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STK39, But Not BST1, HLA-DQB1, and SPPL2B Polymorphism, Is Associated With Han-Chinese Parkinson's Disease in Taiwan

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Abstract: Neuroinflammation is emerging as an important pathway involved in Parkinson's disease (PD) pathogenesis. Herein, we investigated the effect of 4 top PD-associated genetic variants in Caucasians listed on the top risk loci identified by meta-analysis of genome wide-association studies in PDGene database (http://www.pdgene.org/top_results), including serine threonine kinase 39 (*STK39*) rs1955337, bone marrow stromal cell antigen 1 (*BST1*) rs11724635, major histocompatibility complex, class II, DQ beta 1 (*HLA-DQB1*) rs9275326, and signal peptide peptidase-like 2B (*SPPL2B*) rs62120679, by genotyping 596 Han-Chinese patients with PD and 597 age-matched control subjects. Compared with subjects with *STK39* rs1955337 GG genotype, those with TT genotype had a 1.64-fold increased risk of PD (95% confidence interval: 1.13–2.39, $P = 0.010$). The recessive model also demonstrated an increased PD risk in TT genotype (odds ratio: 1.59, 95% confidence interval: 1.12–2.27) compared with the other genotypes (GT + GG). PD patients demonstrate a similar genotypic and allelic frequency in *BST1* rs11724635, *HLA-DQB1* rs9275326, and *SPPL2B* rs62120679 compared with controls. These findings suggested that the *STK39* rs1955337 TT genotype is a risk factor for Han-Chinese patients with PD in Taiwan. The ethnic discrepancies of the other 3 genetic variants may indicate a distinct genetic background of neuroinflammation between PD patients in Han-Chinese and Caucasians.

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Abbreviations: *ATP13A2* = ATPase type 13A2, *BST1* = bone marrow stromal cell antigen 1, *DNAJC13* = dnaJ (Hsp40) homolog, subfamily C, member 13, *DNAJC6* = dnaJ (Hsp40) homolog, subfamily C, member 6, *EIF4G1* = eukaryotic translation initiation factor 4 gamma, 1, EOPD = early-onset Parkinson's disease, GWAS = genome-wide association studies, *HLA-DQB1* = major histocompatibility complex, class II, DQ beta 1, *LRRK2* = leucine-rich repeat kinase 2, *PARK2* = parkin, PD = Parkinson's disease,

PINK1 = PTEN-induced putative kinase 1, *SNCA* = alpha-synuclein, SNP = single-nucleotide polymorphism, *SPP2B* = signal peptide peptidase-like 2B, *STK39* = serine threonine kinase 39, *SYNJI* = synaptotagmin-1, *VPS35* = vacuolar protein sorting-associated protein 35.

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, involving progressive loss of the nigro-striatal dopaminergic neurons. In addition, the pathogenesis of PD is associated with the presence of eosinophilic cytoplasmic inclusion bodies (Lewy bodies) with enrichment of α -synuclein in the ventral midbrain.¹ Alpha-synuclein (*SNCA*), parkin (*PARK2*), PTEN-induced putative kinase 1 (*PINK1*), *DJ-1*, leucine-rich repeat kinase 2 (*LRRK2*) ATPase type 13A2 (*ATP13A2*), vacuolar protein sorting-associated protein 35 (*VPS35*), eukaryotic translation initiation factor 4 gamma, 1 (*EIF4G1*), synaptotagmin-1 (*SYNJI*), dnaJ (Hsp40) homolog, subfamily C, member 6 (*DNAJC6*), and dnaJ (Hsp40) homolog, subfamily C, member 13 (*DNAJC13*) have been identified to be the causative genes for familial and early-onset PD (EOPD).² Owing to the discovery of these causative genes, several pathogenic pathways were identified, which includes accumulation of aberrant or misfolded proteins, mitochondrial dysfunction, increased oxidative stress, impaired ubiquitin-proteasome function, failure of autophagy-lysosome and mitophagy, and deficits in synaptic exocytosis and endocytosis and endosomal trafficking.² Genome-wide association studies (GWAS) also have identified novel genetic associations with PD and these genes are linked to the previously known pathogenic pathways and other less recognized pathways such as neurotransmission, vascular pathology, transcriptional dysregulation, inflammation, as well as immune dysfunction.³

