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ORIGINAL RESEARCH

Lack of Association of *FLT3* rs2504235 and Absence of *SLITRK1* var321 in Patients with Tic Disorders from Guangdong Province, China

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Objective: Tic disorders (TDs) are highly polygenic and heritable neurodevelopmental disorders characterized by the presence of movements (motor tics) and/or vocalizations (phonic tics). *SLITRK1* is a pathogenic variation of TD, and in a recent genome-wide association study in those of European ancestry, a single-nucleotide polymorphism (rs2504235) in the *FLT3* gene was significantly associated with TDs/Tourette's syndrome. However, these results need to be proved in different populations. This study aimed to determine whether these two genetic variants were also associated with TD patients in south China.

Methods: A total of 116 child TD patients and 114 healthy controls were included. All children underwent peripheral blood sampling for genomic DNA extraction. Gene fragments with two single-nucleotide polymorphisms were amplified by PCR and sequenced by Sanger chain termination before genotype analysis.

Results: *SLITRK1* var321 was not observed in any of the TD patients or controls. No significant difference was observed in allelic frequencies or genotypic distributions of rs2504235 between TD patients and controls.

Conclusion: Our results provide no evidence to support the previous conclusion that *SLITRK1* var321 plays a major role in TDs, and *FLT3* rs2504235 was not significantly associated with TDs in our cohort.

Keywords: tic disorders, Tourette's syndrome, *SLITRK1*, SLIT and NTRK like family member 1, *FLT3*, Fms related receptor tyrosine kinase 3

Introduction

Tic disorders (TDs) are childhood-onset neurodevelopmental disorders characterized by sudden, rapid, recurrent, arrhythmic movements (motor tics) and/or vocalizations (phonic tics). TDs are more common in boys, with a male: female ratio of 3–4:1.[1,2] Tics most commonly involve the head, neck, and upper body, most begin before the age of 18 years, and they can be suppressed for variable periods.[3] TDs typically have an onset at age 6–8 years,[4] and the mean age of peak tic severity is 10±2.4 years.[5,6]

In the DSM-5,[6] ICD-10,[7] and CCMD-3,[8] TDs are classified into three types: transient/provisional TD (TTD/PTD), chronic TD (CTD), and Tourette's syndrome (TS). CTD is then divided into chronic motor TD (CMTD) and chronic phonic TD (CPTD). According to existing classifications, TS varies from CMTD in only one way: in TS, it is a requirement that both multiple motor tics and at least one phonic tic be present, while in CMTD it is required that only motor tics be present.[6,7]

Recent studies have estimated that the prevalence of TS in children in the general population is 0.3%–0.9%,[1,9–11] while that of CMTD is 0.5%–1.65%.[1,9–11] Due to this additional criterion regarding the added presence of phonic tics, TS

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in the community is rarer than CMTD.[12,13] Accordingly, the prevalence of PTD, the mildest form of all primary TDs is much higher — 5%–47%.[14] TD is often comorbid with other psychiatric conditions, mainly attention-deficit/hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD) and non-OCD anxiety disorders, mood disorders, disruptive behavior disorders, pervasive developmental disorders, and problems with sleep.[15–18]

Several decades of investigation have confirmed that TDs are highly polygenic and heritable, with multiple genetic variants widely distributed throughout the genome. Multiple candidate genes (eg, *DRD2*, *DRD4*, *5-HT2C*, *SERTSLITRK1*, *IMMP2L*, *CNTNAP2*, *HDC*, *PNKD*, and *NLGN4*) in multiple neural systems, including dopaminergic, serotonergic, and histaminergic pathways, have been identified through linkage studies and structural genomic aberrations, in which very rare genetic variants with large effects were found in TD patients and families.[14,19–22]

Recently, genome-wide association studies (GWASs) and gene-based analyses of the largest samples thus far of TD/TS patients of European ancestry showed that the *FLT3* gene was significantly associated postcorrection with TDs on 18,079 gene tests (P=8.9×10^{-7}). The most significant single-nucleotide polymorphism (SNP) in the *FLT3* locus, rs2504235 (ENST00000241453.12:c.1206–1461T>C), was the only SNP to surpass the GW significance threshold (OR 1.16, P=2.1×10^{-8}) on primary meta-analysis and was significantly associated with *FLT3* expression in both the cerebellum (P=6.5×10^{-10}) and cerebral cortex (P=2.6×10^{-11}).[23]

We are interested in whether rs2504235 has a significant association with TDs in Chinese, so we screened it in TD patients of Guangdong Province China. We also screened another pathogenic mutation in the 3′UTR of *SLITRK1* var321 (ENST00000674365.1:c.*689G>T), which alters the binding of *SLITRK1* mRNA to microRNA hsa-miR189 and affects neurite outgrowth.[24] Several replication studies have investigated the involvement of *SLITRK1* var321 in TS pathogenesis, though its role has not been elucidated.[25–33] In this study, 116 patients with TDs were investigated to explore the potential role of *SLITRK1* var321 and *FLT3* in disease pathogenesis.

