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DLG2, but not TMEM229B, GPNMB, and ITGA8 polymorphism, is associated with Parkinson's disease in a Taiwanese population

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ABSTRACT

Transmembrane or membrane-associated protein dysfunction is increasingly recognized as an important mechanism of pathogenesis in Parkinson's disease (PD). Previous genome-wide association studies and their meta-analysis in PD genes have identified several risk foci in transmembrane protein-encoding genes. Herein, we investigated the effect of 4 such PD-associated genetic variants reported in Caucasians, including discs-large membrane-associated guanylate kinase scaffolding protein 2 (*DLG2* rs3793947), transmembrane protein 229B (*TMEM229B* rs1555399), glycoprotein nonmetastatic melanoma protein B (*GPNMB* rs199347), and integrin subunit alpha 8 (*ITGA8* rs7077361). A total of 1185 Taiwanese subjects comprising 592 PD patients and 593 unrelated age-matched controls were genotyped. *DLG2* rs3793947 AA genotype showed a significantly lower prevalence in female PD patients compared to the female controls ($p = 0.019$). The recessive model analysis also demonstrated a reduced PD risk for females in AA genotype (odds ratio = 0.573, 95% confidence interval: 0.379–0.868, $p = 0.008$). The frequencies of *TMEM229B* rs1555399 and *GPNMB* rs199347 genotypes and alleles were similar in PD patients and controls. *ITGA8* rs7077361 was not polymorphic in all subjects of this study. These data suggested that *DLG2*, but not *TMEM229B*, *GPNMB*, and *ITGA8*, influenced the risk of PD in Taiwan.

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1. Introduction

Compiling evidence supports a complex genetic and environmental contribution to Parkinson's disease (PD), with monogenetic forms of PD representing 5%–10% of cases in most populations (Gasser, 2001). Twenty years of genetic research in PD has identified mutations in several genes causing monogenetic forms of the disorder, namely *SNCA*, *LRRK2*, *PARKIN*, *PINK1*, *DJ-1*, *VPS35*, and *EIF4G1* (Puschmann, 2013). Genome-wide association study (GWAS) and subsequent meta-analysis have also identified at least 28 single-nucleotide polymorphism (SNP) variants that modify disease risk, with *SNCA*, *MAPT*, *GBA*, *SYT11*, *HLA-DQB1*, and *GAK-DGKQ* pointed as major risk foci for sporadic PD (International Parkinson Disease Genomics et al., 2011; Nalls et al., 2014; Pankratz et al., 2012). The majority of studies were conducted using samples from Caucasian populations (Do et al., 2011; Edwards et al., 2010; International Parkinson Disease Genomics et al., 2011;

International Parkinson's Disease Genomics and Wellcome Trust Case; Control, 2011; Lill et al., 2012; Pankratz et al., 2012; Pihlstrom et al., 2013; Saad et al., 2011; Sharma et al., 2012; Simon-Sanchez et al., 2011). To date, only 2 Asian GWAS have been published (Foo et al., 2017; Satake et al., 2009). The Japanese GWAS identified *PARK16* and *BST1* as new loci and confirmed *SNCA* and *LRRK2* as risk loci (Satake et al., 2009). The East Asian GWAS did not identify Asian-specific loci, whereas it confirmed a strong association of *SNCA*, *LRRK2*, *MCCC1*, and 14 other previous reported loci with PD (Foo et al., 2017). These 2 Asian GWAS studies failed to demonstrate *MAPT* as risk loci and *MAPT* was nonpolymorphic in East Asian GWAS, indicating that some of the genetic loci for PD are ethnic specific.

Nevertheless, analyzing individual susceptibility variants is of limited value in explaining the mechanistic steps for complex diseases like PD wherein a combination of variants in key genes and pathways may influence fundamental disease processes. By combining pathways approaching for both GWAS and gene expression results, Edwards et al. identified 3 pathways potentially important for the pathogenesis of PD, including focal adhesion, axonal guidance, and calcium signaling (Edwards et al., 2011). These pathways are regulated largely by transmembrane proteins. More

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than 6000 SNPs have been identified in *DLG2* that encodes a transmembrane protein as PD risk loci, and SNP rs3793947 is listed as one of the top results in Caucasian populations (http://www.pdgene.org/top_results). Along with 3 other PD SNPs in genes encoding transmembrane or membrane-associated proteins (*TMEM229B*, *GNPMB*, *ITGA8*), we sought to investigate whether transmembrane protein dysfunction could modulate the risk of developing PD in Taiwanese population.

