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REVIEW

Revisiting the T-cell receptor alpha/delta locus and possible associations with multiple sclerosis

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A role for T cells in the pathogenesis of multiple sclerosis (MS) is well supported, evidenced by myriad immunological studies, as well as the unequivocal genetic influence of the major histocompatibility complex (MHC). Despite many attempts, no convincing genetic associations have been made between T-cell receptor (TCR) gene loci and MS. However, these studies may not be definitive because of small sample sizes and under-representative marker coverage of the chromosomal regions being investigated. To explore potential roles between the TCR alpha locus and MS, we have genotyped a large family-based cohort, including 1360 affected individuals and 1659 of their unaffected first-degree relatives, at 40 single-nucleotide polymorphism (SNP) markers within the TCR alpha/delta locus. This represents the largest TCR alpha-MS study to date. From this screen, we identified three potential loci of interest in TCR alpha variable and constant gene regions using the transmission disequilibrium test. Although SNPs implicating each of these regions of interest will require genotyping in independent replication cohorts, these findings suggest a role for TCR gene polymorphisms in MS susceptibility. In the context of these findings we review the evidence.
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Introduction

Both genetic and environmental factors contribute to susceptibility to multiple sclerosis (MS).[1,2] The major locus determining disease risk for MS lies within the major histocompatibility complex (MHC) class II region.[3] Although it is well established that the extended haplotype *HLA-DRB1*1501–HLA-DQA1*0102–HLA-DQB1*0602* is associated with MS susceptibility, complex epistatic interactions between other *HLA-DRB1* alleles, as well as between other genes within the MHC, are known to occur and together constitute the major determinants of MS risk.[4–8] Additional loci of much smaller effect outside of the MHC have also been recently identified,[9–16] and it is likely that other causative loci remain to be discovered.[1]

Parent-of-origin effects have been noted in several epidemiological studies[17–20] and in studies investigating transmission of *HLA-DRB1* alleles.[21,22] These parent-of-origin effects, in conjunction with studies examining the influence of migration and month-of-birth, imply that epigenetic and/or gene–environment interactions are also likely to contribute to MS susceptibility.[2,23] Principal among the list of potential environmental factors are sunlight exposure and vitamin D production.[2,23] The identification of a vitamin D response element upstream of the primary risk allele, *HLA-DRB1*1501*, so far provides one of the most tangible links between environmental and genetic factors, and is highly suggestive of a fundamental functional role for vitamin D in MS susceptibility via MHC antigen presentation and the early development of T-cell immunity.[24]

It is widely believed that T cells are the main driver of autoimmune responses and inflammation in MS.[25] Initially it was thought that $CD4^+$ T helper type 1 cells were the primary mediators of MS pathogenesis, but mounting evidence in support of a function for other T helper cell subsets now exists, in particular T helper-17 cells.[26–28] However, the cellular interplay among these cell types in directing pathogenesis remains incompletely understood. Furthermore, analyses of whole blood gene expression levels in MS patients and controls reveal that primary differences between these groups exist with regard to dysregulation of T-cell-specific gene sets and pathways.[29]

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Although a role for T cells in MS seems indisputable, no consistent and replicable genetic associations have been made between polymorphisms at T-cell receptor (TCR) loci and MS, despite suggestive links to both TCR beta and alpha genes.[30–43] A possible explanation for the observed inconsistency between studies investigating TCR gene loci and MS could be a lack of power to discover associations, because of small sample sizes and unrepresentative marker coverage of the TCR regions investigated. Given these limitations, it is reasonable to conclude that, although no strong associations have been identified within the TCR loci, these regions cannot be unequivocally ruled out on the basis of previous studies alone.

Here we review, in brief, TCR functional and genetic diversity, specifically at the TCR alpha/delta locus. In addition, we review previous linkage and association studies investigating the influence of TCR alpha and delta genes on MS, and we report new data from a screen of a large cohort of MS families using a panel of 40 single-nucleotide polymorphism (SNP) markers located within the TCR alpha/delta gene region. This survey is the most extensive conducted to date and highlights potential regions of interest pertaining to MS susceptibility within the TCR alpha locus.