Neuroinflammation and immune dysfunction is emerging as an important pathway involved in PD pathogenesis.^{4–6} A pathway-based analysis of the data from 2 independent GWAS has shown that genes involved in the “regulation of leucocyte/lymphocyte activity” and “cytokine-mediated signaling” confer an increased susceptibility to PD.⁷ Interestingly, epidemiological studies have also shown decreased risk of PD in people who take nonaspirin, nonsteroidal anti-inflammatory drugs.⁸ Several genetic variants involved in inflammatory pathways, such as serine threonine kinase 39 (*STK39*) rs1955337, *BST1* rs11724635, major histocompatibility complex, class II, DQ beta 1 (*HLA-DQB1*) rs9275326, and signal peptide peptidase-like 2B (*SPPL2B*) rs62120679 were listed on the top risk loci by meta-analysis of GWAS in Caucasian.^{9,10} Although a number of genetic studies have shown the association between genetic variants involved in the inflammatory pathways and PD in Caucasian,¹¹ these genetic associations in Han-Chinese are

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limitedly revealed. To provide more evidence for inflammatory gene loci contributing to PD across different populations, we conducted a case-control study by examining the genotypic and allelic frequencies of *STK39* rs1955337, *BST1* rs11724635, *HLA-DQB1* rs9275326, and *SPPL2B* rs62120679 in 596 Taiwanese PD patients and 597 control subjects.

SUBJECTS AND METHODS

Ethics Statement

This study was performed under a protocol approved by the institutional review boards of Chang Gung Memorial Hospital (ethical license No: 102-5614A3) and all examinations were performed after obtaining written informed consents.

Patient Population

Patients with PD were enrolled from the neurological clinics of Chang Gung Memorial Hospital-Linkou Medical Center. Two neurologists specialized in movement disorders (Y-RW and C-MC) confirmed the diagnosis of PD according to the UK PD Society Brain Bank clinical diagnostic criteria.¹² We also recruited age, sex, and ethnic-matched unrelated healthy individuals as controls.

Genetic Analysis

Four genetic loci (*STK39* rs1955337, *BST1* rs11724635, *HLA-DQB1* rs9275326, and *SPPL2B* rs62120679) involved in inflammatory pathways were selected from the top 20 risk loci identified by meta-analysis in PDGene database (http://www.pdgene.org/top_results). The single-nucleotide polymorphism (SNP) genotyping was performed by Agena MassARRAY platform with iPLEX gold chemistry SNP, San Diego, CA). By following the manufacture guide, the specific PCR primer and extension primer sequences (Table 1) were designed with Assay Designer software package (v.4.0). One microliter of Genomic DNA sample (10 ng/ μ L) was applied to multiplex PCR reaction in 5 μ L containing 1 unit of Taq polymerase, 500 nmol of each PCR primer mix, and 2.5 mM of each dNTP (Agena, PCR accessory and enzyme kit). Thermocycling was at 94°C for 4 min followed by 45 cycles of 94°C for 20 s, 56°C for 30 s, and 72°C for 1 min, than 72°C for 3 min. Unincorporated dNTPs were deactivated using 0.3 U of shrimp alkaline phosphatase. The single base extension reaction was using iPLEX enzyme, terminator mix, and extension primer mix followed by 94°C for 30 s followed by 40 cycles of 94°C for 5 s, and 5 inner cycle of 56°C for 5 s and 80°C for 5 s, than 72°C for 3 min Agena, iPLEX gold kit). After the addition of a cation exchange resin to remove residual salt from the reactions, 7 nL

of the purified primer extension reaction was loaded onto a matrix pad of a SpectroCHIP (Agena). SpectroCHIPS were analyzed using a MassARRAY Analyzer 4, and the calling by clustering analysis with TYPER 4.0 software.

Statistical Analysis

The genotypes of all variants in the PD patients and the controls did not deviate from the Hardy Weinberg equilibrium. We used χ^2 test to compare allele and genotypic frequencies between the PD patients and the controls. To account for the multiple comparisons, the 2-tailed *P* values <0.0125 were judged to be statistically significant using Bonferroni correction. For the recessive model, we had a power greater than 0.8 to detect association when the odds ratio was greater than 1.5.

RESULTS

A total of 1193 subjects, including 596 PD patients (female/male: 272/324) with the current age of 68.68 \pm 10.82 years, and 597 normal controls (female/male: 315/282), were recruited. Only 1 proband with familial PD in the same family was included. The mean age at onset of PD symptoms was 62.8 \pm 11.1 years (range 19–93). The mean age of recruitment of controls was 60.0 \pm 12.7 years (range 17–89). *STK39* rs1955337 TT genotype showed a higher prevalence in PD than GG genotype did (odds ratio [OR] = 1.64, 95% CI: 1.13–2.39, *P* = 0.010, Table 2). This finding was also present in the recessive model with statistical significance (OR = 1.59, 95% CI: 1.12–2.27, *P* = 0.010). The T allele showed a greater frequency in PD than the C allele did on the borderline of statistical significance (OR = 1.21, 95% CI: 1.02–1.43, *P* = 0.030). The frequencies of *BST1* rs11724635, *HLA-DQB1* rs9275326, and *SPPL2B* rs62120679 genotypes and alleles were similar in both PD patients and controls (Tables 3–5).