2. Material and methods

2.1. Subjects

This study included a total of 1185 Taiwanese subjects comprising 592 PD patients and 593 controls, all of whom were enrolled from the Neurological clinics of Chang Gung Memorial Hospital-Linkou Medical Centre. The diagnosis of PD was made in accordance with the U.K. Parkinson's Disease Society Brain Bank clinical diagnostic criteria by 2 neurologists specialized in movement disorders (Y.-R.W. and C.-M.C.). Healthy control individuals of similar ethnic, gender, and age were from the same region as the PD patients. The mean age at onset of PD symptoms was 62.7 ± 11.1 years. The mean age of recruitment was 60.0 ± 12.7 years for controls. This study was conducted under a protocol proved by the institutional review boards of Chang Gung Memorial Hospital (ethical license number: 102-5614A3). All examinations were performed after obtaining written informed consents.

2.2. Genetic analysis

Four genetic loci (*DLG2* rs3793947, *TMEM229B* rs1555399, *GNPMB* rs199347, and *ITGA8* rs7077361) related to transmembrane proteins or membrane-associated proteins were selected from the risk foci identified by GWAS meta-analysis in PDGene database (<http://www.pdgene.org/gwas>). The SNP genotyping was performed by Agena MassARRAY platform with iPLEX gold chemistry (Agena, San Diego, CA, USA) following the manufacturer's protocol. The sequences of specific polymerase chain reaction (PCR) primers and extension primers (Supplementary Table S1) were designed with Assay Designer software package (v.4.0).

One μL of genomic DNA sample (10 ng/ μL) was added to multiplex PCR reaction in 5 μL containing 1 unit of Taq polymerase, 500 nmol of each PCR primer mix, and 2.5 mM of each deoxynucleotide (Agena, PCR accessory and Enzyme kit). Thermocycling was set at 94 °C for 4 minutes, followed by 45 cycles of 94 °C for 20 seconds, 56 °C for 30 seconds, and 72 °C for 1 minute, and 72 °C for 3 minutes. Unincorporated deoxynucleotides were deactivated using 0.3 units of shrimp alkaline phosphatase. The single base extension reaction was using iPLEX enzyme, terminator mix, and extension primer mix with thermocycling set up at 94 °C for 30 seconds, followed by 40 cycles of 94 °C for 5 seconds, and 5 inner cycle of 56 °C for 5 seconds, and 80 °C for 5 seconds, then 72 °C for 3 minutes (Agena, iPLEX gold kit). Following 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.

2.3. Statistical analysis

Hardy-Weinberg equilibrium for genotype frequencies of the patients and controls were assessed with an exact test. The Pearson's χ^2 test was used to compare the frequencies of genotypes and alleles between PD patients and controls. To account for the

multiple comparisons, the 2-tailed p values <0.0125 were considered statistically significant using Bonferroni method. For the recessive model, we had a power greater than 0.8 to identify an association when the odds ratio was less than 0.6.

3. Results

A total of 1185 subjects were recruited in this study, including 592 patients with PD (female/male: 269/323) and 593 normal controls (female/male: 312/281). Only 1 proband in the 2-generation PD family was included to minimize the skew caused by the other family member carrying the same genetic polymorphism. The mean age of PD symptoms onset was 62.7 ± 11.1 years and that of controls upon recruitment was 60.1 ± 12.7 years. The distributions of *DLG2* rs3793947 AA genotype showed a trend of lower prevalence in the PD patients compared to the controls (19.6% vs. 23.1%) (Table 1). Further analysis separating all subjects by different genders revealed that the AA genotype is significantly less in female PD patients ($p = 0.019$), which became highly significant in the recessive model (odds ratio = 0.573, 95% confidence interval: 0.379–0.868, $p = 0.008$). The distributions of *DLG2* genotypes and the allele frequency did not differ between PD and controls in male subjects. The frequencies of *TMEM229B* rs1555399 (Table 2) and *GNPMB* rs199347 (Table 3) genotypes and alleles were similar in PD patients and controls. *ITGA8* rs7077361 was not polymorphic in all subjects of this study (data not shown).

4. Discussion

This study shows that *DLG2* rs3793947 polymorphism AA genotype has a significant protective effect for PD. We failed to replicate the association of *GNPMB* and *TMEM229B* with PD shown by previous study in Caucasians (Nalls et al., 2014). It has been shown that *ITGA8* rs7077361 polymorphism, although associated with PD in Caucasians (Simon-Sanchez et al., 2009), is very rare in Chinese Han population (Fang et al., 2016). This study further suggested that *ITGA8* might not be polymorphic in Taiwanese population.

