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Does IL-17F Play a Role in Etiology of TS? A Family Based Study

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Abstract: **Previous studies have suggested a critical role for interleukin IL-17F in innate and adaptive immunity in vivo and its abnormal expression was found to play a bridging role in several neurological disorders. In this study, we investigated the association between functional polymorphisms in *IL-17F* and Tourette's syndrome (TS) in a Chinese Han population. We recruited 407 TS nuclear family trios (325 male cases and 82 female cases each with their parents) and 417 controls (321 male and 96 female), and performed TaqMan allelic discrimination real-time PCR to genotype two polymorphisms in *IL-17F*, rs1889570 and rs763780. The transmission disequilibrium test (TDT) and haplotype relative risk (HRR) were used to estimate genetic susceptibility. In addition, we designed a classic case–control study to identify differences in the genetic distributions of these polymorphisms. No transmission disequilibrium was found between the *IL-17F* tag polymorphisms rs1889570 and rs763780 and TS (rs1889570: TDT=1.35, P=0.266, HRR=1.327, χ^2=3.812, P=0.051, 95%CI=0.999-1.763, haplotype-based HRR (HHRR)=1.127, χ^2=1.371, P=0.242, 95%CI=0.923-1.376; rs763780: TDT=3.10, P=0.092, HRR=0.74, χ^2=3.00, P=0.083, 95%CI=0.526-1.041, HHRR=0.75, χ^2=3.146, P=0.076, 95%CI=0.546-1.031). The allelic frequencies and genotypic distributions were compared by Pearson's chi-square test, which also indicated there was no remarkable difference between the TS patients and the controls. Our research indicated that the genetic variants of rs763780 and rs1889570 in *IL-17F* may not play a crucial role in the pathogenesis of TS in a Chinese Han population. However, these findings should be confirmed in other ethnic populations.**

Keywords: Tourette's syndrome; IL-17F, Transmission disequilibrium test; Haplotype relative risk; Haplotype-based haplotype relative risk

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1. Introduction

Tourette's syndrome (TS) is an early onset complex neuropsychiatric disorder named after the French neurologist Georges Gilles de la Tourette in 1885 [1]. It is characterized by multiple motor and one or more vocal tics lasting longer than a year with complications such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), poor impulse control, and other coexisting behavioral problems [2,3] that seriously affect a child's learning and daily life. The prevalence of TS was reported to be 0.1–1% in children and adolescents between 5 and 18 years old [4], and the proportion of affected males to females was about 3–4:1 [5]. Following decades of study, etiological suggestions for TS include neuroimmunological effects cause by infection, psychosocial stressors, and androgen and genetic factor, but its precise etiology and pathogenesis remain unclear [3,6]. Among them, genetic factors play important roles and candidate genes included *DRD1* (dopamine receptor D1) [7], *ADR* (adrenergic receptor) [8], *5-HT* (5-hydroxytryptamine receptor) [9], *SLITRK1* (slit and trk-like family member 1) [10], and *NLGN4* (neuroligin 4) [11] have been shown to be associated with the development of TS.

Immune dysfunction in TS is caused by molecular mimics (the structure of homologous or similar antigens contact the immune system inducing the generation of cross-reactive antibodies), which increase the risk for the development of autoimmune phenomena and increase the abundance of inflammatory cytokines [12,13]. Dale et al. [14] found a distinct increase in the morbidity of motor tics concurrent with an outbreak of group A β-hemolytic streptococcal (GABHS) infection. Several auto-neuronal antibodies and inflammatory cytokines induced by streptococcal infection and detected in a small number of patients with TS, were suggested to target the basal ganglia, contributing to the symptoms associated with TS [15]. In addition, cytokines are known to be important mediators of the immune/inflammatory pathway [16]. Cheng et al. [17] reported significant differences in the concentrations of

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the serum interleukins IL-6, IL-1β, and IL-17, and the antistreptolysin O antibody, as well as autoantibody positivity in TS patients.