T-cell receptors

The expression of TCRs on the surface of T lymphocytes is central to the proper establishment of T-cell-mediated adaptive immunity. Unlike membrane-bound immunoglobulins and antibodies expressed by B cells, which can directly bind antigens in the extracellular environment, TCR antigen recognition is dependent on the presentation of short antigen peptides by MHC proteins expressed on the surface of other cells.[44] The direct molecular interaction between the peptide:MHC complex and the T cell via an expressed TCR greatly influences TCR gene usage and has a fundamental part in shaping T-cell/expressed TCR repertoires within a given individual, particularly during T-cell maturation and differentiation.[44] Although a genetic association between the MHC and MS is well supported, how particular human leukocyte antigen (HLA) proteins contribute to disease at the molecular level is not clear. The regulation of the MS susceptibility allele, *HLA-DRB1*1501*, by vitamin D via a haplotype-specific vitamin D response element provides a model in which irregular HLA expression/self-peptide presentation could influence negative selection of autoreactive T cells in the thymus during early development, and thus contribute to susceptibility.[24]

Until recently, little was known at a fine scale about TCR gene usage and repertoire diversity, even within T-cell populations of healthy individuals. However, recent applications of high-throughput sequencing techniques have allowed for the ascertainment of TCR repertoires both within total T-cell populations,[45] as well as specific T-cell subsets.[46] These techniques may prove to be useful tools for more effectively identifying biases in TCR gene usage and repertoire diversity in human disease, including MS where such differences have been investigated between affected and unaffected individuals, as well as in identical twins discordant for disease.[33,47–49]

Although it is true that maturing T-cell populations are largely shaped by T-cell–TCR interactions with MHC as well as self and non-self peptides, the expressed TCR repertoire of naïve T-cell populations is greatly influenced by the extensive potential for diversity provided by combinatorial splicing of the TCR genes themselves.[50] TCR genes are located at three regions in the genome, 14q11.2 (TCR alpha, delta), 7q34 (TCR beta) and 7p14 (TCR gamma).[51] Each of these regions are comprised of sets of related gene segments that are somatically recombined to form transcripts that ultimately code for alpha/beta or delta/gamma TCR heterodimeric protein chains. These protein chains are formed by combinations of variable (V), joining (J), diversity (D) and constant (C) region gene segments (beta and delta chains), or by only V, J and C gene segments (alpha and gamma chains). Each chain of the TCR heterodimer is comprised of a leader-peptide region, three framework regions that contribute to TCR protein structure, and three complementary determining regions (CDRs) that interact directly with the peptide:MHC complex.[44,52] Each of the three CDRs are involved in peptide:MHC binding, however, CDR3 diversity is generally considered to be most important.[52] Taken together, both the number of different gene segments at each locus, as well as different combinations of alpha and beta, or delta and gamma chains, have the potential to create a vast number of unique TCR proteins.[50] Moreover, the addition of non-template nucleotides, and the imprecise joining of gene segments during somatic recombination, further enhances TCR diversity.[53]

The T-cell alpha/delta locus

The TCR alpha locus (14q11.2) spans approximately 1 Mb of chromosome 14 and contains a single C region segment, as well as 52 J and 44–46 V region functional gene segments.[51,54,55] The TRAV genes comprise 32–34 subgroups. Five of the alpha V gene segments are shared with TCR delta, in that they can be used to form either alpha or delta chains. The remaining TCR delta C, D, J and V gene segments also reside within the TCR alpha locus, although TCR delta-specific V and J segments are fewer in number (V, $n=3$; J, $n=4$). Also in contrast to TCR alpha, the TCR delta germline repertoire includes three functional *D* gene segments.[51,54,55] Additionally, TCR alpha and delta-specific enhancers are located within the locus.[56,57] A complete, and fully annotated, map of the TCR alpha/delta locus can be found at http://www.imgt.org.[55]

