Relationship between T-cell receptor α gene polymorphisms and symptomatic differences in patients with narcolepsy type 1

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Abstract

Background: Recent genome-wide association studies have identified an important role of T-cell receptor α (TRA) gene in the development of narcolepsy type 1. However, the role of TRA haplotype polymorphisms in the symptomatic diversity of narcolepsy remains unclear. This study aimed to investigate whether TRA polymorphisms can influence the symptomatic diversity of narcolepsy.

Methods: Totally, 903 patients with narcolepsy type 1 were included in the study. Patients were divided into different groups according to their symptoms. First, 13 genotyped single nucleotide polymorphisms in the TRA were assessed for their association with symptoms of narcolepsy. We used the Chi-square test to determine differences in genotype frequencies in patients with narcolepsy. Further, we identified the haplotypes and variations of the TRA and tested their association with the symptoms of narcolepsy using a logistic regression model.

Results: According to the results of the logistic regression, TRA haplotypes TG and CT were significantly associated with auditory hallucination, with odds ratios of 1.235 (95% confidence interval [CI], 1.012–1.507) and 1.236 (95% CI, 1.012–1.511), respectively (P < 0.05).

Conclusions: The patterns of haplotype in TRA (haplotypes TG and CT) are associated with hypnagogic auditory hallucination in patients with narcolepsy type 1. However, further studies are needed to confirm our results and explore the underlying mechanisms.

Keywords: Narcolepsy; T-cell receptor α gene; Symptomatic subtype; Haplotype; Precision medicine

Introduction

In the last decades, significant progress has been made in the fields of immunotherapy and immunoprecision medicine.1,2 Due to the advanced genome sequencing method and detailed genetic data, immune therapy and monitoring based on precision medicine have been successfully applied to several diseases including cancers, infectious diseases, allergies, and asthma.3-6 The T-cell receptor (TCR) was suggested to play a crucial role in immunity. The clinical trials involving TCR-engineered T-cell immune therapy have shown some clinical responses.2 Narcolepsy type 1 (NT1) is a chronic immune-mediated disease caused by a hypocretin-1 deficiency,7-9 which is associated with the autoimmune process targets a peptide unique to hypocretin-producing neurons via specific human leucocyte antigen (HLA)-peptide-TCR interactions.10 Recently, hypocretin-specific T cells were detected in the blood and cerebrospinal fluid of patients with narcolepsy,11 which provided evidence that T cells play an important role in the onset of narcolepsy.

The gene encodes the TCR, which plays a prominent role in antigen presentation and T-cell activation, is T-cell receptor α (TRA) gene, which is a strong candidate gene for narcolepsy susceptibility. Several genome-wide association studies (GWASs) have revealed that the large TRA locus encoding the α-chain of the TCR showed strong association with the risk for narcolepsy,10,12,13 independent of the HLA, across Caucasians, Asians, and African Americans.10,12,14

Narcoleptic patients present a wide range of symptoms including excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations, which are the traditional tetrad of narcolepsy.6 The symptoms of different patients vary greatly. Only a minority of patients...
Two or three symptoms occur in approximately 30% of narcoleptic patients.\(^{16}\) EDS is the most common presenting and disabling symptom and is required for the diagnosis of narcolepsy.\(^{15,17}\) Cataplexy is the most specific symptom of NT1.\(^{15,18}\) The estimated prevalence of hypnagogic hallucinations ranges from 30% to 80% of patients and that of sleep paralysis ranges from 25% to 50%.\(^{18,19}\) The presence of different narcolepsy symptoms is associated with different qualities of life and psychological impairments.\(^{20}\) Thus, reducing the symptoms of narcolepsy is one of the important aims of treatment, including the possible immunotherapy in the future.

Despite the importance of TRA in narcolepsy risk and in the field of immunoprecision medicine, the role of TRA haplotype polymorphisms in the symptomatic diversity of narcolepsy remains unclear since it has not been extensively investigated. Therefore, in this retrospective study, we aimed to investigate the association between the single nucleotide polymorphisms (SNPs) and haplotype-tagging polymorphisms of TRA and the symptom diversity of narcolepsy in a Chinese population.

Methods

Ethical approval

The research protocols were approved by the Institutional Review Board Panel on Medical Human Subjects at the Peking University People’s Hospital. Informed consent was obtained from all subjects.