Methods

Subjects

A total of 116 unrelated children (93 boys and 23 girls) with TDs were enrolled in this study. Of these, 33 had only TS, 33 only TTD, and 50 only CTD. They were evaluated at Guangzhou Women and Children's Medical Center and the First Affiliated Hospital of Jinan University, Guangzhou. A total of 114 unrelated healthy control subjects matched in age and sex were recruited from individuals who underwent a regular health examination during the same period as the control group. We implemented this study design and all related procedures in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. All parents signed an informed-consent document before blood tests were performed. TD diagnosis followed the criteria of the DSM-5,[6] ICD-10,[7] and CCMD-3.[8] The age at which first tics presented was 2–15 (7.61±2.51). All children underwent peripheral blood sampling for genotype analysis.

Genetic Analysis

Genomic DNA was prepared from peripheral blood using a whole-blood genomic DNA minikit (SimGen, Hangzhou, China). PCR tests were performed with a total volume of 30 μL containing 50–100 ng genomic DNA, 0.6 μL of each 10 μM primer (Table 1), 12.5 μL premix Taq (Takara Taq version 2.0). PCR amplification was performed in a programmable thermal cycler system (Eppendorf Mastercycler nexus). Cycling conditions for PCRs were set at one cycle at 94°C for 5 minutes, 35 cycles at 94°C for 30 seconds, 62°C for 30 seconds, and 72°C for 40 seconds, and one final cycle for extension at 72°C for 10 minutes. PCR products were loaded into 2% agarose gel containing GoldView (Solarbio) for

Table 1 Primers for *FLT3* and *SLITRK1*

Fragment	Forward (5′→3′)	Reverse (5′→3′)
FLT3	GCAGCCCTATGACTTCCCGT	GGTTCACCGTGTTAGCCAGG
SLITRK1 var321	CTCTTACCTGATAAGTTCCATCG	GCAGCCTAAGCACTAGAGTGAC

electrophoresis. Amplified DNA fragments were sent to Guangzhou Tianyihuiyuan Gene Technology for Sanger sequencing (Figure 1).

Statistical Methods

SPSS 20.0 was used for data analysis. Genotype and allele frequencies are expressed as percentages. The fitness of the genotype and allele was tested using the Hardy-Weinberg equilibrium test,[34,35] and polymorphism differences between TD patients and control groups were analyzed using single-marker χ^2 tests. The genotype quality controls were minor-allele frequency (MAF) >0.1, Hardy–Weinberg equilibrium >0.001, and call ratio >95%. The threshold for all statistical tests was set as 0.05.

Results

Genetic Distribution

The Hardy–Weinberg equilibrium results showed that the genetic distribution of all subjects reached equilibrium (P=0.199, P>0.05; Table 2), proving that the experimental population came from the same Mendelian population.

Baseline Clinical Characteristics

The male:female ratio for the cohort was 4.04:1. Mean age at onset was 7.61±2.51 years, with mean age of boys (7.59 ±2.56 years) similar to girls (7.70±2.36; P=0.859). Mean age of TTD patients (6.67±2.38 years) was significantly lower than the mean age of CTD (7.98±2.46; P=0.019) and TS (8.00±2.54; P=0.030). Of the 54 children aged >6 years who underwent psychological evaluation, 24 were diagnosed with ADHD (TTD 5, CTD 9, TS 10). Five cases of TTD, seven of CTD, and eleven of TS were assessed for mood, including five cases of combined anxiety (CTD 2, TS 3), three of depression (CTD 1, TS 2), and six of compulsion (TTD 1, CTD 1, TS 4).

