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Narcolepsy is strongly associated with the T-cell receptor alpha locus

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Narcolepsy with cataplexy, characterized by sleepiness and rapid onset into REM sleep, affects 1 in 2,000 individuals[1,2]. Narcolepsy was first shown to be tightly associated with HLA-DR2 (ref. 3) and later sublocalized to DQB1*0602 (ref. 4). Following studies in dogs[5] and mice[6], a 95% loss of hypocretin-producing cells in postmortem hypothalami from narcoleptic individuals was reported[7,8]. Using genome-wide association (GWA) in Caucasians with replication in three ethnic groups, we found association between narcolepsy and polymorphisms in the *TRA@* (T-cell receptor alpha) locus, with highest significance at rs1154155 (average allelic odds ratio 1.69, genotypic odds ratios 1.94 and 2.55, $P < 10^{-21}$, 1,830 cases, 2,164 controls). This is the first documented genetic involvement of the *TRA@* locus, encoding the major receptor for HLA-peptide presentation, in any disease. It is still unclear how specific HLA alleles confer susceptibility to over 100 HLA-associated disorders[9]; thus, narcolepsy will provide new insights on how HLA–TCR interactions contribute to organ-specific autoimmune targeting and may serve as a model for over 100 other HLA-associated disorders[9].

An autoimmune etiology has been suggested for narcolepsy but never proven despite decades of intensive research[10,11]. Narcolepsy is recognized to be familial, and despite the strong association with HLA-DQB1*0602, is not fully explained by the HLA locus[1]. To identify additional susceptibility loci for narcolepsy, we undertook a genome-wide association study. We selected Caucasian cases from North America and Europe, together with geographically and ethnically matched controls. All cases were HLA-DQB1*0602 positive and all had clear-cut cataplexy. Among the 23% for whom we had measurements of hypocretin-1, all were found to be hypocretin deficient. Potential controls were typed using sequence-specific PCR, and only those who were also HLA-DQB1*0602 positive were included. The sample was comprised of 807 cases and 1,074 controls of mixed European ancestry: 415 cases and 753 controls were recruited from the United States and Canada; 392 cases and 321 controls were

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Table 1 SNP markers of interest from the genome-wide association study

SNP	Chr	Position (bp)	Minor allele	Freq controls (*n*)	Freq cases (*n*)	χ^2 (MH)	*P* (MH)	OR (95% CI)	χ^2 (BD)	*P* (BD)
rs1154155	14	22072524	C	0.14 (1,067)	0.24 (796)	54.11	1.90×10^{-13}	1.87 (1.58–2.21)	2.49	0.29
rs12587781	14	22069457	C	0.15 (917)	0.25 (622)	53.19	3.03×10^{-13}	1.96 (1.63–2.35)	1.66	0.20
				0.14 (1,066)[a]	0.24 (794)[a]	60.42[a]	7.65×10^{-15}[a]	1.93 (1.63–2.28)[a]	1.61[a]	0.45[a]
rs1263646	14	22087370	G	0.16 (1,069)	0.25 (797)	47.74	4.86×10^{-12}	1.77 (1.50–2.09)	0.40	0.82
rs5770917[b]	22	49364219	G	0.05 (1,063)	0.04 (796)	1.07	0.30	0.84 (0.61–1.16)	1.90	0.39

The top three genome-wide significant markers are listed, together with data obtained for rs5770917, previously found to be associated with narcolepsy in a Japanese population[17]. We genotyped 1,074 controls and 807 cases using SNP Affymetrix Array platforms (500K and 6.0). MH, Mantel-Haenszel; BD, Breslow Day heterogeneity test; OR, odds ratio. [a]Affymetrix 6.0K marker after genotypes were completed using TaqMan (see text). [b]Note that 388 of the 796 narcolepsy genotypes were previously reported for this marker by Miyagawa *et al.*[17].

recruited from European centers. For the GWA study, subjects were genotyped using the Affymetrix Mapping 500K array set or Genome-Wide SNP Array 6.0. Homogeneity in ancestry and case-control matching was verified by cluster and principal component analysis[12]. In addition, we compared the allele frequency of 107 of 400 SNPs known to predict European substructure and found no significant differences after Bonferroni correction[13].