Study population

We performed a study consisting of 1062 patients with NT1. Briefly, the patients were recruited from the Sleep Laboratory of the Peking University People’s Hospital, a unit which evaluates patients with sleep disorders and receives referrals from all over China. The medical record of all the patients with narcolepsy was reviewed and re-diagnosed by clinical experts to ensure that they all met the diagnostic criteria for NT1 according to the third edition of the International Classification of Sleep Disorders-3.\(^{21}\) These criteria include (A and B must be met): A. The patient has been experiencing daily periods of irresistible need to sleep or daytime lapses into sleep occurring for at least 3 months; B. The presence of one (or both) of the following: (1) Cataplexy and a mean sleep latency of ≤8 min and two or more sleep-onset rapid eyes movement (REM) sleep periods (SOREMPs) on a multiple sleep latency testing (MSLT) performed according to standard techniques. A SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnography may replace one of the SOREMPs on the MSLT; (2) Cerebral spinal fluid hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or ≤1/3 of mean values obtained in normal subjects with the same standardized assay. Patients were all Chinese, and most of them were Han ethnicity (95.2%). Clinical data included presence or absence of cataplexy, sleepiness, sleep paralysis, hypnagogic hallucination, disturbed nocturnal sleep, and the degree of impairment of life quality. Trained interviewers used structured questionnaires to collect information on demographic variables, medical history, and medications. All the patients had EDS and cataplexy. Only 14.6% (132) of them exhibited all four symptoms. Most patients with narcolepsy (31.5%) exhibited only EDS and cataplexy. The distribution of different symptoms among different individuals is presented in Supplementary Table 1, http://links.lww.com/CM9/A68.

Genotyping, quality control, and genetic loci selection

SNP genotyping and quality control have been described in detail elsewhere.\(^{22}\) In brief, samples were genotyped and analyzed using the Affymetrix Axiom CHB array and Affymetrix Genotyping Console (Affymetrix, Inc., Cambridge, Massachusetts, USA). Totally, 13 SNPs of the TRA gene, which were previously discovered narcolepsy risk loci from GWAS studies published before September, 2018 or discovered in the GWAS study using our own data, including rs227000, rs1258667, rs227017, rs8016421, rs1154153, rs1154155, rs1154158, rs1263638, rs1263640, rs7153643, rs1263642, rs1263645, and rs1263647 were genotyped (the TRA polymorphisms of healthy controls are shown in Supplementary Table 2, http://links.lww.com/CM9/A68). All samples used in the current study achieved a genotype call rate of >99%. Totally, 903 of the 1062 narcolepsy cases were included for further analysis after quality control.

Statistical analysis

We used the Chi-square test to assess whether the SNPs were in Hardy-Weinberg equilibrium and to determine differences in genotype frequencies between patients with narcolepsy. Statistical significance was set at a two-sided P-value of less than 0.05. We defined statistical significance using the Bonferroni correction and set the experiment-wide association significance threshold at 5.6 × 10\(^{-3}\) for single-variant analysis (0.05/9 variants tested). For the SNPs in linkage disequilibrium (LD), only one SNP was included in the single-variant analysis. Analyses of LD between SNPs of TRA were performed to identify the existing haplotype blocks. The association of the TRA haplotypes with the clinical features of narcolepsy was evaluated using a logistic regression model. Odds ratio (OR), 95% confidence interval (CI), and P-value were calculated. We used Haploview (version 4.2, Broad Institute, USA) to calculate the LD of selected SNPs. The subsequent statistical analyses were performed using R statistical software (version 3.5.0, R Development Core Team, The New Zealand).