Association Between rs2504235 and TD

Genotypic distributions of rs2504235 within *FLT3* were 63.79% (C/C), 35.34% (C/T), and 0.87% (T/T). Mean age of C/T (8.37±2.70) patients was significantly older than the mean age of C/C (7.24±2.30) patients (P=0.020). In children with TDs, we found no association between TD classification, genotypic distribution of rs2504235, or sex (P>0.05). No significant differences were observed in allelic frequencies or genotypic distribution of rs2504235 between patients and controls (P=0.157, P=0.199). MAF of rs2504235 was 0.185 (43 of 232) in the TD cohort and 0.189 (43 of 228) in controls, with no significant difference (P>0.05). Furthermore, we did not observe any novel nonsynonymous variation in the region covered. Results of association analyses between patients and controls are shown in Table 3.

Association Between *SLITRK1* var321 and TDs

Genotypic distribution of *SLITRK1* var321 (NM_052910.2:c.*689G>A) was 100 (G/G) among the 116 patients with TDs. This suggested that *SLITRK1* var321 was not a major component of the pathogenesis of TDs.

Discussion

Only two GWASs on TS have been published,[23,36] with no SNPs meeting the criteria for GW significance ($p<5\times10^{-8}$) and one reaching marginal GW significance (rs7868992, located in an intronic region of *COL27A1*; $P=1.85\times10^{-6}$) in 1,285 cases and 4,964 ancestry-matched controls of European ancestry, including two European-derived population isolates.[36] The most recent TS GWAS[23] with the largest sample (4,819 cases, 9,488 controls) identified one significant GW locus within *FLT3* on chromosome 13, rs2504235 (OR 1.16, $P=2.13\times10^{-8}$). It was also significantly associated with *FLT3* expression in both in the cerebellum and cerebral cortex.[23] FLT3, a member of the type III receptor tyrosine—kinase family, is expressed almost exclusively in the hematopoietic compartment. FLT3 induces dimerization and activation of its intrinsic tyrosine-kinase activity. Activation of FLT3 mediates cell survival, cell proliferation, and differentiation of hematopoietic progenitor cells. FLT3 activity has been implicated in several diseases, most prominently acute myeloid leukemia, where around a third of patients carry an activating mutant of *FLT3*. Overactivity of FLT3 has also been implicated in autoimmune diseases, such as rheumatoid arthritis.[37]

