

Family-Based Analysis Combined with Case–Controls Study Implicate Roles of PCNT in Tourette Syndrome

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Objective: Tourette syndrome (TS) is a childhood-onset neuro-developmental disorder and the genetic factors play an important role in its etiology. As pericentrin (PCNT) binds to disruption-in-schizophrenia 1 (DISC1) and is a risk factor for many mental illnesses, we aimed to investigate the effect of PCNT on TS in the Chinese Han population.

Methods: Five tag single nucleotide polymorphisms (SNPs) (rs17371795, rs2839227, rs2839228, rs6518291 and rs9983522) in *PCNT* were screened in 407 TS nuclear family trios and 506 healthy persons by the TaqMan assays real-time. A common case–control study was designed to recognize differences in the genetic distributions. Additionally, we conducted a family based association study including transmission disequilibrium test, haplotype relative risk, and haplotype-based haplotype relative risk for these SNPs.

Results: The allele frequencies revealed a significant difference of rs17371795, rs2839227 and rs2839228 between TS patients and controls (for rs17371795: $P=0.002$, $OR=0.691$, 95% $CI=0.547–0.874$; for rs2839227: $P=0.001$, $OR=0.682$, 95% $CI=0.540–0.860$; for rs2839228: $P=0.028$, $OR=0.775$, 95% $CI=0.618–0.973$) and genotypic distributions showed a positive association only in rs17371795 and rs2839227 (for rs17371795: $P=0.010$; for rs2839227: $P=0.008$). Moreover, only rs2839227 remained significant after Bonferroni correction ($P<0.01$).

Conclusion: Our study suggested genetic variability at the PCNT locus may be associated with TS risk in the Chinese Han population.

Keywords: Tourette syndrome, PCNT, TDT, HRR, case-control study

Introduction

Tourette syndrome (TS) is a common developmental neuropsychiatric disorder characterized by involuntary repetitive motor or vocal tics which begins at early childhood and lasts for more than one year.¹ To date, many researchers have shown that TS is related to a variety of environmental factors such as maternal smoking and low birth weight,² but the kind of factors that could explain the special performance and severity of TS have not been found. Twins, candidate genes, and similar studies have indicated important findings about the obvious genetic susceptibility of TS.³ Although great progress has been made in studies of to explain the etiopathogenesis of TS, including genetic, neurodevelopmental, neurotransmitter, and neuroimmunological hypotheses, the clear development of TS is poorly unknown.

There is compelling evidence indicating that TS is a genetic disorder with complex inheritance and involves the interplay of complex polygenic influences and environmental risk factors operating on brain developmental processes, such as an aberrant distribution of interneurons in the cortico-striatal–thalamo-cortical circuit.⁴ Identification

of those disease-related candidate genes will not only catapult our understanding of the biological pathways and mechanisms leading to TS, but will also inform the molecular diagnostics and novel therapeutic interventions that are needed to make progress in this rapidly growing field. Although many candidate genes including *DRD1-DRD5*, *DAT*, *COMT*, *MAO*, *5-HT*, *HDC*, *NLGN4*, and *NRXN1* were associated with TS,⁵⁻¹² none has been found as causative TS susceptibility due to genetic heterogeneity.

As a large centrosomal coiled-coil protein, pericentrin (PCNT) affects interneuron migratory cell behavior autonomously and disrupts proper distribution of dLGE-derived olfactory bulb interneurons,¹³ suggesting it plays an important role in brain development. PCNT can interact with disrupted-in-schizophrenia 1 (DISC1) and fasciculation and elongation protein-zeta 1 (FEZ1). DISC1 participates in neurite growth by its interaction with FEZ1; moreover, the PCNT-binding region of DISC1 overlaps with the interacting region with FEZ1,¹⁴ which has been implicated in schizophrenia in interneuron development. Recent studies have proved that polymorphisms of PCNT have a positive effect on the development of mental diseases such as schizophrenia, major depressive disorder (MDD), and bipolar disorder.^{15,16} Given that children with TS often suffer from a variety of psychiatric illnesses, such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety disorders, depression, and other behavioral problems which may share common causing genes, we hypothesized that PCNT may be involved in the development of TS, which is also a neurodevelopmental disorders starting in childhood. Therefore, our study is to assess the potential relationship between PCNT and TS in the Chinese Han population.