We conducted allele-based association tests in SNPs with allele frequency above 5% in controls using the Mantel-Haenszel test[14] in three groups of subjects defined by platform and location of typing (Affymetrix 500K typed at UCSF; Affymetrix 6.0 typed at UCSF; Affymetrix 6.0 typed at Institut fur Humangenetik, Munich, Germany). The χ^2 quantile-quantile plot showed a slight deviation from the expected χ^2 distribution, and an inflation factor λ of 1.11 was estimated (**Supplementary Fig. 1** online). However, the plot also showed the presence of three extreme outlier χ^2 values of 47.7, 54.1 and 60.4 (**Table 1** and **Supplementary Fig. 1**). These three SNPs, all on chromosome 14, clearly exceeded the genome-wide significance level of 9.1×10^{-8}. Other nominally significant associations ($P < 10^{-6}$) are reported in **Supplementary Table 1** online.

The three top markers were in high linkage disequilibrium (LD) and are located within an 18-kb segment of the *TRA@* locus containing the TRA joining (J) segment subregion (14q11.2; **Fig. 1**). Of interest, one of the markers of nominal significance ($P = 5.2 \times 10^{-7}$), rs17231, is located within the V segment region of the *TRB@* (T-cell receptor beta) locus (7q34). Genome-wide significant SNPs were genotyped using TaqMan assays (Applied Biosystems) in an independent sample of 1,057 cases (using the same diagnostic criteria) and 1,104 controls (matched by ancestry) as a replication study. The Caucasian replication sample contained 718 individuals, of whom 542 were recruited from the United States and Canada (259 cases, 283 controls), and 176 from Europe (104 cases, 72 controls). The Asian sample included 866 Japanese (433 cases, 433 controls) and 300 Koreans (128 cases, 172 controls). Finally, we studied 277 African Americans (133 cases, 144 controls).

As shown in **Table 2**, the three SNPs located within the *TRA@* locus replicated with high significance across the three major ethnic groups combined and showed significant effects individually in the Caucasian and Asian subsamples. In the African American sample, although the odds ratios (ORs) trended in the same direction, formal significance was not reached owing to small sample size and low allele frequencies (**Table 2**).

According to HapMap data[15], the three SNPs are located within a 37-kb region of increased LD across ancestry groups (CEU, YRI, CHB-JPT). The localized haplotype block structure among these populations differs, with highest LD between rs12587781 and rs1154155 extending in opposite directions in Europeans versus Asians. In all ethnic groups, rs1263646, a SNP located closer to the *TRAC* gene, showed a smaller OR, suggesting that the association peaks in the *TRAJ* segment region (**Fig. 1**). Further, ORs differed significantly for rs12587781 but not rs1154155 between Caucasians and Asians (**Table 2**). This was likely explained by the difference in LD patterns across the two ethnicities. Whereas rs1154155 and rs12587781 are in almost complete LD in Caucasians ($r^2 = 0.96$), LD is substantially weaker in Asians ($r^2 = 0.57$; **Fig. 1**). In Asians, rs1154155 had a stronger impact on risk (OR = 1.54) than did rs12587781 (OR = 1.34).

To further evaluate this pattern, we estimated the frequency of haplotypes AA, AC, CA, CC for rs12587781 and rs1154155 in Asian cases and controls. For cases, the frequencies were 0.318, 0.003, 0.109 and 0.571, respectively. For controls, the frequencies were 0.381, 0.005, 0.154 and 0.460, respectively. We note that the OR is increased for