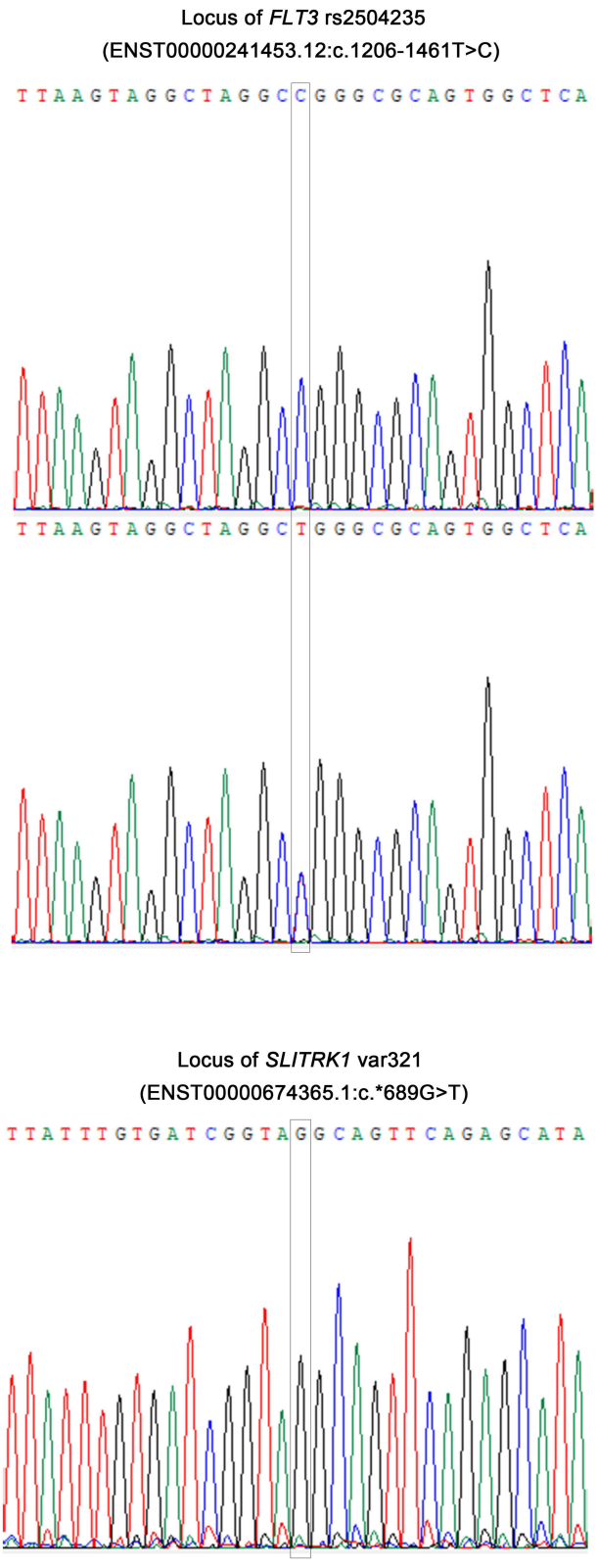

Figure 1 Sanger sequencing chromatograms of the targeted DNA fragments: locus of *FLT3* rs2504235 and *SLITRK1* var321.

Our results showed that there was no SNP-frequency difference between TD patients and controls, similar to the results of replication research on rs2504235 with significant GW associations in an independent case–control replication sample from Iceland (706 cases, 6,068 controls).[23] One of the possible reasons is the genetic background and population

Table 2 Hardy–Weinberg equilibrium test results

	n	Genotypic distribution of rs2504235			Allele frequency of rs2504235	
		G/G	G/A	A/A	G	A
Actual frequency	116	74 (63.79%)	41 (35.34%)	1 (0.87%)	189 (81.47%)	43 (18.53%)
Theoretical frequency	116	76.99 (66.37%)	17.52 (15.10%)	3.98 (3.43%)		

Table 3 Association analysis of patients and controls

SNP	Allele (major/minor)	Minor-allele frequency			Genotypic distribution[a] of rs2504235		
		Patients	Controls	*P*[b]	Patients	Controls	*P*[b]
rs2504235	G/A	0.185	0.189	0.157	74/41/1	77/31/6	0.199

Notes: [a]Number of participants (major homo/hetero/minor homo); [b]patients vs controls (χ^2 test).
Abbreviation: SNP, single-nucleotide polymorphism.

characteristics between Chinese and Europeans. In data from the China Metabolic Analytics Project, the MAF of rs2504235 is 0.179 (http://www.mbiobank.com/search/?searchContent=rs2504235), close to our results of 0.185 (43 of 232) in the TD cohort, 0.189 (43 of 228) in controls, and 0.168 in East Asians in the 1,000 Genomes Project. This MAF value was lower than the 0.38 obtained in a second GWAS.[23] Another possible reason is that rs2504235 has no significant association with *FLT3* expression in the Chinese population. Unfortunately, we cannot collect expression-level data on genes, including *FLT3*, in the brains of Chinese TD patients. As we know, there have been no reports on *FLT3* being associated with any TD and its expression and function in brain tissue. Consequently, future larger-scale GWASs in the Chinese population should aid in identifying individual genes underlying susceptibility to TS.

In 2005, Abelson et al screened 174 unrelated patients with TS and identified a noncoding missense variant (ENST00000674365.1:c.*689G>T, or c.2977+2067G>A), named var321, in the 3′UTR,[24] and *SLITRK1* was considered one of TS candidate genes. Since that initial study[24] several replication studies have investigated the involvement of *SLITRK1* var321 in TS pathogenesis, but with complex results. Several studies did not find any involvement.[25–33] However, in a study on Ashkenazi Jewish patients with TS, five unrelated parents of Ashkenazi Jewish ancestry had var321, and only three transmitted it to their children.[38] In addition, a study on screened samples of TS patients and their families found var321 in parents of two unrelated TS probands, but no transmission of the variant to probands. Only one of those parents was diagnosed with TS. As such, the prevalence of var321 in all TS individuals was 0.1% (one of 1,048).[39] In this study, we did not observe *SLITRK1* var321 in the investigated TD cohort. However, considering our small study sample and the low MAF of these two variants, it is necessary to expand the sample size to further evaluate whether *SLITRK1* var321 and *FLT3* rs2504235 variants are related to TD in the Chinese population.

Conclusion

Our results suggest that *SLITRK1* var321 is unlikely to play a major role in TD in the Chinese population. *FLT3* rs2504235 was not significantly associated with TD in our cohort.

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Disclosure

The authors report no potential conflicts of interest in this work.

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