As mentioned above, diversity between genes within the TCR alpha region contribute to the potential for combinatorial diversity during somatic recombination. In addition to intralocus variation, the presence of two or more alleles has been noted for many of the alpha V and J gene segments.[51,55] To further investigate TCR alpha/delta nucleotide diversity, Mackelprang *et al*.[58] utilized a V gene-based genomic sequencing approach in 40 individuals from four ethnic backgrounds (Chinese, African-American, Northern European, Mexican), generating sequence in V gene exons, introns, and 5′ and 3′ flanking regions. From this 284 SNPs were identified, 51 of which were nonsynonomous, coding for amino acid changes. They also showed that nucleotide diversity, in

general, was higher in CDRs than framework regions, although, heterozygosity within the CDRs was not higher than that found within neutral sequence, suggestive of purifying selection.[58] Nine SNPs were also identified in recombination signal sequences, which, given that recombination signal sequences are essential to the process of V(D)J rearrangement, suggests that these polymorphisms could contribute to biased gene usage.[58]

Initial analyses of linkage disequilibrium (LD) within the TCR alpha locus using 24 V region SNP markers and two microsatellite markers revealed the occurrence of LD at distances ranging from 0 to 150 Kb, the most significant LD localizing to three concentrated regions.[59] Strikingly, although Mackelprang *et al*.[58] observed similar patterns from analyses of three separate SNP-based data sets, in that particular regions within the locus exhibited high LD, they also observed that in 64% of V genes where at least two common SNPs were found, these SNPs were not in LD. These findings have important implications for disease-association studies within the TCR alpha/delta locus, and imply that rather dense panels of markers may be required to reveal or exclude associations between these genes and disease.[58,59]

Reviewing the TCR alpha/delta locus and MS

The strong association between the MHC and MS made TCR genes early candidates for MS susceptibility loci. Martell *et al*.[30] first proposed a genetic link to a TCR locus. Using restriction fragment length polymorphism (RFLP) analysis they found evidence for an association to the TCR alpha locus in a French patient cohort.[30] As might have been expected at the time, genotype frequency differences between MS affected individuals ($n = 46$) and non-MS affected individuals ($n = 142$: insulin-dependent diabetes = 61, rheumatoid arthritis = 39, healthy controls = 42) were significant after stratification for the presence of HLA-DR2 (Martell *et al*.[30]), which is the HLA haplotype that includes the primary MS susceptibility allele, *HLA-DRB1*1501*. This provided initial evidence for an interaction of MHC and TCR in MS.

Numerous studies of MS and TCR alpha followed over the next decade, however, results were conflicting and inconclusive (Table 1). Oksenberg *et al*.[31,32,37] did not confirm an association of MS to the TCR alpha locus in an initial screen,[31] but later reported associations of both TRAV and TRAC region polymorphisms in two separate patient cohorts (USA and Australia).[32] Suggestive additive effects of HLA-DR2 and the TCR alpha C region polymorphism were also noted in an Australian cohort.[36] In this study, a hierarchical log-linear analysis did not reveal three-way interactions between MS, HLA-DR2 and TRAV and TRAC regions, but the combination of HLA-DR2 and a TRAC polymorphism reportedly affected relative risk.[37]

Subsequent association studies investigating the role of TCR alpha polymorphisms in Canadian, Swedish, Belgian and Northern Irish populations with equivalent or larger sample sizes compared with those above were unable to replicate these findings.[34,35,39,40] Also, in two of these studies, no interaction between HLA-DR2 and TRA genotypes was observed.[35,39] Additionally, Hillert *et al*.[35] found no significant differences in TRA genotype frequencies when MS patients were partitioned for relapsing/remitting and chronic progressive disease course.