Results

Demographic and clinical characteristics

The demographic and clinical data of the patients with narcolepsy are presented in Table 1. Among these patients, 860 (95.2%) were of Chinese Han ethnicity, 285 (31.6%) were women, 618 (68.4%) were men, and 18 (2.0%) had a family history of narcolepsy.
| Characteristics                      | Value               |
|-------------------------------------|---------------------|
| Male, n (%)                         | 618 (68.4)          |
| Han ethnicity, n (%)                | 860 (95.2)          |
| Diagnostic delay (years), median (Q1, Q3) | 2 (0–8)           |
| Age of onset (years), median (Q1, Q3) | 9 (7–13)           |
| Inflammation before onset, n (%)    | 39 (4.3)            |
| Cataplexy, n (%)                    | 903 (100)           |
| Sleep paralysis, n (%)              | 331 (36.7)          |
| Hypnagogic hallucinations, n (%)    | 525 (58.1)          |
| Number of symptoms, n (%)           |                    |
| 1                                   | 284 (31.5)          |
| 2                                   | 356 (39.4)          |
| 3                                   | 242 (26.8)          |
| Familial history, n (%)             | 18 (2.0)            |
| Self-report impairment of life quality, n (%) | 99 (11.0)  |
| No impairment                       |                     |
| Small impairment                    | 244 (27.0)          |
| Great impairment                    | 254 (28.1)          |
| Body mass index (kg/m²), median (Q1, Q3) | 22.4 (18.9–26.4)  |
| CSF hypocretin (pg/mL), median (Q1, Q3) | 17.8 (12.7–30.5)     |
| Mean sleep latency (min), median (Q1, Q3) | 2.6 (1.8–4.0)     |
| Mean REM latency (min), median (Q1, Q3) | 1.7 (1.1–2.8)      |

CTF: Cerebral spinal fluid; REM: Rapid eye movement.

**Association between SNPs of TRA and clinical features of narcolepsy**

According to the Chi-square test, we examined the association between the individual genetic variant and symptoms of narcolepsy. After the Bonferroni correction, only the association of rs7153643 with visual hallucination was statistically significant. The association between each individual SNP and the symptoms of narcolepsy is summarized in Table 2.

**Construction of TRA haplotypes**

In addition to the association between SNPs and symptomatic diversity of narcolepsy, we observed that the SNPs in TRA were in LD with each other, forming several haplotypes. Considering the SNPs in TRA gene were in LD, we constructed TRA haplotype in order to explore the association between haplotype block and symptoms of patients with narcolepsy in subsequent analysis.

Totally, 13 SNPs were identified including rs227000, rs12588667, rs227017, rs8016421, rs1154153, rs1154155, rs1154158, rs1263638, rs1263640, rs7153643, rs1263642, rs1263645, and rs1263647. Three haplotype blocks formed by rs227017, rs1154153, and rs1154158; rs1263638 and rs1263640; and rs1263645 and rs1263647, were associated with auditory hallucination in patients with narcolepsy. As shown in Table 3, the higher TRA SNPs haplotype frequency of CT (OR = 1.236, 95% CI 1.012–1.511, P = 0.038) and TG (OR = 1.235, 95% CI 1.012–1.507, P = 0.038) were associated with an increased risk for auditory hallucination. The ATG haplotype (OR = 0.775, 95% CI 0.609–0.987, P = 0.039) and CA haplotype (OR = 0.810, 95% CI 0.663–0.988, P = 0.038); however, were more frequently observed in patients with narcolepsy who did not experience auditory hallucination. Haplotypes with a frequency of <1% were excluded from the analysis. Therefore, the three haplotype blocks were significantly associated with auditory hallucination in patients with narcolepsy.

**Discussion**

The present study reports two main findings. First, we identified the main haplotype blocks among patients with narcolepsy in the Chinese population. Second, we demonstrated that the different distributions of haplotypes of the TRA were significantly associated with auditory hallucination in patients with NT1.

The major strengths of the current study are as follows: (1) Our study comprised a large number of Chinese patients with phenotype and genotype data consistently collected using the same procedure for years; (2) We identified the distribution of haplotypes in the TRA, without ambiguity, in a Chinese population with narcolepsy; and (3) We extensively examined the impact of TRA on the symptomatic diversity of narcolepsy.

A previous study conducted in both Europeans and Asians only Japanese and Koreans) participants also constructed the haplotype blocks of TRA; however, the haplotype blocks of TRA that we constructed were different from those reported in that study.

A possible explanation is that the patients with narcolepsy in our study are all Chinese, and the Chinese population may have a distinctive genetic structure and distinctive TRA haplotypes.