The relationship between *DLG2* and PD has been implicated in few GWAS reports (Foo et al., 2017; Fung et al., 2006; Nalls et al., 2014). Fung et al. suggested a trend that *DLG2* rs10501570 polymorphism reduced PD risk in Caucasians (Fung et al., 2006). Despite including Fung's data in their GWAS meta-analysis, Nalls et al. demonstrated the trend of protective effect for another *DLG2* polymorphism (rs3793947) in Caucasian PD patients (Nalls et al., 2014) (Table 4). A recent Asian PD GWAS demonstrated a consistent association at *DLG2* rs7479949, which was close to genome-wide significance (Foo et al., 2017). However, the association of *DLG2* rs3793947 with PD was not confidently imputed in this Asian GWAS. Our study further shows a strong protective effect of *DLG2* rs3793947 AA genotype in female Asian population. This is, to our best knowledge, the first report that *DLG2* rs3793947 minor allele is protective in female Asian PD patients.

DLG2 encodes a membrane-associated protein that belongs to a membrane-associated guanylate kinase protein family. *DLG2* has been shown to interact with glutamate receptors such as α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (Elias et al., 2006; Kruger et al., 2013) and Fyn-dependent tyrosine phosphorylation of NR2 subunits of N-methyl-D-aspartate receptors (Brenman et al., 1996; Chen and Roche, 2007; Levy et al., 2015; Tao et al., 2003). Glutamate-mediated excitotoxicity has been implicated as a pathogenic mechanism in PD. An increase in intracellular calcium levels by the excessive activation of N-methyl-D-aspartate receptors can activate cell death pathways and lead to apoptosis (Mody and MacDonald, 1995). Vaarmann et al. suggested that the absence of dopamine (DA) caused by striatal DA depletion in PD may result in an

Table 1Frequency of genotype and allele frequencies of *DLG2* rs3793947 among PD patients and controls in Taiwan

DLG2 rs3793947	Genotype/allele	PD (%)	Control (%)	χ^2	Odds ratio (95% CI)	<i>p</i>
All (n = 1185)						
Genotype	GG	166 (28.0)	171 (28.8)	0.202	1.000	
	GA	310 (52.4)	285 (48.1)		1.121 (0.858–1.464)	0.404
	AA	116 (19.6)	137 (23.1)		0.872 (0.629–1.209)	0.412
Dominant model	GG	166 (28.0)	171 (28.8)	-	1.000	
	GA+AA	426 (72.0)	422 (71.2)		1.040 (0.808–1.339)	0.761
Recessive model	GA+GG	476 (80.4)	456 (76.9)	-	1.000	
	AA	116 (19.6)	137 (23.1)		0.811 (0.614–1.072)	0.141
Allele	G	642 (54.2)	627 (52.9)	-	1.000	
	A	542 (45.8)	559 (47.1)		0.947 (0.806–1.113)	0.508
Male (n = 604)						
Genotype	GG	95 (29.4)	88 (31.3)	0.824	1.000	
	GA	155 (48.0)	133 (47.3)		1.080 (0.745–1.565)	0.686
	AA	73 (22.6)	60 (21.4)		1.127 (0.720–1.754)	0.601
Dominant model	GG	95 (29.4)	88 (31.3)	-	1.000	
	GA+AA	228 (70.6)	193 (68.7)		1.094 (0.773–1.549)	0.337
Recessive model	GA+GG	250 (77.4)	221 (78.6)	-	1.000	
	AA	73 (22.6)	60 (21.4)		1.075 (0.731–1.582)	0.712
Allele	G	345 (53.4)	309 (55.0)	-	1.000	
	A	301 (46.6)	253 (45.0)		1.066 (0.849–1.337)	0.583
Female (n = 581)						
Genotype	GG	71 (26.4)	83 (26.6)	0.019	1.000	
	GA	155 (57.6)	152 (48.7)		1.192 (0.809–1.757)	0.374
	AA	43 (16.0)	77 (24.7)		0.653 (0.400–1.065)	0.088
Dominant model	GG	71 (26.4)	83 (26.6)	-	1.000	
	GA+AA	198 (73.6)	229 (73.4)		1.011 (0.698–1.463)	0.955
Recessive model	GA+GG	226 (84.0)	235 (75.3)	-	1.000	
	AA	43 (16.0)	77 (24.7)		0.573 (0.379–0.868)	0.008
Allele	G	297 (55.2)	318 (51.0)	-	1.000	
	A	241 (44.8)	306 (49.0)		0.843 (0.669–1.063)	0.149

Key: CI, confidence interval; PD, Parkinson's disease.

uninhibited glutamate-induced calcium signaling and subsequent cell death (Vaarmann et al., 2013). How *DLG2* rs3793947 AA genotype affects *DLG2* functional change and cell death pathway regulation requires further investigation.