Linkage-based approaches examining the TCR alpha locus and MS were also unable to confirm any associations. Using RFLP and a TRA probe, Lynch *et al*.[36] screened 99 individuals from 44 multiplex families (USA), including 34 individuals with definite MS, 26 of which were HLA-DR2-positive and identified no evidence for linkage. Hashimoto *et al*.,[34] in addition to their association-based method, assessed haplotype sharing at the TCR alpha locus in 30 concordant MS sibling pairs using identity by descent. Compared with what would be expected by random segregation, they found no indication for haplotype sharing between three TRAV and TRD region RFLP polymorphisms.[34] Finally, no support for linkage was found in two separate sibling-pair cohorts from the British Isles.[38] In Eoli *et al*.,[38] 49 pairs were screened using two RFLP assays and 82 additional pairs were screened at a single microsatellite marker. Identity by descent analysis did not reveal excess haplotype sharing in the 49 pairs typed for TRAV and TRAC region RFLP polymorphisms.[38] Additionally, neither identity by descent nor identity by state identified significant haplotype sharing in the sibling-pairs typed at the microsatellite locus, and no effect was observed in the subset of these patients who were also *HLA-DRB1*15*-positive.[38]

Conflicting results have also been observed for the TCR beta locus and MS,[40–42] although these will not be discussed in detail here. The exact reasons for the inconsistencies described above are unknown. With regard to TCR alpha and MS, both Hillert *et al*.[35] and Hashimoto *et al*.[34] suggested that discrepancies between studies could be a result of inaccurate RFLP genotyping, as this methodology is sensitive to confounding errors that arise from incomplete enzyme cleavage. Additionally, the use of improperly matched controls has also been raised.[34] Hashimoto *et al*.[34] addressed this issue by using multiple matched control groups for comparison, including an insulin-dependent diabetes patient cohort. Also, the first described association by Martell *et al*.[30] included multiple control groups (see above). As mentioned above, an association was identified when control groups were pooled and both MS and controls were stratified for the presence of the HLA-DR2 haplotype.

Additional commonalities exist among these studies, and are perhaps more relevant given what is now known about the genetics of MS, as well as the TCR alpha/delta locus in general. In addition to associations between the MHC and MS, which is thought to account for at least 50% of genetic susceptibility,[60] many other causative loci have also been discovered.[9–16] It is interesting to note that, compared to effects exerted by the MHC, these loci contribute little to the overall risk of MS. Bearing in mind that loci of very small effect are likely what remain to be identified, estimates of required sample sizes for association and linkage studies aiming to uncover genes of this nature exceed those used by the studies discussed above.[1,61] What is more, even within the MHC, the story is not as clear as once thought. Recent findings suggest that multiple MHC class I and class II alleles, likely influence risk of MS through *cis* and *trans* epistatic interactions, in some cases serving protective functions.[4–8]

Table 1 Summary of linkage and association studies: TCR alpha/delta and MS

Study	*MS patient sample*	*Population*	*Approach*	*Method*	*Findings*
Martell *et al*.[30]	46MS, 142 Non-MS	France	Association	RFLP	Association after stratification for DR2
Oksenberg *et al*.[31]	28MS, 70 Non-MS	USA	Association	RFLP	No association
Oksenberg *et al*.[32]	28MS, 70 Non-MS/48MS, 50 Non-MS	USA/Australia	Association	RFLP	Association to TRAV and TRAC polymorphisms
Hashimoto *et al*.[34]	47 FMS, 47 SMS, 223 Non-MS	Canada	Association/IBD	RFLP	No association
Hillert *et al*.[35]	105MS, 100 Non-MS	Sweden	Association	RFLP	No association
Lynch *et al*.[36]	14 families (99 total, 34MS)	USA	Linkage	RFLP	No association
Sherritt *et al*.[37]	49MS, 50 Non-MS	Australia	Association	RFLP	DR2 and TRAC together increase relative risk
Eoli *et al*.[38]	117 families (49 pairs/82 pairs)	British Isles	IBD, IBS	RFLP/msat	No association
Vandevyver *et al*.[39]	71MS, 67 Non-MS	Belgium	Association	RFLP	No association
Droogan *et al*.[40]	180MS, 113 Non-MS	Northern Ireland	Association	msat	No association

Abbreviations: FMS, familial MS; IBD, identity by descent; IBS, identity by state; MS, multiple sclerosis; msat, microsatellite marker; RFLP, restriction fragment length polymorphism; SMS, sporadic MS; TCR, T-cell receptor.