IL-17, located on chromosome 6p12, encodes an important pro-inflammatory cytokine with a broad range of biological activity, including stimulating the production of several other cytokines (IL-1β, IL-6, and the tumor necrosis factor TNF-α) and glutamate [18]. IL-17 can also enhance the excitability of neurons [19-21] and it plays a key in several neurological disorders [22]. The IL-17 family includes six structurally-related members (IL-17A–F), among which IL-17A and IL-17F share the highest homology (about 50%) [22]. IL-17F and IL-17A can form homodimers or IL-17A/F heterodimers, which jointly play a role in various autoimmune diseases [23]. IL-1β and TNF-α are expressed mainly in the central nervous system and can activate transient receptor potential vanilloid 1 (TRPV1), which may indicate they can regulate neurotransmitter release, synaptic plasticity, and neuronal death [18, 20, 21].

In previous researches, our group found no statistically significant differences between several interleukins and TS [24, 25], although TS was indeed closely related to immune imbalance [13]. To further investigate the immune genetic mechanisms of TS, continuing relevant experiments are required. The polymorphism rs763780, located in exon 3 of *IL-17F*, can lead to a His-to-Arg substitution at amino acid 161 (H161R) of IL-17F. The polymorphism rs1889570 is located in the promoter region of *IL-17F*. These two tag single nucleotide polymorphisms (SNPs) have been associated with various immune/inflammatory diseases [26,27]. Moreover, rs763780 and rs1889570 are good representatives for *IL-17F* because they are inherited independently from each other (linkage disequilibrium between the two SNPs is 0.1%). We hypothesized that there may be an association between *IL-17F* (rs1889570 and rs763780) and TS. In the present study, we collected new nuclear family trios and combined them with other samples from a previous study in our group to investigate the associations between *IL-17F* rs763780 and rs1889570 and susceptibility to TS based on a classical case–control and family-based study design in a Chinese Han population.

2. Materials and Methods

2.1. Subjects

All of the 407 TS nuclear family trios and 417 controls were admitted to the Affiliated Hospital of Qingdao University, Linyi People's Hospital, Fujian People's Hospital, Rizhao People's Hospital, Dongying Central Hospital of Shengli Oilfield between May 2013 and March 2015. Clinical characteristics and demographic including age, clinical symptoms, gender were collected in a clinical database. TS patients comprised 325(79.85%) male and 82(20.15%) female, aged between 3 and 22 years old. Controls were gender-matched to the TS patients, aged between 15 and 42 years old. As TS is an early onset disorder, age is not taken as a matching factor. So the Mean ± SD ages of cases and controls were 12.62±3.31 and 24.58±5.60 respectively. All TS patients were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria (DSM-IV). All controls had no psychiatric histories, brain organic disease and mental retardation, as determined by physical and laboratory examinations. The present study was approved by the ethics committee of the corresponding hospitals. All participants signed informed consents prior to taking part in the study.

Table 1 The original data used in this study

genotype	rs1889570				genotype	rs763780			
	parents	case	non-trans	control		parents	case	non-trans	control
AA	119	59	63	60	CC	8	1	3	7
AG	391	208	177	189	CT	156	73	91	70
GG	304	140	167	168	TT	650	333	313	340

2.2. Genotyping

Genomic DNA was extracted from 200μl EDTA-buffered peripheral venous blood using Qiagen DNA extraction kit (Germany).Genotype of polymorphisms of IL-17F rs1889570 and rs763780 were conducted by the TaqMan assays Real-Time platform. Taqman primers and probes were synthesized by Applied Biosystems of Life Technologies (USA).The rs763780 primers sequence were 5'-GTGGATATGCACCTCTTACTGCACA-3'(F) and 5'-GGTGGATGACAGGGGTGACGCAGGT-3'(R); rs1889570 primers sequence were 5'-GAGCAATAAAGGTGAAAAAGACAGTCTT-3'(F) and 5'-GAGGGGAGGACCCTTCCTGAAT-3'(R). PCR mixture contained 1.25μl 20×SNP Genotyping Assay, 12.5μl 2×PCR Master Mix, and 11.25μl DNA and DNase-free water. The Amplifications were carried out in aC1000™ thermal cycler system with the following conditions: 95℃ for 3min, followed by 45 cycles at 95℃ for 15s and 60℃for 1min. For each cycle, fluorescence signals ware detected by VIC/FAM-labeled probes. Allelic discrimination was performed by the Bio-Rad CFX manager 3.0 software.