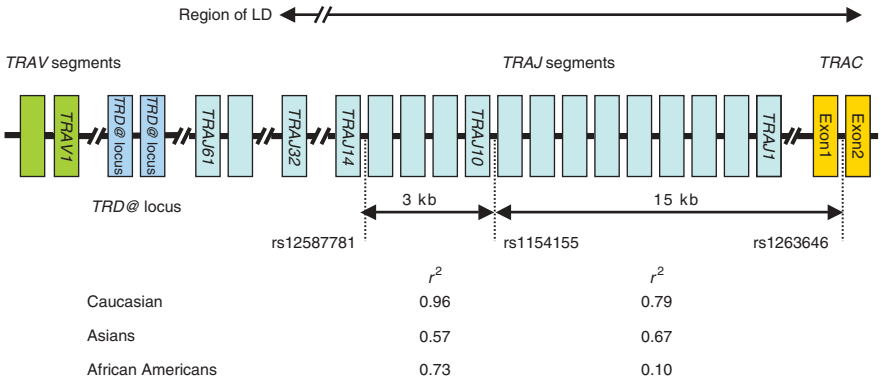

Figure 1 Schematic representation of the *TRA@* locus and of SNPs associated with narcolepsy. The *TRA@* locus consists of clusters of V and J segments and exons of the C region. The T-cell receptor delta locus (*TRD@*) resides within the *TRA@* locus. A 40-kb region of LD encompasses half of the *TRAJ* segments and is flanked by *TRAJ32* and the second exon of the *TRAC* gene. Within this region, three SNPs are highly associated with narcolepsy, separated by 3 and 15 kb, successively. In Caucasians, the association is equivalent with rs12587781 and rs1154155 (**Tables 1** and **2**), and LD is extremely high ($r^2 = 0.97$ and 0.94; 1,154 cases and 1,425 controls, respectively). In contrast, the association is stronger with rs1154155 than rs12587781 in Asians (**Table 2**), a phenomenon explained by the lower LD in this ancestry group ($r^2 = 0.62$ and 0.52; 553 cases and 603 controls, respectively). Intermediate LD was seen in African-American individuals ($r^2 = 0.74$ and 0.71; 124 cases and 142 controls, respectively). The association with rs1263646 is weaker across all ancestry groups, most notably Asians and African Americans (**Table 2**). These results, depicted as values for cases and controls combined in this figure, illustrate the value of trans-ethnic mapping.

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Table 2 Replication of SNP markers discovered in the GWA study

Ancestry	rs12587781	rs1154155	rs1263646
Caucasian	C	C	G
Freq controls (*n*)	0.14 (352)	0.14 (348)	0.16 (351)
Freq cases (*n*)	0.22 (353)	0.22 (343)	0.24 (353)
χ^2	17.08	17.04	13.66
P	3.58×10^{-5}	3.67×10^{-5}	2.19×10^{-4}
OR (95% CI)	1.79 (1.36–2.37)	1.80 (1.36–2.39)	1.65 (1.26–2.15)
Asians	C	C	G
Freq controls (*n*)	0.61 (601)	0.47 (599)	0.45 (600)
Freq cases (*n*)	0.68 (552)	0.57 (549)	0.51 (553)
χ^2	11.09	26.76	9.81
P	8.70×10^{-4}	2.30×10^{-7}	1.73×10^{-3}
OR (95% CI)	1.34 (1.13–1.59)	1.54 (1.31–1.82)	1.30 (1.10–1.53)
African Americans	C	C	G
Freq controls (*n*)	0.11 (142)	0.08 (138)	0.133 (139)
Freq cases (*n*)	0.13 (124)	0.10 (113)	0.165 (124)
χ^2	0.70	0.74	1.08
P	0.40	0.39	0.30
OR (95% CI)	1.25 (0.74–2.13)	1.31 (0.71–2.42)	1.29 (0.80–2.09)

Within the subset of Caucasian controls with HLA information, allele frequencies at the three SNPs did not differ between DQB1*0602 positive ($n = 469$) and negative ($n = 1,352$) individuals.

haplotype CC versus AA (1.49, 95% CI = 1.24–1.79) but not for haplotype CA versus AA (0.85, 95% CI = 0.64–1.12). Thus, rs12587781 seems to have no effect after controlling for rs1154155, suggesting that rs1154155 may have functional significance or is in high LD with another causative SNP nearby. SNPs with $r^2 > 0.8$ with rs1154155 are known to exist from HapMap data. This SNP is located 176 bp 3′ to *TRAJ10*, a J segment without known coding polymorphisms. Genotype analysis suggested a dosage effect (CC versus AA Mantel-Haenszel OR = 2.55, 95% CI = 1.92–3.38; AC versus AA Mantel-Haenszel OR = 1.94, 95% CI = 1.68–2.25) (**Table 3**).