Materials and Methods

Subjects

All participants in the study were recruited between October 2014 and November 2017 at the Affiliated Hospital of Qingdao University and Linyi People's Hospital in China. This project was approved by the Human Ethics Committee of Affiliated Hospital of Qingdao University, and the protocols were in accordance with the Declaration of Helsinki. Written informed consents were acquired from all participants or their legal guardians. All patients were independently diagnosed by two experienced developmental behavior pediatrics specialist and psychiatrist according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition criteria. We recruited

407 TS nuclear family trios and 506 controls, among them TS patients comprised 265 (65.59%) males and 142 (34.89%) females aged from 6 to 15 and controls comprised 384 (75.89%) males and 122 (24.11%) females aged from 22 to 45. Because TS is an early-onset mental disorder, the age is excluded as a matching factor. So the 8.87 ± 3.24 ages of cases and controls were 24.58 ± 5.60 , respectively. The controls were excluded from psychiatric disorders, history of inherited diseases and so on.

Genotyping Analysis

The DNA extraction kit (Qiagen, Hilden, Germany) was applied to extract genomic DNA from 200 μ L of EDTA-buffered peripheral venous blood. The genetic distribution of the five tag single nucleotide polymorphisms (SNPs) in PCNT (rs17371795, rs2839227, rs2839228, rs6518291 and rs9983522) were screened by the TaqMan assays Real-Time polymerase chain reaction (PCR). The design of TaqMan probes and primers were completed by Applied Biosystems of Life Technologies and the primer sequences were as follow: for rs17371795, 5'-CTGTGTTGGCCAGCATGGT-3'(F) and 5'-CGGCCTGGCTGGTGAAG-3'(R); for rs2839227, 5'-GAACAGTTGAAGTGGCATTTCCT-3'(F) and 5'-GAATC AAGGCTGGACAGATGTCT-3'(R); for rs2839228, 5'-CGAGAAATTCAGTGC GGAACA-3'(F) and 5'-GTCAAA ATCGTTTGGTGAAGAGAGT-3'(R); for rs6518291, 5'-TGTTGCCTGGTGTGTC ACTGA-3'(F) and 5'-GACATCG GATCTGCCACAGA-3'(R); for rs9983522, 5'-AGCTG CGTATCGAGCACTCA-3'(F) and 5'-CGCTGTTTCTCCC TCTCTCT-3'(R). In a 25- μ L PCR reaction mixture were included 1.25 μ L 20 \times SNP Genotyping Assay, 12.5 μ L 2 \times PCR Master Mix, and 11.25 μ L DNA in DNase-free water and a C1000TM thermal cycler system was used to perform PCR amplification with following conditions: 95°C for 3 min, followed by 45 cycles of 95°C for 15 s and 60°C for 1 min. All steps were carried out following the instructions, and we could detect the fluorescent signal from VIC/FAM-labeled probes in each cycle. Bio-Rad CFX manager 3.0 software was used to analysis genotype discrimination.

Statistical Analysis

All the data were analyzed using statistical software package SPSS 26.0. First, Pearson's chi-square test provided a method to compare the differences in genotypic and allelic frequencies between patients and controls. Then the transmission disequilibrium test (TDT), the haplotype relative risk (HRR), and the haplotype-based haplotype relative risk (HHRR) were applied to assess the genetic

association of TS nuclear family trios; 95% confidence intervals (CIs) and odds ratios (ORs) were used to show the relative risk degree. Furthermore, all of the statistical significance was set at $P < 0.05$. Lastly, a Bonferroni correction test was carried out to increase the precision of the results and P values < 0.01 were considered significant.

Result

Case–Control Study

All participants were divided into cases (407 TS individuals, 265 males and 142 females, mean age 8.87 ± 3.24 years) and controls (506 healthy subjects, 384 males and 122 females, mean age 24.58 ± 5.60 years). All controls followed the laws of Hardy-Weinberg equilibrium (rs17371795, $\chi^2 = 3.048$, $P = 0.081$; rs2839227, $\chi^2 = 0.706$, $P = 0.294$; rs2839228, $\chi^2 = 0.232$, $I = 0.629$; rs6518291, $\chi^2 = 0.384$, $I = 0.535$; rs9983522, $\chi^2 = 0.059$, $P = 0.807$).

The allelic frequencies were analyzed by Pearson's chi-square test revealing a significant difference of rs17371795, rs2839227, and rs2839228 between TS patients and controls. Moreover, rs2839227 maintained significance after Bonferroni correction ($P < 0.01$) while the other two were negative. In addition, genotypic distributions also showed positive association with TS including rs17371795 and rs2839227 and both of them failed to remain significant after Bonferroni correction ($P < 0.01$). The rest of the SNPs were not identified to be different in both groups. The results indicated that SNPs (rs17371795, rs2839227, and rs2839228) in *PCNT* may play a potential role in the pathology of TS. All the results are shown in Table 1.