DISCUSSION

The present study shows that the *STK39* rs1955337 affects risk of PD in Taiwanese population, while *BST1* rs11724635, *HLA-DQB1* rs9275326, and *SPPL2B* rs62120679 demonstrate absent association with PD. It is worthy to note that the minor allele frequency of *STK39* rs1955337 in controls of this study (32.9%) is compatible with that (31.7%) in Chinese + Japanese dataset from 1000 Genome but very different from that (8.3%) in Northern Europeans from Utah dataset from 1000 Genome (<http://www.1000genomes.org/home>). Most of these results are not consistent with those of Caucasian cohorts, suggesting the differential effect of neuroinflammatory gene loci on PD risk between Eastern and Western populations.

TABLE 1. Sequences of Primers Used in This Study

SNP	Forward	Reverse	Extended
<i>STK39</i> rs1955337	ACGTTGGATGCCTAG CCCACATTACTGACC	ACGTTGGATGCAAATTT TTGTAGGAGTCAG	AGTCACCCCAATACATAGT
<i>BST1</i> rs11724635	ACGTTGGATGTAGAGG AAAACAGAGGGTGG	ACGTTGGATGGCAATA TCACACACTTCAAG	GAGGGTACAAGGGAAG
<i>HLA-DQB1</i> rs9275326	ACGTTGGATGCTCTTAA CTTCTTTCTAGCC	ACGTTGGATGATGGGT CTAGTCAGGAGAG	GAGGAAATCACACAGTAA TGTAATAAT
<i>SPPL2B</i> rs62120679	ACGTTGGATGGAGT CCTTAGGCAAAAAGGTG	ACGTTGGATGCAAAG CCCTTAACCAACCAC	GCTGCAAGCTCTCGCCCC

TABLE 2. Genotype and Allele Frequency of Polymorphism *STK39* rs1955337 Among Parkinson's Disease (PD) and Controls in Taiwan

	PD (%)	Controls (%)	OR (95% CI)	P Value
Genotype frequency				
GG	240 (40.3%)	262 (43.9%)	1.00	
GT	269 (45.1%)	277 (46.4%)	1.06 (0.83–1.35)	0.638
TT	87 (14.6%)	58 (9.7%)	1.64 (1.13–2.39)	0.010
Dominant model				
GG	240 (40.3%)	262 (43.9%)	1.00	
GT + TT	356 (59.7%)	335 (56.1%)	1.16 (0.92–1.46)	0.206
Recessive model				
GT + GG	509 (85.4%)	539 (90.3%)	1.00	
TT	87 (14.6%)	58 (9.7%)	1.59 (1.12–2.27)	0.010
Allele frequency				
Major allele (G)	749 (62.8%)	801 (57.1%)	1.00	
Minor allele (T)	443 (37.2%)	393 (32.9%)	1.21 (1.02–1.43)	0.030

OR = odds ratio.

The *STK39* encodes a serine/threonine kinase (STE20/SPS1-related proline–alanine-rich protein kinase) with roles in stress and inflammatory pathways.^{13,14} The PD-associated loci in *STK39*, such as rs1955337, rs2102808, and rs3754775, have been reported in the studies from Caucasian and Ashkenazi Jewish populations.^{9,15,16} However, the associations in Han-Chinese have not been consistently replicated. Li et al demonstrated a negative result for the association between *STK39* rs2102808 and PD susceptibility in Han-Chinese.¹⁷ Again, a study by Wang et al found no significant difference in allele and genotype frequencies of *STK39* rs2102808 and rs3754775 between PD patients and control group in Han-Chinese population.¹⁸ Our study, for the first time, demonstrates the association of rs1955337 with PD susceptibility in Han-Chinese, which is consistent with the finding in Caucasian populations. Recently, by next-generation sequencing, a new risk loci 352G >T in *STK39* was found to be associated with sporadic PD patients in China.¹⁹ These associations of *STK39*

variants with PD may suggest a role of inflammation and stress in PD pathogenesis, whereas the functional consequence of the *STK39* variants should be further investigated.

