table 1 Allelic and genotypic frequencies of two polymorphisms in the *MHC2TA* gene in Spanish patients and healthy controls

***MHC2TA* rs3087456**	**Patients with RA (n = 350)**	**Patients with MS (n = 396)**	**Patients with CD (n = 329)**	**Patients with UC (n = 361)**	**Controls (n = 519)**
AA	185 (52.8)	203 (51.3)	181 (55)	203 (56.2)	296 (57)
AG	141 (40.3)	168 (42.4)	126 (38.3)	139 (38.5)	192 (37)
GG	24 (6.8)	25 (6.3)	22 (6.7)	19 (5.3)	31 (6)
A	511 (73)	574 (72.5)	488 (74.1)	545 (75.5)	784 (75.5)
G	189 (27)	218 (27.5)	170 (25.8)	177 (24.5)	254 (24.5)
***MHC2TA* rs4774**	**Patients with RA (n = 350)**	**Patients with MS (n = 396)**	**Patients with CD (n = 319)**	**Patients with UC (n = 344)**	**Controls (n = 509)**
GG	210 (60)	225 (56.8)	188 (58.9)	188 (54.7)	284 (55.8)
GC	119 (34)	146 (36.8)	109 (34.2)	137 (39.8)	192 (37.7)
CC	21 (6)	25 (6.3)	22 (6.9)	19 (5.5)	33 (6.5)
G	539 (77)	596 (75.2)	485 (76)	513 (74.6)	760 (74.7)
C	161 (23)	196 (24.7)	153 (24)	175 (25.4)	258 (25.3)

CD, Crohn's disease; MS, multiple sclerosis; RA, rheumatoid arthritis; UC, ulcerative colitis.
Values are n (%).

and the G/C haplotype increased the risk of rheumatoid arthritis ($p = 0.05$; OR 1.77 (95% CI 0.95 to 3.3)). These haplotypes could be inferred more precisely by using the Arlequin software, and the above-mentioned results were corroborated (table 2). Overall differences in the frequencies of these haplotypes were found in rheumatoid arthritis ($p = 0.008$; $\chi^2 = 11.8$) and multiple sclerosis ($p = 0.098$; $\chi^2 = 6.3$) cohorts. Two haplotypes conferring either risk or protection to both autoimmune diseases were observed by comparison with controls. The effect of these haplotypes on susceptibility/protection seems to be more pronounced in rheumatoid arthritis than in multiple sclerosis, and no effect on IBD could be detected (table 2). Although it could be argued that insufficient statistical power hampered the detection of the *MHC2TA* gene effect on IBD, the comparison of haplotypes by 4×4 contingency tables evidenced a significant difference between rheumatoid arthritis and IBD cohorts (rheumatoid arthritis vs Crohn's disease: $p = 0.008$, $\chi^2 = 11.75$ and rheumatoid arthritis vs ulcerative colitis: $p = 0.03$, $\chi^2 = 8.95$). We proved by using a stepwise procedure that the association of the protection and risk haplotypes with rheumatoid arthritis was primary in both cases (A/C effect in absence of the G/C haplotype: $p = 0.012$; OR 0.72 (95% CI 0.55 to 0.94) and G/C effect in the absence of the A/C: haplotype $p = 0.045$, OR = 1.5 (0.99 to 2.29)).

We tested whether this *MHC2TA* gene is primarily associated with patients carrying the predisposing *MHCII* genes or whether it is an independent genetic factor. The shared epitope is the genetic susceptibility factor with a higher effect on rheumatoid arthritis. In fact, when the *MHC2TA* G/G risk haplotype was compared in patients with rheumatoid arthritis after conditioning for the Shared epitope, a significant difference was observed between the Shared epitope-positive and Shared epitope-negative subgroups ($p = 0.029$; 8.2% vs 4%). In the Shared epitope-positive subpopulation, the comparison with controls yielded an OR = 1.81 (95% CI 1.1 to 2.97; $p = 0.012$), whereas for the Shared epitope-negative patients with rheumatoid arthritis, no significant difference with controls could be detected and also an OR <1 was found. As mentioned, the DRB1*1501 is the main risk factor found in multiple sclerosis; however, no significant difference could be detected between 1501-positive and 1501-negative patients, neither in the polymorphisms independently analysed nor in the frequency of the haplotypes (data not shown).

DISCUSSION

This work supports the study of Swanberg *et al*,[28] showing increased susceptibility to rheumatoid arthritis and multiple sclerosis depending on the *MHC2TA* gene. Our data shed some light in the interpretation of apparently conflicting published reports, and indicated that the causal polymorphism originally described is essentially a genetic marker without a direct influence on disease prevalence. The genotype/allele frequencies of that variant did not significantly differ between Spanish patients and controls, in contrast with the association observed in the Swedish population; however, two hapolotypes altered the predisposition to both diseases in the Spanish cohorts tested. These two haplotypes showed primary effects independent of each other, suggesting that both carry as yet unidentified genetic factors leading to the increase/decrease in disease susceptibility.