There have been reports indicating gender being a factor of PD risk. While *GRN* rs8548 TT genotype increases the risk of PD in women (Chang et al., 2013), *NR4A2* IVS6 +18inG polymorphism demonstrates a reduced risk of PD in women (Chen et al., 2007).

Table 2Frequency of genotype and allele frequencies of *TMEM229B* rs1555399 among PD patients and controls in Taiwan

TMEM229B rs1555399	Genotype/allele	PD (%)	Control (%)	χ^2	Odds ratio (95% CI)	p
All (n = 1185)						
Genotype	AA	172 (29.1)	174 (29.3)	0.583	1.000	
	TA	288 (48.6)	302 (51.0)		0.965 (0.740–1.258)	0.791
	TT	132 (22.3)	117 (19.7)		1.141 (0.824–1.581)	
Dominant model	AA	172 (29.1)	174 (29.3)	-	1.000	
	TA + TT	420 (70.9)	419 (70.7)		1.014 (0.789–1.303)	0.913
Recessive model	TA + AA	460 (77.7)	476 (80.3)	-	1.000	
	TT	132 (22.3)	117 (19.7)		1.167 (0.883–1.546)	0.278
Allele	A	632 (53.4)	650 (54.8)	-	1.000	
	T	552 (46.6)	536 (45.2)		1.059 (0.901–1.245)	0.486
Male (n = 604)						
Genotype	AA	96 (29.8)	94 (33.5)	0.373	1.000	
	TA	151 (46.7)	133 (47.3)		1.112 (0.770–1.606)	0.573
	TT	76 (23.5)	54 (19.2)		1.378 (0.879–2.161)	
Dominant model	AA	96 (29.7)	94 (33.5)	-	1.000	
	TA + TT	227 (70.3)	187 (66.5)		1.189 (0.843–1.677)	0.325
Recessive model	TA + AA	247 (76.5)	227 (80.8)	-	1.000	
	TT	76 (23.5)	54 (19.2)		1.294 (0.873–1.916)	0.199
Allele	A	343 (53.1)	321 (57.1)	-	1.000	
	T	303 (46.9)	241 (42.9)		1.177 (0.937–1.477)	0.161
Female (n = 581)						
Genotype	AA	76 (28.3)	80 (25.6)	0.742	1.000	
	TA	137 (50.9)	169 (54.2)		0.853 (0.580–1.256)	0.421
	TT	56 (20.8)	63 (20.2)		0.936 (0.580–1.509)	
Dominant model	AA	76 (28.3)	80 (25.6)	-	1.000	
	TA + TT	193 (71.7)	232 (74.4)		0.876 (0.606–1.265)	0.479
Recessive model	TA + AA	213 (79.2)	249 (79.8)	-	1.000	
	TT	56 (20.8)	63 (20.2)		1.040 (0.694–1.555)	0.852
Allele	A	289 (53.7)	329 (52.7)	-	1.000	
	T	249 (46.3)	295 (47.3)		0.961 (0.763–1.211)	0.735

Key: CI, confidence interval; PD, Parkinson's disease.

Table 3Frequency of genotype and allele frequencies of *GPNNB* rs199347 among PD patients and controls in Taiwan

GPNNB rs199347	Genotype/allele	PD (%)	Control (%)	χ^2	Odds ratio (95% CI)	<i>p</i>
All (n = 1185)						
Genotype	TT	316 (53.4)	307 (51.8)	0.897	1.000	0.605
	TC	227 (38.3)	235 (39.6)		0.938 (0.738–1.194)	
	CC	49 (8.3)	51 (8.6)		0.933 (0.612–1.424)	
Dominant model	TT	316 (53.4)	307 (51.8)	-	1.000	0.579
	TC + CC	276 (46.6)	286 (48.2)		0.938 (0.746–1.178)	
Recessive model	TC + TT	543 (91.7)	542 (91.4)	-	1.000	0.841
	CC	49 (8.3)	51 (8.6)		0.958 (0.637–1.445)	
Allele	T	859 (72.6)	849 (71.6)	-	1.000	0.600
	C	325 (27.4)	337 (28.4)		0.953 (0.797–1.141)	
Male (n = 604)						
Genotype	TT	177 (54.8)	156 (55.5)	0.974	1.000	0.829
	TC	119 (36.8)	101 (36.0)		1.038 (0.738–1.461)	
	CC	27 (8.4)	24 (8.5)		0.992 (0.549–1.790)	
Dominant model	TT	177 (54.8)	156 (55.5)	-	1.000	0.977
	TC + CC	146 (45.2)	125 (45.5)		1.029 (0.746–1.420)	
Recessive model	TC + TT	296 (91.6)	257 (91.5)	-	1.000	0.860
	CC	27 (8.4)	24 (8.5)		0.977 (0.550–1.736)	
Allele	T	473 (73.2)	413 (73.5)	-	1.000	0.936
	C	173 (26.8)	149 (26.5)		0.963 (0.805–1.152)	
Female (n = 581)						
Genotype	TT	139 (51.7)	151 (48.4)	0.797	1.000	0.447
	TC	108 (40.1)	134 (42.9)		0.876 (0.622–1.233)	
	CC	22 (8.2)	27 (8.7)		0.885 (0.482–1.626)	
Dominant model	TT	139 (51.7)	151 (48.4)	-	1.000	0.694
	TC + CC	130 (48.3)	161 (51.6)		0.877 (0.633–1.216)	
Recessive model	TC + TT	247 (91.8)	285 (91.3)	-	1.000	0.431
	CC	22 (8.2)	27 (8.7)		0.940 (0.522–1.692)	
Allele	T	386 (71.7)	436 (69.9)	-	1.000	0.837
	C	152 (28.3)	188 (30.1)		0.913 (0.708–1.177)	

