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Association of Tyrosyl-DNA Phosphodiesterase 1 Polymorphism With Tourette Syndrome in Taiwanese Patients

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Background: Genetic, environmental, immunological, and hormonal factors contribute to the etiology of Tourette syndrome (TS). From the genetic standpoint, TS is a heterogeneous disorder. In our previous study, we found that a single nucleotide polymorphism (SNP) of x-ray repair cross-complementing group 1 (*XRCC1*), a DNA repair gene, was associated with TS. Previous studies also showed that tyrosyl-DNA phosphodiesterase 1 (TDP1) interacts with XRCC1 to repair damaged DNA. However, the relationship between TS and SNPs of *TDP1* gene is unknown. Therefore, the aim of this study was to test the hypothesis that if the *TDP1* SNP, rs28365054 (c.400G>A, Ala134Thr), was associated with TS or not. *Methods:* A case-control study was designed to test the hypothesis. A total of 122 TS children and 106 normal children participated in the study. We used polymerase chain reaction to identify the SNP, rs28365054, of the *TDP1* gene in the TS patients and the normal children. *Results:* A polymorphism at position rs28365054 in the *TDP1* gene had a significant difference ($P < 0.05$) in the genotype distributions between the TS patients and the control group. The AG genotype was a risk factor for TS with an odds ratio of 2.26 for the AG versus AA genotype (95% CI 1.08–4.72). *Conclusion:* The findings of this study suggested that variants in the *TDP1* gene might play a role in TS susceptibility. J. Clin. Lab. Anal. 27:323–327, 2013.

Key words: Tourette; TDP1; SNP; Taiwan; DNA repair

INTRODUCTION

Tourette syndrome (TS) is a neurodevelopment disorder. It is characterized by involuntary, repetitive motor or vocal tics. So far, the precise etiology of TS is still unknown. However, there are evidences demonstrating genetic, environmental, immunological, and hormonal factors, which contribute to the etiology of TS. (1–3). From the genetic standpoint, TS is a heterogeneous familial disorder (4, 5). Candidate genes involved in TS are dopamine receptor gene (6, 7), dopamine β-hydroxylase gene (6, 8), dopamine-associated transporter gene (9), etc. However, none of these genes has been identified as a causative TS susceptibility gene. Hence, we made an assumption that other genes might be involved in TS.

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Tyrosyl-DNA phosphodiesterase 1 (TDP1) is a DNA 3′-end processing enzyme, which expresses almost equally throughout the central nervous system (10). This enzyme can repair DNA single strand breaks (SSBs) resulting from oxidative attack by endogenous reactive oxygen species (ROS) (11). It repairs SSBs via hydrolyzing the bond between the 3′-end of DNA and stalled DNA topoisomerase 1 (TOP1) (12). Therefore, TDP1 plays a major role in protecting nonproliferating cells from genotoxic consequences of oxidative stress.

Previous experiments have shown that the cerebellums of TS patients have robust activities during tic release (13–15) and TS patients have smaller cerebellums than normal children (16). These experiments imply that cerebellums may be involved in the pathogenesis of TS. Besides, people already know that mutation of *TDP1* gene (H493R) will result in spinocerebellar ataxia with axonal neuropathy-1 (SCAN1), which is a childhood-onset disorder (17) and that knockout of *TDP1* gene ($TDP1^{-/-}$) will lead to progressive age-related cerebellar atrophy (18). In addition, it has been shown that a genetic variation in the DNA repair gene XRCC1 (X-ray repair cross-complementing group 1) has an association with TS (19). Hence, we assumed *TDP1* SNPs might have an association with TS. In order to verify this hypothesis, we did a case-control study and chose an SNP at position rs28365054 (c.400G>A, Ala134Thr) in the *TDP1* gene to test whether this SNP would have an association with TS.