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2.3. Statistical analysis

Genotype data of parents and controls were tested by Hardy-Weinberg equilibrium (HWE). Then all the data was counted using statistical software package SPSS 21.0. The genetic association of TS nuclear family trios was analyzed by TDT, HRR and haplotype-based haplotype relative risk (HHRR). Furthermore, differences in genotypic and allelic frequencies between cases and controls were compared by Pearson's chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to show the relative risk degree. All of the Statistical significance was set at $P<0.05$.

Table 2 Results of the TDT for two genetic loci in IL-17F in 407 family trios

transmitted allele	rs1889570			rs763780	
	non-transmitted allele			non-transmitted allele	
	A	G		C	T
A	119	207	C	8	67
G	184	304	T	89	650
results($\chi2$,P,OR)	1.350,0.266, 0.950			3.102, 0.092, 0.872	
95%CI	0.710-1.270			0.405-1.876	

3. Results

3.1. Family-based study

All the original data used for the family-based study and classic case–control analysis are included in Table 1. We verified that the genotype of the biological parents of the TS patients conformed to HWE (rs1889570: $\chi2=0.138$, $P=0.710$; rs763780: $\chi2=0.011$, $P=0.956$). The transmitted and non-transmitted groups were not statistically different in the TDT (rs1889570: TDT=1.35, P=0.266; rs763780: TDT=3.102, P=0.092) (Table 2). Our data also indicated that there was no statistically significant difference in the HRR between the transmitted and non-transmitted haplotypes (rs1889570: HRR=1.327, $\chi2=3.812$, $P=0.051$, 95%CI=0.999-1.763; rs763780: HRR=0.74, $\chi2=3.00$, $P=0.083$, 95%CI=0.526-1.041) (Table 3). To increase the efficiency of the test, we assessed the TS cases using HHRR and found that results supported no relationship between *IL-17F* rs1889570 and rs763780 and TS, as revealed by the TDT and HRR analyses (rs1889570: HHRR=1.127, $\chi2=1.371$, $P=0.242$, 95%CI=0.923-1.376; rs763780: HHRR=0.75, $\chi2=3.146$, $P=0.076$, 95%CI=0.546-1.031) (Table 3).

3.2. Classic case–control analysis

The controls in our study were in accordance with HWE, which ensured the reliability of Pearson's chi-square test (rs1889570: $\chi2=0.335$, $P=0.563$; rs763780: $\chi2=2.243$, $P=0.134$). Table 4 shows the genotypic distributions and allelic frequencies of rs1889570 and rs763780 between cases and controls. No significant differences were observed at the two SNP sites (rs1889570: genotypic distributions: $\chi2=3.342$, $P=0.188$; allelic frequencies: $\chi2=1.564$, $P=0.211$, OR=1.135, 95%CI=0.931-1.384; rs763780: genotypic distributions: $\chi2=4.515$, $P=0.105$; allelic frequencies: $\chi2=0.348$, $P=0.555$, OR=0.906, 95%CI=0.653-1.257).

Table 3 Results of the HRR and HHRR analysis for two genetic loci in *IL-17F* in 407 family trios

group	HRR				HHRR			
	rs1889570		rs763780		rs1889570		rs763780	
	A(+)	A(-)	C(+)	C(-)	A	G	C	T
transmitted allele	267	140	74	333	326	488	5	739
non-transmitted	240	167	94	313	303	511	7	717
results($\chi2$,P,OR)	3.812, 0.051, 1.327		3.000, 0.083, 0.740		1.371,0.242, 1.127		3.146,0.076,0.750	
95%CI	0.999-1.763		0.526-1.041		0.923-1.376		0.546-1.031	

4. Discussion

TS is an inherited and childhood-onset chronic neurodevelopmental disorder [41]. The clinical symptoms include persistent multiple motor tics along with at least one vocal tic that occur in response to movement or as an involuntary movement, which transiently relieves the sensation [28]. Advances in science and technology and changes of lifestyle have revealed that the etiology of TS is more complex than was once thought and involves, for example, genetic predisposition, low birth weight, anoxia neonatorum, severe social pressure or stress, streptococcal infection, and misuse of drugs [3]. Most inflammatory reactions that are accompanied by an imbalance of cytokines are involved in the autoimmune-related pathogenesis of

TS [16,29]. Harris et al. [30] considered the inflammatory response and immune dysregulation found after GABHS infection were associated with TS due to the molecular mimicry between surface GABHS antigen and neuronal antigen. Morer et al. [15] subsequently confirmed the presence of anti-neuronal antibodies and immunologic cytokines. Leckman et al. [16] found elevated serum levels of IL-12 and TNF-α in TS patients. In addition, the concentrations of serum antistreptolysin O antibody, IL-6, IL-17, and IL-1β, as well as autoantibody positivity were shown to be significantly different between TS patients and controls in a Chinese population [17].