Heterogeneity has been shown to exist with regard to extended MHC class I (A and B) and class II *HLA-DRB1*15* containing haplotypes, in that particular *HLA-DRB1*15* and MHC class I (A/B) paired haplotypes exhibit transmission distortion, while others do not, implying that not all *HLA-DRB1*15* extended haplotypes confer susceptibility.[6] This raises the possibility that heterogeneity in MS-associated HLA haplotypes could contribute to reported discrepancies in TCR alpha and MHC interactions. Finally, estimates of LD at the TCR alpha locus also raise potential problems for studies using a limited number of polymorphisms to draw inference about associations or lack thereof in the TCR alpha region. Given that estimates of LD within TCR alpha do not extend the length of the locus but instead cluster within specific regions,[58,59] it is fair to conclude that while previous studies may have had the power to reveal an association, they were underpowered in their ability to exclude large regions, let alone the TCR alpha/delta locus as a whole.

Revisiting TCR alpha/delta polymorphisms and MS

Considering the limitations of previous studies discussed above, further research is necessary to provide conclusive evidence for either the exclusion or inclusion of TCR alpha/delta genes as loci contributing to MS susceptibility. To address this, we have undertaken the most comprehensive study of this region to date. We have genotyped a total of 3019 individuals (1858 female and 1161 male) from 738 Canadian families, including 1360 individuals with definite MS and 1659 of their unaffected first-degree relatives for 40 SNP markers spanning the TCR alpha/delta locus (Methods used are listed in the legend of Table 2). Patients used in this study were collected as part of the ongoing Canadian Collaborative Project on the Genetic Susceptibility to MS.[62] Allelic transmissions of the 40 SNPs were analyzed in this cohort using the transmission disequilibrium test[63,64] (Supplementary Table 1). The transmission disequilibrium test is a family-based test of LD and is a powerful method for the detection of associations between disease causing loci or linked markers.[63,64] From our analysis four SNPs were found to be significant (Table 2): rs10151098 ($P=0.0264$), rs12880912 ($P=0.0484$), rs1569297 ($P=0.0011$) and rs1263646 ($P=0.0027$). Only rs1569297 remained significant after correction for multiple comparisons ($P=0.0444$). rs1569297 is located between the genes *TRAV39* and *TRAV40*, within 1 Kb of *TRAV39*, and approximately 10 Kb from *TRAV40*. Both *TRAV39* and *TRAV40* genes have known allelic variants, although only *TRAV40* variants differ in amino acid sequence.[58] The two nearest SNPs flanking rs1569297 are approximately 26 and 18 Kb away, and neither exhibits significant transmission distortion (rs17183456, $P=0.1381$; rs916048, $P=0.9034$). To assess whether the allelic transmission observed at rs1569297 is indicative of an association to either of the two proximal TRAV genes, or to variation in putative regulatory sequences, will require further genotyping at additional loci.