Why we chose the SNP, rs28365054, to investigate its relationship with TS? In our previous study we found that an SNP of XRCC1, a DNA repair gene, was associated with TS (19). TDP1 plays a role in DNA repair through interactions with DNA ligase III (LIG III) (17), a partner of the critical DNA repair protein XRCC1 (20). Therefore, we assumed that SNPs located in the region that encodes LIG III binding domain of *TDP1* [i.e. the *N*-terminus (1–150 amino acids) of TDP1] (17) might associate with TS. There are three nonsynonymous SNPs (rs35114462, rs35455108, and rs28365054) located in this region (Table 1). Because the SNP rs28365054 alters the protein structure (i.e. changes a hydrophobic alanine to a hydrophilic threonine and changes a small amino acid to a medium one) much more than the other two SNPs (21), we chose the SNP rs28365054 to investigate the relationship between the *TDP1* variant and TS.

TABLE 1. Physicochemical Properties of Three Nonsynonymous SNPs Located in the Region That Encodes LIG III-Binding Domain of *TDP1* (21)

dbSNP ID	Physicochemical property
rs35114462	Similar physicochemical property
(c. 285 G>T, Glu95Asp)	Both residues are medium size and acidic
rs35455108	Similar physicochemical property
(c.302 C>T, Pro101Leu)	Both residues are medium size and hydrophobic
rs28365054	Change from small size and hydrophobic (A) to medium size and polar (T)
(c.400 G>A, Ala134Thr)	

METHODS

Subjects

All participants enlisted in this study were recruited at China Medical University Hospital in Taiwan. Institutional ethic committee approved this experiment. Informed consents were obtained from all subjects. One hundred and twenty two unrelated children with TS and one hundred and six age-matched normal controls participated in this experiment. The diagnosis of TS was made at the Department of Pediatric Neurology and followed the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). These criteria contain: the presence of multiple motor and at least one vocal tic (not necessarily concurrent); a waxing and waning course, with tics evolving in a progressive manner; the presence of tic symptoms for at least 1 year; the onset of symptoms before age 21 years; the absence of a precipitating illness (e.g., encephalitis, stroke, or degenerative disease) or medication; the observation of tics by a knowledgeable neurologist; and marked distress or significant impairment in social, occupational, or other important areas of functioning.

Determination of *TDP1* Gene Variants by PCR-RFLP

Genomic DNA was extracted from peripheral blood samples by a Genomic DNA extraction kit (Blossom, Taipei, Taiwan). A single nucleotide polymorphism (SNP) across near 5′ region (rs28365054) was selected from public dbSNP database. In order to identify allele preference for the SNP, PCR-RFLP was used for genotype analyses. In brief, PCR reactions were performed in a total volume of 25 μl, containing 50 ng of genomic DNA and specific primers (forward 5′- ATA CAG ATT CAG TTT TAC CTC C -3′ and reverse 5′- CTC TAG TGA GGT AAA ACT GGA A -3). PCR amplification protocol was set as 95°C for 5 min, followed by 35 cycles of 95°C for 30 sec, 60°C for 30 sec, and 72°C for 1 min, and one last elongation step at 72°C for 7 min. A 312 bp (base-pair) size of PCR product was generated and genotyping was performed by restriction enzyme DraI (New England Biolabs) in a total volume of 20 μl at 37°C for overnight.

The digested fragments were ascertained by agarose gel electrophoresis, and stained with ethidium bromide.

Statistical Analysis

Adherence to Hardy–Weinberg equilibrium was tested to ensure data quality by using a chi-square test. Also, we used the chi-square test to analyze whether the *TDP1* SNP (rs28365054) had an association with TS under all models of inheritance except for the additive model. A Cochran-Armitage trend test was used to test whether this SNP had an association with TS in the additive model. Statistical analysis of the odds ratios (OR) and 95% confidence interval (CI) were carried out with SPSS version 10.0 software (Chicago, IL) based on the allele and genotype frequencies. Only P values below 0.05 were considered as significant.