In our group, we previously conducted a correlation analysis of immune-related genes, such as *IL-1*, *IL-8*, *IL-12β* and *TNF-α*, with TS susceptibility in a Chinese Han population. Most of our previous results showed no significant correlations [24, 25]. However, the important pro-inflammatory cytokine IL-17 has been found to play a bridging role between innate and adaptive immunity in vivo [19, 31, 32]. The abnormal expression of IL-17 and IL-17R has been shown to play a critical role in the etiology of many central nervous system diseases such as autoimmune diseases, neurodegenerative diseases, and ischemic brain injury [19]. Based on these results, in this study, we examined the association between two polymorphisms in *IL-17* and TS. The genes encoding two members of the IL-17 family, IL-17F and IL-17A, are located adjacent to each other on chromosome 6p12 associated with juvenile myoclonic epilepsy (JME) [22, 33, 34]. Immunohistochemistry demonstrated that IL-17F and IL-17R are distributed mainly in neurons, glial cells, and endothelial cells, and could induce the release of other inflammatory cytokines (IL-1β, IL-6, and TNF-α) then destroy the blood–brain barrier [18]. Besides, IL-17 can be triggered by nitric oxide synthase (NOS) and cause astrocyte cell to produce large amounts of nitric oxide [35]. Neurotransmitter glutamate was shown to be excited by excessive release of nitric oxide, leading to local neural circuits "excitement-check" imbalances, which caused abnormal neurons and excessive synchronization discharge that were related to neuropsychiatric disorder [20]. The indirect activation of TRPV1 was found to cause the influx of $Ca^{2+}$and Na^{+} in the cerebral cortex and limbic system (such as hippocampus and central amygdale) and selectively affect synaptic connections of interneurons projected on hippocampus [36,37]. Therefore, TRPV1 may lead to neuronal loss, which is one of the important pathological features of tic [38].

Table 4 Comparison of genotypic and allelic frequencies for two genetic loci in IL-17F between case and control groups

group	rs1889570					rs763780				
	genotype			allele		genotype			allele	
	AA	AG	GG	A	G	CC	CT	TT	C	T
case	59	208	140	326	488	1	73	333	75	739
control	60	189	168	309	525	7	70	340	84	750
χ2	3.342			1.564		4.515			0.348	
P	0.188			0.211		0.105			0.555	
OR				1.135					0.906	
95%CI				0.931-1.384					0.653-1.257	

The above results suggested that IL-17F may be an important cytokine in the pathogenesis of TS. In addition, a number of family and twin studies have shown that genetic factors play important roles in the onset of TS [39, 40]. In this study, we used a case–control method combined with a family-based analysis to estimate the genetic distributions of rs1889570 and rs763780 in *IL-17F* of TS patients in a Chinese Han population. The two selected tag SNPs were independently inherited and could be taken as representatives of *IL-17F* (LD: r^2=0.1%). The family-based analyses included TDT, HRR, and HHRR. This method helped dispel the absence of consistency in the genetic background, avoided false positive results and phenomenon related to a layered group structure, and effectively averted the deviation in results from the stratification population, to precisely identify disease susceptibility genes. The family-based analysis found no significant differences in allelic frequency and genotype distribution of the two SNPs in *IL-17F* between the transmitted and non-transmitted groups. To compare the TS patients and uncorrelated normal controls, we increased the classic case–control analysis. Again, we found no significant difference between the two groups. Therefore, we consider our results are reliable and the two polymorphisms in *IL-17F* had no relationship with TS in this study.

To our knowledge, this is the first report about the association between the polymorphisms of *IL-17F* and TS in a Chinese Han population investigated by a family-based study and case–control analysis.