Family-Based Study

A family-based study was carried out to further validate the possible genetic association between *PCNT* and TS in 407 nuclear families through TDT, HRR, and HHRR. No positive statistics given by TDT and HRR showed evidence for an association between the *PCNT* SNPs studied and 407 trios. HHRR was employed to assess the efficiency of the analyses and exhibited the same results. All results are shown in Tables 2–4.

Discussion

TS is a complex neuropsychiatric disease possibly resulting from an interaction between genetic, biological, psychological, and environmental factors,^{12,17} with onset ratio about 3–4:1 in male and female.¹⁸ Children with TS often present a variety of comorbidity, such as attention ADHD,

OCD, dyslexia, anxiety disorders, sleep abnormalities, depression, and other behavioral problems that can cause impairments including distress, social impact, and interference with activities.^{19–22} However, neither the genetic nor other reported factors have been expounded clearly enough to help with diagnosis or treatment for TS. Considering that TS is usually accompanied with a lot of comorbidity, recent research has paid more attention to some candidate genes of these comorbidities, such as *PCNT*, a candidate gene of dyslexia.²³

Located at 21q22.3, *PCNT* encodes the pericentrin protein extensively expressed in the centrosomes and plays an important role for the normal functioning of the centrosomes and the cytoskeleton, and for cell-cycle progression.²⁴ A potential role for *PCNT* is bound to the *DISC1* in the etiology of nervous disorders.²⁵ A large number of studies have showed that *DISC1* was strongly associated with many psychiatry such as schizophrenia, MDD, and bipolar disorder.^{26–28} Miyoshi and his colleagues have reported that the *DISC1-PCNT* interactions might be implicated in the pathophysiology of mental illness by their putative effect on centrosomal function.²⁵ Anitha et al. have indicated that mRNA expression of *PCNT* in peripheral blood lymphocytes and in the brain in patients with bipolar disorder and MDD was obviously higher than in controls, suggesting that *PCNT* may be involved in the pathophysiology of bipolar disorder.¹⁶ Additionally, rs2249057 polymorphism in *PCNT* was associated with schizophrenia.²⁸ A Japanese study has shown that polymorphisms of *PCNT* were associated with MDD in the Japanese population.¹⁵ Another team found that increased expression of *PCNT* was associated with bipolar disorder in Japan.¹⁶ These studies suggested a potential link between *PCNT* and psychiatric disorders. As a result, *PCNT* has become the focus of many psychiatric diseases.

Recently, Endoh-Yamagami et al. have indicated that *PCNT* is required for proper migration of olfactory bulb interneurons, which provided a basis for the association of *PCNT* with interneuron defects in human schizophrenia. They also found that *PCNT* is necessary for proper positioning of dopaminergic interneurons and GABAergic interneurons in the olfactory bulb.¹³ At the same time, *PCNT* mutant mice have shown a reduction in olfactory bulbs and abnormalities of GABAergic interneurons in the prefrontal cortex. On the other hand, as GABA was rich in the central system as a central inhibitory neurotransmitter, clonazepam can improve tic symptoms in some TS patients, possibly by increasing GABA activity.²⁹ Therefore, we suspect that *PCNT* mutation might lead to tic disorder due to abnormal GABA interneurons