Tests for transmission bias were also stratified by the presence or absence of the susceptibility allele *HLA-DRB1*1501*, and differential transmission in these strata was tested with a χ^2 test. Dyment *et al*.[43] observed an over transmission of the TCR beta haplotype, *BV25S1*1-BV26S1*1-BV2S1*1*, after stratification for *HLA-DRB1*1501*, although this association was not confirmed in a replication cohort.[43] The MHC class II activator gene, *CIITA*, has also recently been shown to increase risk in MS families positive for *HLA-DRB1*1501* (Bronson *et al*.[65]). We did not observe differential transmission at any of the TCR alpha loci genotyped here based on the presence or absence of *HLA-DRB1*1501* (Supplementary Table 2). However, when comparing paternal and maternal transmissions with *HLA-DRB1*1501*-positive versus *HLA-DRB1*1501*-negative offspring (Supplementary Table 3), significant differences in allelic transmissions were observed for two tightly linked SNPs ($r^2=0.973$, HapMap CEU panel) flanking the gene *TRAV17* (Table 3). Allele A at rs972684, and allele C

at rs932230 were over transmitted maternally and under transmitted paternally to *HLA-DRB1*1501*-positive offspring (rs972684, $P = 0.002028$; rs932230, $P = 0.001178$; Table 3), whereas no transmission distortion was observed maternally or paternally to offspring that were *HLA-DRB1*1501*-negative (rs972684, $P = 0.7606$; rs932230, $P = 0.4243$). Maternal over transmission and paternal under transmission was also observed at both SNPs without stratifying for the presence of *HLA-DRB1*1501* (rs972684, $P = 0.015$; rs932230, $P = 0.004$), although transmissions were less significant (Supplementary Table 4).

Table 2 Data from TDT analysis for SNPs with significant *P*-values and SNPs associated to narcolepsy

SNP	*A1*	*ALL TR*	*ALL NT*	*OR*	P	*PC*
rs10151098	A	346	290	1.19	**0.0264**	0.61
rs12880912	G	321	373	0.86	**0.0484**	0.81
rs1569297	T	125	182	0.69	**0.0011**	**0.0444**
rs12587781[a]	G	183	186	0.98	0.8759	1
rs1154155[a]	G	176	181	0.97	0.7913	1
rs1154156	A	265	271	0.98	0.7955	1
rs1263646[a]	G	61	99	0.62	**0.0027**	0.0984

Abbreviations: A1, transmission allele; ALL, transmissions from mothers and fathers; IBD, identity by descent; NT, not transmitted; OR, odds ratio; P, *P*-value; PC, corrected *P*-value 10 000 permutations; SNP, single-nucleotide polymorphism (marker identification); TDT, transmission disequilibrium test; TR, transmitted.
[a]SNPs associated to narcolepsy.[66] Significant *P*-values are indicated in bold.
Methods: informed consent was obtained from all subjects and experiments performed for this investigation comply with current ethics and guidelines. Total genomic DNA, extracted from whole blood from the CCPGSMS study,[62] was used for genotyping, performed using the Sequenom MassEXTEND protocol (http://www.sequenom.com). All genotypes were generated blind to pedigree structure and disease status. Only conservative and moderate genotyping calls were accepted in this study. Samples having aggressive or low probability quality genotypes were reanalyzed. Samples had previously been genotyped for *HLA-DRB1* with either low- or high-resolution allele-specific PCR amplification.[3,4] Individuals for whom consistent genotypes could not be obtained for each locus were removed from the study. SNP alleles were tested for association with the TDT,[63] performed using PLINK analysis package.[70] The TDT counts the number of times an allele is transmitted to affected offspring from heterozygous parents. The χ^2 distribution was used to assess significance. To correct for multiple testing, permutation tests were performed (10 000 permutations). Within each family, the transmission status of each allele was permutated randomly in a fashion that preserved the IBD status of affected offspring and the haplotypic relationships between alleles.

Genetic-epidemiological studies clearly indicate that maternal effects contribute to MS risk. In a Canadian cohort, the transmission of the *HLA-DRB1*1501* allele was greater from mothers to affected offspring than it was from fathers, implicating maternal HLA-specific epigenetic and/or gene–environment interactions.[21] The allelic transmissions observed here for rs972684 and rs932230 contribute to a growing understanding of parent-of-origin effects in MS susceptibility. Moreover, the fact that maternal over transmission at these loci was stronger on the stratification for the presence of *HLA-DRB1*1501* implicates a potential role for a specific MHC–TCR interaction in MS.