BST1 encodes a stromal cell line-derived glycosylphosphatidylinositol-anchored glycoprotein that facilitates pre-B-cell growth.²⁰ *BST1* rs11724635 is associated with PD risk in Caucasian populations.²¹ A study from China reported that the minor allele A conferred a weak signal of developing PD.²² However, this association was not recapitulated in Japanese and Han-Chinese in Taiwan.^{23,24} Belonging to the HLA class II beta chain paralogs, HLA-DQB1 plays a central role in the immune system by presenting peptides derived from extracellular proteins.²⁵ The association of *HLA-DQB1* rs9275326 T allele with PD risk reduction has been recently shown by Nall's meta-analysis of GWAS in Caucasians.⁹ Our study, for the first time, tested this association in Han-Chinese and the result was negative. *SPPL2B* encodes a GXGD family of aspartic proteases, which triggers cytokine expression by

TABLE 3. Genotype and Allele Frequency of Polymorphism *BST1* rs11724635 Among Parkinson's Disease (PD) and Controls in Taiwan

	PD (%)	Controls (%)	OR (95% CI)	P Value
Genotype frequency				
CC	183 (30.7%)	197 (33.0%)	1.00	
CA	296 (49.7%)	296 (49.6%)	1.08 (0.83–1.39)	0.576
AA	117 (19.6%)	104 (17.4%)	1.21 (0.87–1.69)	0.260
Dominant model				
CC	183 (30.7%)	197 (33.0%)	1.00	
CA + AA	413 (69.3%)	400 (67.0%)	1.11 (0.87–1.42)	0.396
Recessive model				
CA + CC	479 (80.4%)	493 (82.6%)	1.00	
AA	117 (19.6%)	104 (17.4%)	1.16 (0.86–1.55)	0.327
Allele frequency				
Major allele (C)	662 (55.5%)	690 (57.8%)	1.00	
Minor allele (A)	530 (44.5%)	504 (42.2%)	1.10 (0.92–1.29)	0.268

OR = odds ratio.

TABLE 4. Genotype and Allele Frequency of Polymorphism *HLA-DQB1* rs9275326 Among Parkinson's Disease (PD) and Controls in Taiwan

	PD (%)	Controls (%)	OR (95% CI)	P Value
Genotype frequency				
CC	495 (83.1%)	504 (84.4%)	1.00	
CT	96 (16.1%)	88 (14.7%)	1.11 (0.81–1.52)	0.514
TT	5 (0.8%)	5 (0.8%)	1.02 (0.27–3.81)	0.978
Dominant model				
CC	495 (83.1%)	504 (84.4%)	1.00	
CT + TT	101 (16.9%)	93 (15.6%)	1.11 (0.81–1.51)	0.523
Recessive model				
CT + CC	591 (99.2%)	592 (99.2%)	1.00	
TT	5 (0.8%)	5 (0.8%)	1.00 (0.27–3.74)	0.998
Allele frequency				
Major allele (C)	1086 (91.1%)	1096 (91.8%)	1.00	
Minor allele (T)	106 (8.9%)	98 (8.2%)	1.09 (0.82–1.46)	0.551

OR = odds ratio.

TABLE 5. Genotype and Allele Frequency of Polymorphism *SPPL2B* rs62120679 Among Parkinson's Disease (PD) and Controls in Taiwan

	PD (%)	Controls (%)	OR (95% CI)	P Value
Genotype frequency				
TT	265 (44.5%)	253 (42.4%)	1.00	
CT	258 (43.3%)	265 (44.4%)	0.93 (0.73–1.19)	0.556
CC	73 (12.2%)	79 (13.2%)	0.88 (0.61–1.27)	0.499
Dominant model				
TT	265 (44.5%)	253 (42.4%)	1.00	
CT + CC	331 (55.5%)	344 (57.6%)	0.92 (0.73–1.56)	0.468
Recessive model				
CT + TT	523 (87.8%)	518 (86.8%)	1.00	
CC	73 (12.2%)	79 (13.2%)	0.92 (0.65–1.29)	0.612
Allele frequency				
Major allele (T)	788 (66.1%)	771 (64.6%)	1.00	
Minor allele (C)	404 (33.9%)	423 (35.4%)	0.93 (0.79–1.11)	0.431

OR = odds ratio.

cleaving transmembrane domain of tumor necrosis factor α .²⁶ *SPPL2B* rs62120679 C allele has been identified as a significant risk variant for PD in Caucasians.⁹ Here, we found this association may not be present in Han-Chinese. All of these results demonstrate the potential ethnic divergence of these genetic variants, suggesting a distinct genetic background of neuroinflammation between Han-Chinese and Caucasian PD patients.

Our study provides important genetic information about PD patients in Han-Chinese and the ethnic-specific effect of the genes associated with PD. However, these genetic analyses do not clarify the epigenetic effect and gene–gene interaction, as well as the association of other SNPs within the tested genes and PD. The potential impact of environmental factors on development of PD in individuals carrying these genetic variants still needs to be clarified. For example, Chen et al found *BST1* rs11724635 interacted with well water drinking to increase the risk of PD.²³ Nevertheless, our finding indicates the potential of *STK39* rs1955337 affects the risk in developing PD and suggests ethnic discrepancies in the other 3 PD-associated genetic

variants in Han-Chinese. More large series of case-control studies of genotyping *STK39* variants in the PD patients of other Asian populations, and functional approaches to study their potential neuroinflammatory mechanisms for PD are warranted.

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