Population attributable risks[16] for *TRA@* rs1154155C in Caucasians and in Asians were 20% and 42%, respectively. The increased frequency of rs1154155[C] in Asians likely contributes to the reported increased prevalence in Japan[1] despite lower HLA-DQB1*0602 frequency[4]. Our identified *TRA@* rs1154155[C] polymorphism showed no interaction with the nominally significant *TRB@* rs17231[T] polymorphism in the GWA data in our preliminary analyses (OR interaction = 1.2, $P = 0.24$). In our much larger sample, we also did not replicate a previously published rs5770917 association in Japanese narcolepsy (**Table 1**), suggesting an ancestry-specific effect[17]. Further, interactions between rs5770917 and rs1154155 were nonsignificant in Caucasians, Asians and African Americans (OR interaction = 0.88, $P = 0.66$ in all samples).

The *TRA@* locus encodes the α-chain of the TCRαβ-heterodimer, a protein expressed by T lymphocytes[18]. The T-cell receptor is a unique protein that interacts with both HLA class I (CD8 in cytotoxic T cells) and HLA class II (CD4 in helper T cells), including the DQαβ heterodimer denoted DQ0602, encoded by HLA-DQB1*0602 and the closely linked HLA-DQA1*0102 allele. The *TRA@* locus, like the *TRB@* and the immunoglobulin variable heavy and light chain loci, is unusual in undergoing somatic cell recombination. *TRA@* and *TRB@* recombination occurs in the thymus, resulting, after deletion of autoreactive clones and positive selection, in the generation of T-cell clones with unique *TRA@* and *TRB@* recombined loci. In the *TRA@* locus, recombination occurs between the 5′ area of one of the 46 functional variable (V) segments[19] and the 3′ area of one of the 49 functional J segments[20–22], with additional amino-acid junctional diversity generated by N and P additions in the V-J border region. In the *TRB@* locus, diversity is even more complex and generated by recombination of 48V, 2D and 13J segments[22]. This mechanism produces a diverse repertoire of distinct TCRαβ idiotype–bearing T cells[21], which can be called upon to recognize antigens presented by HLA class I or class II molecules[23].

Unlike most other autoimmune diseases[9], narcolepsy is almost completely associated with a single HLA allele, DQB1*0602, across Caucasians, Asians and African Americans[4]. Considering the tight DQB1*0602 association in narcolepsy, it is logical to hypothesize that the DQB0602 heterodimer should interact with a specific TCRαβ receptor subtype whose occurrence is marked by rs1154155[C], and less strongly by rs17231[T] at both TCR loci. This TCR idiotype would bear specific VJα and VDJβ recombinants, with recognition of a peptide that also binds DQ0602, mediating further immune reaction leading to the destruction of hypocretin-producing cells. Precisely how a J segment region polymorphism such as rs1154155[C] could increase the risk of occurrence of this narcolepsy associated T-cell clone is unknown, but could involve nonrandom VJα choices in recombination[21], as previously reported. Similarly, a polymorphism in the *TRB@* V region could influence VDJ recombination for the complementary TCRβ chain. Less probably, the TCR-DQ association could also occur without the need for peptide binding, through superantigen-like bridging of TCR and DQ, although most known superantigens interact with TCRβ rather than TCRα chains[24]. Further, superantigen bridging typically results in stimulation of large systemic lymphocyte populations carrying specific *TRB@* segments such as that seen in toxic shock syndrome.

Notably, of over ten HLA associated autoimmune diseases that have been subjected to genome-wide analyses and candidate gene

Table 3 Analysis of rs1154155 genotypes in three replication cohorts and combined

Ancestry	AA Case/Ctrl	AC Case/Ctrl	CC Case/Ctrl	OR_{AC}	OR_{CC}	OR_C
African American	90/117	23/20	0/1	1.50 (0.74,3.04)	0.00 (0.00,22.90)	1.31 (0.68,2.52)
Asian	86/161	296/318	167/120	1.74 (1.27,2.39)	2.61 (1.81,3.76)	1.54 (1.30,1.83)
Caucasian	201/259	132/83	10/6	2.05 (1.45,2.89)	2.15 (0.70,6.77)	1.80 (1.35,2.41)
Three replication samples (MH)				1.83 (1.48,2.27)	2.50 (1.80,3.48)	1.59 (1.38,1.83)[a]
All samples (MH)				1.94 (1.68,2.25)	2.55 (1.92,3.38)	1.69 (1.52,1.88)[b]

OR_{AC} is the odds ratio for genotype AC versus AA; OR_{CC} is the odds ratio for genotype CC versus AA; OR_C is the odds ratio for allele C versus A.
[a]$\chi^2 = 42.9$, $P = 5.9 \times 10^{-11}$. [b]$\chi^2 = 94.2$, $P = 2.8 \times 10^{-22}$.

