Original Article

Association of IL-1α rs17561 and IL-1 RN rs315952 polymorphisms with Tourette syndrome: a family-based study

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Abstract: Aim: Immune system dysregulation has been implicated to play a key role in pathogenesis of Tourette syndrome (TS). IL-1α and IL-1RN are important inflammatory cytokines that mediate the inflammation. In this study, we investigated the relationship between single-nucleotide polymorphisms (SNPs) of IL-1α and IL-1RN and the susceptibility to TS in Chinese Han population. Methods: A total of 276 children with TS and their parents were recruited in the study. All DNA from our subjects were genotyped for SNPs of IL-1α rs17561 and IL-1RN rs315952 using predesigned TaqMan SNP genotyping assay. The genetic contributions of two polymorphisms were evaluated using transmission disequilibrium test (TDT) and haplotype relative risk (HRR) design. In addition, to increase the efficiency of the test, the haplotype-based HRR (HHRR) was performed. Results: No significant differences were observed in allelic and genotypic frequency of rs17561 in IL-1α and rs315952 in IL-1RN between the transmitted group and non-transmitted group (for IL-1α rs17561: TDT=0.890, df=1, P=0.402; HRR=1.011, X²=3.016, P=0.082, 95% CI=0.999-1.024; for IL-1RN rs315952: TDT=0.095, df=1, P=0.805; HRR=0.984, X²=0.008, P=0.929, 95% CI=0.695-1.394). Similarly, the analysis of HHRR also did not support a significant association (for IL-1α rs17561: HHRR=1.226, X²=0.915, P=0.339, 95% CI=0.807-1.863; for IL-1RN rs315952: HHRR=0.963, X²=0.094, P=0.759, 95% CI=0.758-1.225). Conclusion: Our results suggest that IL-1α rs17561 and IL-1RN rs315952 polymorphisms may not be associated with susceptibility to TS in Chinese Han population. However, the results still need to be replicated in a larger sample size and different populations.

Keywords: Tourette syndrome, IL-1α, IL-1RN, TDT

Introduction

TS is a childhood-onset chronic neuropsychiatric disorder characterized by multiple, waxing and waning, motor and vocal tics, with a prevalence of 0.77% in children, and boys are affected more common than girls [1]. In addition to having tics, TS patients are commonly associated with other neuropsychiatric comorbidities, such as attention deficit/hyperactive disorder (ADHD) and obsessive compulsive disorder (OCD) [2]. Although the precise etiology is unknown, some evidences implicated that genetic factor contribute to play an important role in the pathogenesis of TS. Up till now, its risk candidate genes have still proven difficult to identify.

Previous studies have suggested that post-infectious autoimmunity and immune deficiency play an important role in the pathogenesis of TS. The exacerbations of TS symptoms may be triggered by group A beta-hemolytic streptococcal (GABHS) infections [3]. Martino et al. showed that TS patients exhibited a higher frequency of group A streptococcus (GAS) infection and anti-basal ganglia antibodies (ABGA) frequency [4]. As cytokine is an important mediator of the
inflammatory pathway, its dysregulation is identified in TS patients, such as elevated serum level of IL-12, TNF-α [5].

As important cytokines, the interleukin 1α gene (IL-1α) can amplify inflammatory response, and the interleukin 1 receptor antagonist gene (IL1RN) reduces inflammatory response by competitively inhibiting IL-1 receptor signaling [6]. As important functional polymorphisms in IL-1α and IL-1RN, rs17561 and rs315952 polymorphisms have been found to involve in several inflammatory-related diseases, including ankylosing spondylitis (AS) and Systemic lupus erythematosus (SLE) [7, 8]. So we guess the two SNPs might implicate to TS through regulating inflammatory response. In this present study, to identify whether polymorphisms of IL-1α rs17561 and IL-1RN rs315952 could be implicated in the susceptibility to TS, a family-based association study was performed to assess the possible genetic association with TS in Chinese Han population.

Materials and methods

The subjects were 276 TS patients and their parents recruited from the Affiliated Hospital of Medical College of QingDao University, Linyi People’s Hospital, Rizhao People’s Hospital and Dongying Central Hospital of Shengli Oilfield. All the subjects signed informed consents and the present study was approved by the ethics committees of the corresponding hospitals. TS patients comprised 234 male and 42 female, aged between 3 and 20 years old. All the patients were diagnosed based on the DSM-IV criteria on TS.