Table 1 Genotype and Allele Frequencies for Cases versus Controls

Gene Loci	Group	Genotype Frequency (%)			Allele Frequency (%)	
		AA	AG	GG	A	G
rs17371795	Case	251 (61.67)	132 (32.43)	24 (5.90)	634 (77.89)	180 (22.11)
	Control	359 (70.95)	128 (25.30)	19 (3.75)	846 (83.60)	166 (16.40)
	χ^2	9.137			9.577	
	P	0.010			0.002	
	OR				0.691	
	95% CI				0.547–0.874	
rs2839227		AA	AG	GG	A	G
	Case	244 (59.95)	141 (34.64)	22 (5.41)	629 (77.27)	185(22.73)
	Control	336 (66.40)	160 (31.62)	10 (1.98)	843 (83.30)	169(16.70)
	χ^2	9.671			10.488	
	P	0.008			0.001	
	OR				0.682	
	95% CI				0.540–0.860	
rs2839228		CC	GC	GG	C	G
	Case	24 (5.90)	138 (33.91)	245 (60.19)	186 (22.85)	628(77.15)
	Control	16 (3.16)	157 (31.03)	333 (65.81)	189 (18.68)	823(81.32)
	χ^2	5.552			4.817	
	P	0.062			0.028	
	OR				0.775	
	95% CI				0.618–0.973	
rs6518291		AA	AG	GG	A	G
	Case	252 (61.92)	135 (33.17)	20 (4.91)	639 (84.16)	175 (15.84)
	Control	335 (66.21)	156 (30.83)	15 (2.96)	826 (81.62)	186 (18.38)
	χ^2	3.269			2.767	
	P	0.195			0.096	
	OR				0.822	
	95% CI				0.653–1.036	
rs9983522		AA	AG	GG	A	G
	Case	24 (5.90)	129 (31.70)	254 (62.40)	179 (32.04)	637 (67.96)
	Control	17 (3.36)	156 (30.83)	333 (65.81)	190 (18.77)	822 (81.23)
	χ^2	3.694			2.478	
	P	0.158			0.115	
	OR				1.202	
	95% CI				0.956–1.512	

in the prefrontal cortex, suggesting that *PCNT* may be associated with TS through GABAergic interneurons.

To verify this hypothesis, we explored five polymorphisms in *PCNT* in the Chinese Han population by combining a case-control study and a family-based association study, which could optimize the design and provide a more reliable result. In our study, allelic frequencies showed a significant difference of rs17371795, rs2839227, and rs2839228 in the case-control study, especially

rs2839227 maintains significant after Bonferroni correction ($P < 0.01$), which infers that *PCNT* might be a risk factor for the development of TS.

As far as we know, this is the first report of an association between *PCNT* and TS in the Chinese Han population. The results of allelic frequencies and genotypic distributions indicate an obvious difference in patients than controls, which suggests that *PCNT* may be a potential susceptibility gene for TS. Nevertheless,

Table 2 The TDT Test Results of Five Genetic Loci in 407 Trios

Non-Transmitted Allele	rs17371795			rs2839227			rs2839228			rs6518291			rs9983522		
		A	G		A	G		G	C		A	G		A	G
Transmitted allele	A	512	122	A	506	123	G	500	128	A	518	121	A	45	132
	G	132	48	G	147	38	C	136	50	G	135	40	G	127	510
TDT result															
χ^2	0.394			0.469			0.242			0.766			0.097		
P	0.572			0.161			0.667			0.417			0.804		
OR	1.526			1.063			1.436			1.268			1.369		
95% CI	1.039–2.242			0.708–1.598			0.984–2.096			0.846–1.901			0.927–2.022		

Table 3 The HRR Results of the Five Genetic Loci in 407 Trios

Group	rs17371795		rs2839227		rs2839228		rs6518291		rs9983522	
	G(+)	G(-)	G(+)	G(-)	C(+)	C(-)	G(+)	G(-)	A(+)	A(-)
Transmitted genotype	155	252	148	259	163	244	149	258	158	249
Non-transmitted genotype	156	251	163	244	162	245	155	252	153	254
Results (χ^2 , P)	0.005	0.942	1.717	0.279	0.005	0.943	0.189	0.664	0.130	0.718
OR (95% CI)	1.010	0.762–1.341	1.169	0.881–1.551	0.990	0.748–1.310	1.065	0.802–1.415	0.949	0.715–1.260

Table 4 The HHRR Results of the Five Genetic Loci in 407 Trios

Group	rs17371795		rs2839227		rs2839228		rs6518291		rs9983522	
	A	G	A	G	G	C	A	G	A	G
Transmitted genotype	644	170	653	161	636	178	653	161	172	642
Non-transmitted genotype	634	180	629	185	628	186	639	175	177	637
Results (χ^2 , P)	0.364	0.546	2.114	0.146	0.226	0.634	0.735	0.391	0.091	0.763
OR (95% CI)	0.930	0.734–1.178	0.838	0.661–1.063	0.945	0.748–1.193	0.900	0.708–1.145	0.964	0.761–1.222

there are several limitations in our study, such as ethnic variations and small sample size. Our work may motivate further studies to examine different populations in a larger sample size. Additionally, as a polygenic disease, the etiology of TS may be the result of multiple gene interactions and affected by different kinds of factors. Therefore, more research is needed to further explore the relationship between *PCNT* and TS.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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