TRA has been identified as one of the narcolepsy-risk genes in international SNP-based GWASs. Some identified variants of TRA can influence the function of the immune system and are relevant to the onset of narcolepsy. Previous studies indicated that the polymorphisms of TRA are associated with the age-at-onset of narcolepsy, and found a different distribution of TRA haplotypes between patients with narcolepsy and controls. Through the haplotype analysis, we found that the haplotype polymorphisms of the TRA were also associated with the symptoms among patients with narcolepsy. Our results confirmed the important role of TRA in the phenotypes of narcolepsy, and indicated that symptomatic sub-types of narcolepsy may exist. This will contribute to the redefinition of the clinical sub-types of narcolepsy based on the concept of precision medicine.
significant association of TRA polymorphisms with symptoms, age-at-onset, and risk of narcolepsy suggests that TCR and related inflammatory processes could contribute to the onset and development of narcolepsy. Our results, as well as those of previous studies, indicate associations and potential interactions among TRA polymorphisms, infection, symptoms, and age-at-onset of narcolepsy.

Our results indicate that the patterns of haplotype in TRA (haplotypes TG and CT) is closely associated with auditory hallucination. The underlying pathophysiology of auditory hallucination remains elusive, but several studies proposed that the primary auditory cortex (A1) may be involved in the generation of auditory hallucinations.\(^2\)\(^5\) Serotonin 2A receptor (5-HT2AR) activation may play a crucial role in inducing hallucinations during sleep paralysis.\(^2\)\(^8\) It has been estimated that although the core underlying pathologic mechanism in narcolepsy is the loss of large quantities of hypocretin (orexin) neurons in the hypothalamus, narcolepsy also considerably affects endocrine, metabolism, and mood regulation systems.\(^2\)\(^9\)

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First, our study only explored the effect of genetic factors associated with different immune processes. Although the symptoms of narcolepsy caused by TCR diversity is closely associated with narcolepsy sub-types with different underlying pathogenesis and mechanisms, which may affect different parts of the brain and present different symptoms. The results also indicate that the diversity of symptoms of narcolepsy caused by TCR diversity is closely associated with different immune processes. Although the underlying mechanism is not yet clear, these results may help to elucidate possible underlying mechanisms in narcolepsy.

Some limitations and shortcomings exist in our study. First, our study only explored the effect of genetic factors associated with different immune processes. Although the diversity of symptoms of narcolepsy caused by TCR diversity is closely associated with different immune processes. Although the underlying mechanism is not yet clear, these results may help to elucidate possible underlying mechanisms in narcolepsy.
on the development of gene sequencing technology, would provide more complete information on the association between TRA and clinical features of narcolepsy. Further studies on the gene-gene and gene-environment interaction should explore the role that TRA plays in the onset and symptomatic diversity of narcolepsy and identify the related underlying molecular mechanisms, to help in the definition of the different sub-types of narcolepsy based on the concept of precision medicine. These studies may shed light on the treatment of narcolepsy symptoms using immunotherapy.

The present study identified the main haplotype blocks among patients with narcolepsy in a Chinese population and demonstrated that the different distributions of haplotypes of the TRA were significantly associated with the symptomatic differences in narcolepsy. These results may help in defining different sub-types of narcolepsy and

| Haplotype | Auditory hallucination | Visual hallucination | Sleep paralysis |
|-----------|------------------------|----------------------|-----------------|
| Block 1   |                        |                      |                 |
| ATG       | 121 (32.1)             | 0.775 (0.609–0.987)  | 0.039           |
| GCA       | 416 (37.9)             | 1.147 (0.939–1.402)  | 0.179           |
| GGG       | 52 (36.6)              | 0.985 (0.690–1.407)  | 0.934           |
| GTG       | 59 (39.6)              | 1.148 (0.814–1.618)  | 0.331           |
| Block 2   |                        |                      |                 |
| CC        | 71 (35.5)              | 0.932 (0.685–1.266)  | 0.651           |
| CT        | 434 (38.8)             | 1.236 (1.012–1.511)  | 0.038           |
| TC        | 155 (33.2)             | 0.801 (0.641–1.000)  | 0.050           |
| Block 3   |                        |                      |                 |
| CA        | 237 (33.9)             | 0.810 (0.663–0.988)  | 0.038           |
| TG        | 413 (38.8)             | 1.235 (1.012–1.507)  | 0.038           |

TRA: T-cell receptor α; OR: Odds ratio; CI: Confidence interval.
treating narcolepsy symptoms using immunotherapy based on the concept of precision medicine.

**Acknowledgements**

The authors thank Prof. Yi-Qun Wu for his valuable consultations and Shi-Ying Wang for her help with the statistical analysis.

**Conflicts of interest**

None.

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