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studies, none has shown consistent association with either TCR locus[25]. Further studies of the TCR loci in narcolepsy may for the first time reveal a role for a specific TCR receptor idiotype in the pathophysiology of an autoimmune disorder.

METHODS

Subjects. Narcolepsy cases were selected as described, 98% of whom are predicted to be hypocretin deficient. The initial sample was comprised of 807 cases and 1,074 Caucasian controls: 415 cases and 753 controls were recruited from the United States and Canada; 392 cases and 321 controls were recruited from European centers.

The Caucasian replication sample contained 718 individuals, of whom 542 were recruited from the United States and Canada (259 cases, 283 controls) and 176 from Europe (104 cases 72 controls). The Asian sample included 866 Japanese (433 cases, 433 controls) and 300 Koreans (128 cases, 172 controls). Finally, we studied 277 African Americans (133 cases, 144 controls). All subjects had given written informed consent approval.

HLA-DQB1*0602 typing. The presence or absence of DQB1*0602 was determined using DQB1 exon 2 sequence-specific primers (**Supplementary Table 2** online). These primers amplify DQB1*0602 and a few exceptionally rare DQB1*06 alleles (allele frequency $<0.5\%$) as a 218-bp PCR product. The assay includes a DRB1 internal positive control.

Analysis of Affymetrix data. We obtained Cel file data for all samples and carried out genotyping using the Birdseed-dev algorithm for Affy 6.0 (Affymetrix Power Tools \apt-1.8.5) ($n = 1544$), and BRLMM for Affy 500K array set chips ($n = 337$). In each genotype-calling group, individual chips with poor call rates (typically $<97\%$) or high heterozygosity were excluded from further analysis. For each Birdseed calling run, SNPs with call rates <0.9, or Hardy-Weinberg $P < 0.01$ in controls were excluded. A total of 549,596 SNPs passed all quality control filters and were included in the final analysis. Genotype data was maintained in our database (Progeny Lab 7), and analyses were done using the PLINK software package (v1.04 26/Aug/2008)[14]. Interaction studies were conducted in the initial set and in replication sets (cases and controls) using PLINK epistasis, which performs a logistic regression including main genotype effects plus an interaction term.

URLs. Birdseed-dev algorithm, http://www.affymetrix.com/products/software/specific/birdseed_algorithm.affx; BRLMM, http://www.affymetrix.com/support/technical/whitepapers/brlmm_whitepaper.pdf; Progeny Lab 7, http://www.progenygenetics.com; PLINK, http://pngu.mgh.harvard.edu/~purcell/plink/.

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

J.H. and J.F. contributed equally to this work. E.M., J.H. and N.R. designed the study. P.-Y.K., L.L., S.H., T.M., J.C., M.A., J.D. and M.K. generated molecular data. J.H., J.F., E.M., N.R., L.L., J.W. and M.K. performed the data analysis. E.M., J.H., J.F. and N.R. wrote the manuscript. E.M., G.M., G.P., S.N., S.H., P.B., Y.H., M.H., B.H., J.M., W.T.L., D.K., M.E., A.D., G.A.R., P.E.H., F.P., B.F., J.-H.J. and S.-P.L. contributed narcolepsy samples. T.G.N.T., L.K., G.T.N., D.S., H.-E.W., G.A.R., C.G., D.F.L., P.V.G., P.P., T.Y., and T.M. provided samples and/or genotypes. E.M. provided financial support.

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Corrigendum: Tiny RNAs associated with transcription start sites in animals

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Erratum: Narcolepsy is strongly associated with the T-cell receptor alpha locus

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