Expression of *MHC2TA* mRNA after stimulation with interferon γ was reportedly lower in peripheral blood cells from individuals with the −168GG risk genotype than in cells from individuals with other genotypes.[28] Therefore, this result suggested that the susceptibility allele was associated with a reduced induction of *MHCII* genes by inflammatory stimuli. The pathogenic mechanism proposed by the authors to justify the increased risk conferred to two autoimmune diseases, rheumatoid arthritis and multiple sclerosis, was a less efficient presentation of antigens to protective, regulatory cells. Differential expression of class II genes has been correlated with rheumatoid arthritis susceptibility and progression.[42] Expression of MHC class I and class II molecules are undetectable or low in a healthy central nervous system.[43 44] However, almost all neurodegenerative diseases are associated with inflammation[45] and full immune activation has been observed in multiple sclerosis, with microglia and astrocytes induced to express MHC class I and class II molecules.[46–48] Our data support the association of the *MHC2TA* gene with those two autoimmune diseases, but our results do not confirm the aetiological role of the promoter polymorphism by itself. Although the susceptibility haplotype holds the −168G risk allele, there exists another haplotype containing this alleles, which does not affect disease predisposition. In fact, haplotype pairs sharing allele in the promoter marker were significantly different between patients with rheumatoid arthritis and controls (A/G vs A/C: $p = 0.012$ and G/G vs G/C: $p = 0.047$). Therefore, the observed functional role of the polymorphism is not directly responsible for these autoimmune conditions, and this fact calls for caution when extrapolating in vitro observations to the more complex in vivo systems.

The lack of association with multiple sclerosis was previously reported for the −168A/G promoter polymorphism and some others in the 3′ untranslated region of the *CIITA* gene, as they were independently analysed and only haplotypes within the 3′ untranslated region of the gene were tested.[49] This result contrasted with the observation that CIITA-deficient mice were resistant to experimental autoimmune encephalomyelitis, an animal model for multiple sclerosis,[50 51] even after adoptive transfer of encephalitogenic CD4 T cells, which argued in favour of the critical importance of C2TA-mediated peripheral antigen presentation. Evidence has mounted against the causative association of the −168A/G *MHC2TA* polymorphism with several diseases, as recently reported[29 30] and also corroborated

Table 2 Frequencies of the *MHC2TA* (rs3087456/rs4774) haplotypes inferred in the Spanish cohorts

HT	Patients with RA (2n = 700)	Patients with MS (2n = 792)	Patients with CD (2n = 646)	Patients with UC (2n = 726)	Controls (2n = 988)
A/G	404 (57.7)	435 (55)	353 (54.7)	397 (54.8)	544 (55)
A/C	107 (15.3)*	137 (17.3)†	127 (19.6)	152 (21)	203 (20.5)
G/G	135 (19.3)	161 (20.3)	136 (21.5)	134(18.5)	192 (19.4)
G/C	54 (7.7)‡	57 (7.2)§	27 (4.2)	42 (5.7)	49 (4.9)

CD, Crohn's disease; HT, haplotype; MS, multiple sclerosis; RA, rheumatoid arthritis; UC, ulcerative colitis.
Values are n (%).
*OR (95% CI) = 0.7 (0.53 to 0.91); p = 0.006.
†OR (95% CI) = 0.83 (0.63 to 1.04); p = 0.08.
‡OR (95% CI) = 1.6 (1.05 to 2.43); p = 0.019.
§OR (95% CI) = 1.49 (0.98 to 2.24); p = 0.047.

by our data. However, we validated the association of the *MHC2TA* gene with two autoimmune disorders. This association seems to grow in parallel to the effect of the MHC susceptibility region on the different diseases: negligent influence shown for IBD, followed by multiple sclerosis and finally rheumatoid arthritis, showing a stronger *MHC2TA* effect mainly in shared epitope-positive patients. Our results clarify the role of the *MHC2TA* gene increasing the risk to these complex inflammatory diseases, and they indicate that the proposed functional link between the promoter polymorphism and autoimmune susceptibility is an oversimplification. Stratification for the HLA genetic risk factors in each condition evidenced a shared epitope dependent association in rheumatoid arthritis, although no significant difference was observed between multiple sclerosis DRB1*1501-positive and DRB1*1501-negative patients. This is the first study analysing the effect of this gene on patients with IBD. The lack of association observed contrasts with the specific role of another member of the Caterpiller family, the *CARD15* gene, an intracellular microbial sensor considered as the pivotal Crohn's genetic risk factor.

Moreover, animal[52] and clinical studies showed that statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) might be effective in multiple sclerosis[53] and rheumatological therapy.[54] These cholesterol-lowering drugs that also display anti-inflammatory effects have been found to inhibit MHC class II expression, although the exact mechanism by which statins show immunomodulatory properties is under debate.[55 56] Given the involvement of the *MHC2TA* gene in this treatment, it would be interesting to consider whether inherited traits influence the interindividual variation in response to treatment.

In conclusion, two *MHC2TA* haplotypes, one conferring risk and another protection, are associated with rheumatoid arthritis and multiple sclerosis in the Spanish population, although no effect of the promoter polymorphism previously described was corroborated in our population. The risk/protection haplotypes would carry as yet undefined functional variants responsible for the observed effects. One could envisage the consequences of the dysregulation of this gene during the development of autoimmune diseases. Studies in larger cohorts using haplotype tags throughout the gene are warranted, as well as the scrutiny of the specific set of patients found to be associated in order to locate the aetiological polymorphisms.

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