Key: CI, confidence interval; PD, Parkinson's disease.

Our study further identifies *DLG2* rs3793947 AA genotype is protective in Asian women. Two mechanisms for this protective effect are proposed. First, the *DLG2* rs3793947 AA genotype might result in lower protein expression or reduced protein function, hence overcoming the excessive excitotoxicity caused by DA deficiency. This is supported by previous studies showing that the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor component of the excitatory postsynaptic current is reduced after *DLG2* knockdown (Elias et al., 2006; Levy et al., 2015). The other possible mechanism is that the sex difference in the PD incidence. Previous studies have demonstrated a significant higher PD incidence rate among men than women (Wooten et al., 2004), and postmenopausal estrogen therapy is associated with a reduced risk of PD in women (Popat et al., 2005). Estrogen facilitates synaptic glutamate release via different presynaptic and postsynaptic dispositions of estrogen receptors between sexes (Oberlander and Woolley, 2016). Few other pathways associated with glutamate release such as calcium/calmodulin kinase kinase (Mizuno and Giese, 2010), α -nitric oxide synthase-1 (McCullough et al., 2005), and neurexin (Born et al., 2015) are also regulated differently

between sexes. *DLG2* might interact with some of these pathways to enhance its protective effect in women with PD.

This study provides important genetic information about the gender-specific effect of the gene associated with PD in Taiwanese. However, there are limitations for this study. First, our results do not exclude the association of other SNPs within *GPNNB* and *TMEM229B* with PD. Second, these genetic analyses do not examine the gene-gene or gene-environment interaction. Nevertheless, our study demonstrates for the first time that female Asian population carrying *DLG2* rs3793947 AA genotype demonstrates a reduced risk of developing PD. Case-control studies for this genetic variant from other Asian populations might be required to support this finding. More studies for *DLG2* signaling pathway would be beneficial in developing new therapeutic strategies.

Disclosure statement

The authors do not have any actual or potential conflicts of interest.

Table 4Comparison of *DLG2* rs3793947 frequencies in GWAS between Caucasian and East Asian PD patients

Study type	Ethnic groups	SNP	Effective allele	Effect allele frequency	OR	<i>p</i>	AA genotype frequency	OR	<i>p</i>
GWAS-M (Nalls et al., 2014)	Mainly Caucasian ^a	rs3793947	A	44.3%	0.929	3.96E-07	-	-	-
GWAS-M (Foo et al., 2017)	East Asian	rs3793947	A	Not confidently imputed					
		rs7479949	C	45.5%	~0.89	5.90E-08 ^b	-	-	-
Association report (present study)	Taiwanese	rs3793947	A	45.8%	0.949	0.508	19.6%	0.811 ^c	0.141 ^c
	Female Taiwanese	rs3793947	A	44.8%	0.843	0.149	16.0%	0.573 ^c	0.008 ^c

Key: GWAS, genome-wide association study; GWAS-M, GWAS meta-analysis; OR, odds ratio; PD, Parkinson's disease; SNP, single-nucleotide polymorphism.

^a Containing 1078 Japanese PD patients (Satake et al., 2009) in a total of 13,708 PD patients analyzed.^b Approaching GWAS significance.^c Genotypic association computed by recessive model.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neurobiolaging.2017.11.016](https://doi.org/10.1016/j.neurobiolaging.2017.11.016).

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