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Nevertheless, our study has several limitations. The most important are the small sample size and single limited area of the population. The relationship between these two genetic polymorphisms in *IL-17F* and TS needs to be examined in a larger sample size and in different populations. Further, we investigated only the two tag SNPs in *IL-17F*, which is not enough to fully represent the association between *IL-17F* and TS. Lastly, because TS is a polygenic disease, its etiology is likely to involve the cumulative effect of multiple genes and be influenced by a wide range of factors. Therefore, more researches are needed to further explore the link between *IL-17F* and TS, in order to acquire further insights into TS etiology.

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Disclosure of conflict of interest

All authors declared no conflicts of interest.

References

[1] Hugh Rickards MD, Woolf I, Cavanna AE. "Trousseau's disease:" A description of the gilles de la tourette syndrome 12 years before 1885[J]. Movement Disorders, 2010, 25(14):2285-2289.

[2] Singer HS. Current issues in Tourette syndrome (pages 1051–1063)[M]. Current trends in life sciences. Today and Tomorrow's Printers and Publishers, 2000:1051-1063.

[3] Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment[J]. Brain, 2000, 3(3):425-462.

[4] Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome: Part 1: The epidemiological and prevalence studies[J]. Journal of Psychosomatic Research, 2008, 65(5):461-472.

[5] Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 2: tentative explanations for differing prevalence figures in GTS, including the possible effects of psychopathology, aetiology, cultural differences, and differing phenotypes[J]. Journal of Psychosomatic Research, 2008, 65(5):473-486.

[6] Robertson MM. The Gilles de la Tourette syndrome: the current status[J]. British Journal of Psychiatry the Journal of Mental Science, 2012, 97(5):166-175.

[7] Tsai IC, Lee CH, Kuo CC, et al. Association analysis between Tourette's syndrome and dopamine D1 receptor gene in Taiwanese children[J]. Psychiatric Genetics, 2005, 14(4):219-221.

[8] Brett PM, Curtis D, Robertson MM, et al. Neuroreceptor subunit genes and the genetic susceptibility to Gilles dela Tourette syndrome[J]. Biological Psychiatry, 1997, 42(10):941-947.

[9] Niesler BB, Hebebrand J, Rappold G. Serotonin receptor genes HTR3A and HTR3B are not involved in Gilles de la Tourette syndrome[J]. Psychiatric Genetics, 2005, 15(4):303-304.

[10] Abelson JF, State MW. Sequence variants in SLITRK1 are associated with Tourette's syndrome[J]. Science, 2005, 310(5746):317-320.

[11] Lawsonyuen A, Saldivar JS, Sommer S, et al. Familial deletion within NLGN4 associated with autism and Tourette syndrome[J]. European Journal of Human Genetics Ejhg, 2008, 16(5):614-618.

[12] Hornig M, Lipkin WI. Immune-mediated animal models of Tourette syndrome[J]. Neuroscience & Biobehavioral Reviews, 2013, 37(6):1120-1138.

[13] Elamin I, Edwards MJ, Martino D. Immune dysfunction in Tourette syndrome[J]. Behavioural Neurology, 2013, 27(1):23-32.

[14] Dale RC. Post-streptococcal autoimmune disorders of the central nervous system[J]. Developmental medicine and child neurology, 2005, 47(11):785-791.

[15] Morer A, Lázaro L, Sabater L, et al. Antineuronal antibodies in a group of children with obsessive-compulsive disorder and Tourette syndrome[J]. Journal of Psychiatric Research, 2008, 42(1):64–68.

[16] Krause DL, Müller N. Suppl 1: The Relationship between Tourette's Syndrome and Infections[J]. Open Neurology Journal, 2012, 6(1):124-128.

[17] Cheng Y, Zheng Y, He F, et al. Detection of Autoantibodies and Increased Concentrations of Interleukins in Plasma from Patients with Tourette's Syndrome[J]. Journal of Molecular Neuroscience, 2012, 48(1):219-224.

[18] Li G, Bauer S, Nowak M, et al. Cytokines and epilepsy[J]. Seizure-Eur J Epilep, 2011, 20(3):249-256.

[19] Xu S, Cao X. Interleukin-17 and its expanding biological functions[J]. Cellular & Molecular Immunology, 2010, 7(3):164-174.

[20] Casamenti F, Prosperi C, Scali C, et al. Interleukin-1beta activates forebrain glial cells and increases nitric oxide production and cortical glutamate and GABA release in vivo: implications for Alzheimer's disease[J]. Neuroscience, 1999, 91(3):831-842.