RESULTS

To ensure data quality, we evaluated whether the distribution of genotype frequencies in the case and control groups was in Hardy–Weinberg equilibrium. The distribution of the genotype frequencies in the control group ($P = 0.30$) but not in the case group ($P = 0.01$) was consistent with the Hardy–Weinberg equilibrium (Table 2). These results indicated that the data were of good quality and could be used for association studies (22).

In order to know whether the *TDP1* SNP rs28365054 was associated with TS, the chi-square test was used because the mode of inheritance for this SNP was unknown and this test is a model-free approach. The results (Table 2) showed that this SNP had an association ($P = 0.0402$) with TS. The AG genotype was a risk factor for TS with an OR of 2.26 (95% CI 1.08–4.72) for the AG versus AA genotype. Next, we tried to ask which mode of inheritance best explained this association. The data (Table 2) showed that there was no model that can best explain this association. Altogether, subjects with the AG genotype at position rs28365054 in the *TDP1* gene tended to have a higher incidence of TS.

DISCUSSION

As we could see from Table 2, tests for Hardy–Weinberg equilibrium (HWE) showed that the distribution of genotype frequencies in the control group did obey HWE. This result indicated that the data were of good quality and could be used for association studies. However, the distribution of the genotype frequencies in the case group ($P < 0.01$) did not obey HWE. Previous studies showed that departure from Hardy–Weinberg equilibrium (DHW) only in the case group can provide additional evidence that there is an association between SNPs and diseases (22). Therefore, a deviation from HWE at rs28365054 in TS patients provided stronger evidence that this SNP had an association with TS.

Table 2 also showed that there were no models (Mendelian inheritance) that can best explain this association. In this study we found that the distribution of genotype frequencies in the TS group did not obey Hardy–Weinberg equilibrium (HWE). Departure from Hardy–Weinberg equilibrium (DHW) may result from failure of the requisite assumptions of HWE (e.g. selection, nonrandom mating, genetic drift, mutation, etc.) (23). Each of these factors will affect the inheritance pattern of this SNP (24). Therefore, more complex models (i.e. non-Mendelian inheritance) may explain this result. For example, epistasis, which could not be used to analyze the data in this study, may explain this association (25). Indeed, it has been demonstrated that *TDP1* and *RAD52* act in the same epistasis group in yeast (26).

So far it is still unclear how the *TDP1* SNP rs28365054 affects the function of TDP1. It has been known that this SNP changes a hydrophobic alanine to a hydrophilic threonine and changes a small amino acid to a medium one (21). Because this SNP is located in the region that encodes LIG III binding domain of *TDP1* (17), it may affect the binding ability of TDP1 to LIG III.

One hypothesis to explain the relationship between *TDP1* SNPs and TS is that *TDP1* SNPs affect genome stability. Chromosomal abnormalities, such as a 9p deletion (27), 18q22.2 deletion (28), t(7;18)(q22;q22.3) (29), t(3;8) (p21.3; q24.1) (30), and a t(1;8)(q21.1;q22.1) (31), have been reported to have an association with TS. TDP1 can repair SSBs (11) and 3′-phosphoglycolate-terminated DNA double-strand breaks (DSBs) (32). In addition, it has been demonstrated that the TDP1-dependent DNA SSB repair pathway suppresses transcription-induced CAG repeat instability (33) and that expanded CAG repeats can lead to Huntington disease (34), myotonic dystrophy type 1 (35), and several types of spinocerebellar ataxias (SCAs) (36). Because TDP1 has the ability to repair DSBs and maintain genome stability, and chromosomal abnormalities are associated with TS, these experiment results may explain why *TDP1* SNP (rs28365054) had an association with TS.