MHC and TCR alpha interactions have been proposed in the etiology of narcolepsy, as this disease—now considered to be autoimmune—has recently been associated to the TCR alpha J gene region.[66,67] Our study was, in part, motivated by these findings because the major susceptibility locus for narcolepsy, *HLA-DQB1*0602*,[68] is part of the MS susceptibility haplotype, which includes *HLA-DRB1*1501* (Lincoln *et al*.[7]). Three SNPs (rs12587781, rs1154155 and rs1263646) in the TRAJ and TRAC gene regions were found to be associated with narcolepsy using patient and control cohorts stratified for the presence of *HLA-DQB1*0602* (Hallmayer *et al*.[66]). The association was found to be strongest at rs1154155 within the TRAJ region.[66] Each of these three narcolepsy-associated SNPs and one additional SNP in close proximity (rs1154156) were included in our study (Table 2). Only rs1263646, located between exons 1 and 2 of the *TRAC* gene, was significant ($P = 0.0027$), but this value did not remain significant after correction for multiple comparisons ($P = 0.0901$). As stated above, stratification for *HLA-DRB1* status did not affect transmission at these four loci (Supplementary Table 2). The fact that we found no strong association between these SNPs, particularly rs1154155, suggests that a similar MHC–TCR interaction likely does not contribute to both MS and narcolepsy. However, as discussed in the previous section, it should be mentioned that early investigations of associations between MS and TCR alpha did implicate the TRAC region, although these findings were not replicated (see above). Furthermore, it is possible that the SNP typed here within the *TRAC* gene could be indicative of an association upstream or downstream of the coding region, which could be revealed by genotyping at additional nearby markers. Interestingly, the enhancer for the TCR alpha locus, which is essential for TCR alpha gene expression, resides downstream of the *TRAC* gene.[69]

Table 3 Maternal and paternal transmissions after stratification for the presence–absence of *HLA-DRB1*1501*

SNP		*DRB1*15-positive offspring*							*DRB1*15-negative offspring*						
	A1	*PAT T*	*PAT NT*	*PAT* P	*MAT T*	*MAT NT*	*MAT* P	*PO* P	*PAT T*	*PAT NT*	*PAT* P	*MAT T*	*MAT NT*	*MAT* P	*PO* P
rs972684	A	42.5	63.5	**0.0414**	68.5	43.5	**0.0182**	**0.0020**	51.5	49.5	0.8423	60.5	53.5	0.5121	0.7606
rs932230	C	42.5	64.5	**0.0334**	71.5	44.5	**0.0122**	**0.0012**	50	55	0.6256	62	55	0.5175	0.4243

Abbreviations: A1, transmission allele; MAT, maternal; NT, not transmitted; PAT, paternal; PO, parent-of-origin; P, *P*-value; TR, transmitted; SNP, single-nucleotide polymorphism (marker identification).
Significant *P*-values are indicated in bold.

Conclusion

TCR genes are fundamental to T-cell function and adaptive immunity. Because of this they make attractive candidate susceptibility loci for diseases with putative autoimmune etiologies. The genetic association of the MHC, in conjunction with evidence for the involvement of T cells in the pathogenesis of MS, implicates a role for *TCR* genes in MS susceptibility. Early linkage and association-based studies provided inconsistent and inconclusive results, but these studies were likely underpowered and confounded by insufficient marker coverage. We have attempted to overcome these limitations by screening 1360 affected individuals in a family-based cohort for 40 SNP markers spanning the TCR alpha/delta locus. This is more comprehensive than previous studies and we have identified three candidate regions in the TCR alpha locus that are potentially associated with MS. However, replication of our findings is necessary, especially in light of previous inconsistencies.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Genes and Immunity website (http://www.nature.com/gene)