[21] Richter F, Natura G, Ebbinghaus M, et al. Interleukin-17 sensitizes joint nociceptors to mechanical stimuli and contributes to arthritic pain through neuronal interleukin-17 receptors

in rodents[J]. Arthritis & Rheumatology, 2012, 64(12):4125-4134.
[22] Zhang X, Angkasekwinai P, Dong C, et al. Structure and function of interleukin-17 family cytokines[J]. Protein & Cell, 2011, 02(1):26-40.
[23] Wright JF, Guo Y, Quazi A, et al. Identification of an interleukin 17F/17A heterodimer in activated human CD4+ T cells[J]. Journal of Biological Chemistry, 2007, 282(18):13447-13455.
[24] Fan H, Shao X, Yi M, et al. Association of IL-1α rs17561 and IL-1 RN rs315952 polymorphisms with Tourette syndrome: a family-based study[J]. International Journal of Clinical & Experimental Pathology, 2015, 8(4):4182-4185.
[25] Liu S, Yi M, Wang M, et al. Association of IL8 −251A/T, IL12B −1188A/C and TNF-α −238A/G polymorphisms with Tourette syndrome in a family-based association study in a Chinese Han population[J]. Neuroscience Letters, 2011, 495(2):155-158.
[26] Jin EH, Choi EY, Yang JY, et al. Significant association between IL-17F promoter region polymorphism and susceptibility to asthma in a Korean population[J]. International Archives of Allergy & Immunology, 2011, 155(2):106-110.
[27] Peng R, Yue J, Han M, et al. The IL-17F sequence variant is associated with susceptibility to tuberculosis[J]. Gene, 2013, 515(1):229-232.
[28] Leckman JF. Phenomenology of tics and natural history of tic disorders[J]. Brain & Development, 2003, 25(1):24-28.
[29] Leckman JF, Katsovich L, Kawikova I, et al. Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome[J]. Biological Psychiatry, 2005, 57(6):667-673.
[30] Harris K, Singer HS. Tic disorders: neural circuits, neurochemistry, and neuroimmunology[J]. Journal of Child Neurology, 2006, 21(8):678-689.
[31] Ma X, Reynolds SL, Baker BJ, et al. IL-17 enhancement of the IL-6 signaling cascade in astrocytes[J]. Journal of Immunology, 2010, 184(9):4898-906.
[32] Kebir H, Kreymborg K, Ifergan I, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation[J]. Nature Medicine, 2007, 13(13):1173-1175.
[33] Takeuchi T. Mutations in, EFHC1 cause juvenile myoclonic epilepsy[J]. Nature Genetics, 36.
[34] Delgadoescueta AV, Bai D, Bailey J, et al. Juvenile myoclonic epilepsy in chromosome 6p12: clinical and genetic advances[J]. Revista De Neurologia, 2002, 35(1):82-86.
[35] Trajkovic V, Stosic-Grujicic S, Samardzic T, et al. Interleukin-17 stimulates inducible nitric oxide synthase activation in rodent astrocytes[J]. Journal of Neuroimmunology, 2001, 119(2):183-191.
[36] Mezey E, Toth ZE, Cortright DN, et al. Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human. Proc Natl Acad Sci USA[J]. Proceedings of the National Academy of Sciences, 2000, 97(7):3655-3660.
[37] Gibson HE, Edwards JG, Page RS, et al. TRPV1 channels mediate long-term depression at synapses on hippocampal interneurons[J]. Neuron, 2008, 57(5):746-759.
[38] Rebecca SN, Liu BS, Lemieux L, et al. Progressive neocortical damage in epilepsy[J]. Annals of Neurology, 2003, 53(3):312-324.
[39] Pauls DL, Cohen DJ, Heimbuch R, et al. Familial pattern and transmission of Gilles de la Tourette syndrome and multiple tics[J]. Archives of General Psychiatry, 1981, 38(10):1091-1093.
[40] Price RA, Kidd KK, Cohen DJ, et al. A twin study of Tourette syndrome[J]. Archives of General Psychiatry, 1985, 42(8):815-820.
[41] Jimenez-Shahed J. Tourette syndrome[J]. Neurologic clinics, 2009, 27(3):737-755.

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