Besides affecting DNA repair capacity, *TDP1* SNPs may affect neuronal proliferation in TS brain during neurodevelopment. In yeast *TDP1* mutation results in unrepaired oxidative DNA damage, which induced an ATM/tel1-dependent apoptotic-like process (37). Another experiment shows that mutation of serine 81 to alanine does not affect TDP1 activity but decreases its stability. Accordingly, $TDP1^{S81A}$ reduces the ability of TDP1 to facilitate cell survival after genotoxic stress (38). TS is a neurodevelopmental disorder. Brain MR images showed that the lenticular nucleus and caudate nuclei of basal ganglia of TS are smaller than those of normal persons

TABLE 2. Genotype and Allele Frequencies of *TDP1* Polymorphism rs28365054 (c.400G>A, Ala134Thr) in TS Patients and Controls

Test	Genotype/allele	Cases number (%)	HWE[a]	Controls number (%)	HWE	*P* value	OR (95% CI)
Genotypic association	GG	32 (26.23)	**0.01**[b]	36 (33.96)	0.30[b]	**0.0402**[b]	1.28 (0.70–2.33)
	GA	74 (60.66)		47 (44.34)			2.26 (1.08–4.72)
	AA	16 (13.11)		23 (21.70)			1
Additive model	GG	32 (26.23)		36 (33.96)		0.9535[c]	
	GA	74 (60.66)		47 (44.34)			
	AA	16 (13.11)		23 (21.70)			
Dominant model	AA+GA	90 (73.77)		70 (66.04)		0.2031[b]	
	GG	32 (26.23)		36 (33.96)			
Recessive model	AA	16 (13.11)		23 (21.70)		0.0860[b]	
	GG+GA	106 (86.89)		83 (78.30)			
Allelic association	G	138 (56.56)		119 (56.36)		n/a[d]	1.02 (0.70–1.47)
	A	106 (43.44)		93 (43.64)			1

[a]HWE: *P* values of the Hardy–Weinberg equilibrium test.
[b]*P* values were calculated using the χ^2 test. *P* values less than 0.05 are highlighted in bold.
[c]*P* value was calculated using the Cochran–Armitage test.
[d]Violate the assumption of the allelic association test (multiplicative model) due to departures from Hardy–Weinberg equilibrium.
OR: odds ratio; 95% CI: 95% confidence interval.

(39–41) and TS patients have structural abnormalities in the substantia nigra (10). The results of these experiments imply that this SNP may affect neuronal proliferation in TS brain during neurodevelopment.

The other hypothesis to explain the relationship between TDP1 SNPs and TS is that *TDP1* SNPs may only play a role in the development of cerebellums in TS patients. Previous studies showed that *TDP1* plays a major role in DNA repair in nonproliferating cells. TDP1 can repair SSBs resulting from oxidative attack by endogenous ROS (11). Although *TDP1* expresses almost equally throughout the central nervous system, mutation (17) or knockout (18) of this gene selectively affects cerebellums. In addition, TS patients have smaller cerebellums than normal children (16), and the result of this study demonstrated that *TDP1* gene SNP (rs28365054) had an association with TS. These experimental results imply that this SNP may play a role in the development of cerebellums in TS patients.

TS is a polygenic disorder (42). This study showed that the *TDP1* SNP (rs28365054) had an association with TS. Therefore, this SNP may interact with other genes to affect the development of TS. First, this SNP may interact with genes that involved in DNA repair pathways. It has been showed that TDP1 interacts with XRCC1 to repair damaged DNA (43) and that a genetic variation (Arg>Gln at codon 399) in the DNA repair gene XRCC1 has an association with TS (19). These findings partly support the hypothesis that the dysregulation of DNA repair pathways is involved in the pathogenesis of TS. Second, dysregulation of DNA repair pathways may result in dysfunction of immune system in TS. Some experiments demonstrated that dysregulation or dysfunction of immune system may be the etiology of TS. In the sera of TS patients antineuronal antibodies could be detected (44). In addition, it has been reported that the interleukin 1 receptor antagonist gene (*IL-1RN*), has an association with TS (45). The interleukin-1 receptor antagonist (IL-1RA) is an endogenous inhibitor of interleukin 1 (IL-1) and modulates a variety of IL-1-related immune and inflammatory responses. DNA breaks mixed with nuclear proteins are strong immunogens (46). Therefore, efficiency of DNA repair in cells is a key factor for inducing immune and inflammatory responses.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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