Genomic DNA was extracted from peripheral blood using standard methods. The polymorphism of IL-1α rs17561 and IL-1RN rs315952 were analyzed by TaqMan assays (Applied Biosystem/AB, USA) using CFX96 Real-Time platform. Then alleles of the two SNPs were determined by the Bio-Rad CFX Manger software.

All data analyses were carried out using the Statistical Package for Social Sciences (Version12.0 for Windows; SPSS, Inc., Chicago, IL). For all data of 276 TS trios, the Hardy-Weinberg equilibrium of the genotype distribution was tested using the chi-square test. The genetic contributions of the SNPs were evaluated using transmission disequilibrium test (TDT) and haplotype relative risk (HRR), and to increase the efficiency of the test, haplotype-based HRR (HHRR) was also performed.

Results

The results of the allelic and genotypic distribution of IL-1α rs17561 and IL-1RN rs315952 showed that both the TS patients group and the parents group conform to the Hardy-Weinberg equilibrium (P>0.05) (Tables 1 and 2). No significant differences were found in allelic and genotypic frequency of two SNPs between the transmitted group and non-transmitted group (for IL-1α rs17561: TDT=0.890, df=1, P=0.402; HRR=1.011, X²=3.016, P=0.082, 95% CI=0.999-1.024; for IL-1RN rs315952: TDT=0.095, df=1, P=0.805; HRR=0.984, X²=0.008, P=0.929, 95% CI=0.695-1.394) (Tables 3 and 4). Similarly, the analysis of HRR was also not support a statistically significant association
Discussion

Previous study showed that post-infectious autoimmunity was implicated in TS pathogenesis. A survey of 50 TS patients found that among 144 separate episodes of symptom exacerbation, 45 (31%) were associated with GABHS infection, 60 (42%) with symptoms of pharyngitis or upper respiratory infection, and six (4%) with GABHS exposure [3]. Church and his colleague further confirmed a role of GAS infection and basal ganglia autoimmunity in TS, in which TS patients exhibit a significant higher frequency of raised ASO titer and positive ABGA [9]. Recently, direct evidences of inflammation in central nervous system have been reported that RNA from basal ganglia area of 4 TS patients showed significantly increased expression of MCP-1 and IL-2 [10]. As an important mediator of the inflammatory pathway, cytokine has been reported may play an important role in the pathogenesis of TS. Leckman et al. [5] found elevated serum level of IL-12 and TNF-α in TS patients and further increased level during periods of symptom exacerbation. Also, serum concentrations of IL-2 were revealed positive associated with tic severity [11].

As two separately important functional polymorphisms in IL-1α which can amplify inflammatory response and IL1RN which reduce inflammatory response by binding IL-1 receptors and inhibiting the activities of pro-inflammatory cytokines IL-1α and IL-1β, rs17561 and rs315952 may have association with multiple sclerosis, obesity and so on [12, 13]. The present study was carried out to estimate the genetic contribution of IL-1α rs17561 and IL-1RN rs315952 by a family-based association study in Chinese Han population with 276 TS trios. Our results showed no significant difference in allelic and genotypic frequency of the two SNPs between transmitted group and non-transmitted group. Chou et al. investigated the distribution of genotypes of IL1RN*1 (rs2234663) and of IL-1β in 159 children with TS and 175 healthy control subjects in Taiwan. They found the number of individuals heterozygotic for IL1RN*1 was significantly greater and the IL1RN*1 allele frequency was significantly higher among patients than among control subjects. However, no significant difference between patients and control subjects in the distribution of genotype and allele frequencies for IL-1β exon 5 and promoter region was observed [14], which was not consistent with our studies. However, further investigation in this area is still needed.

To our knowledge it is the first report that a relationship between the polymorphisms of IL-1α rs17561 and IL-1 RN rs315952 and TS is investigated by a family-based association study in Chinese Han population with 276 TS trios. Our results showed no significant difference in allelic and genotypic frequency of the two SNPs between transmitted group and non-transmitted group. Chou et al. investigated the distribution of genotypes of IL1RN*1 (rs2234663) and of IL-1β in 159 children with TS and 175 healthy control subjects in Taiwan. They found the number of individuals heterozygotic for IL1RN*1 was significantly greater and the IL1RN*1 allele frequency was significantly higher among patients than among control subjects. However, no significant difference between patients and control subjects in the distribution of genotype and allele frequencies for IL-1β exon 5 and promoter region was observed [14], which was not consistent with our studies. However, further investigation in this area is still needed.

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Disclosure of conflict of interest

None.
References


