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Identification of Risk Loci for Parkinson Disease in Asians and Comparison of Risk Between Asians and Europeans
A Genome-Wide Association Study

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IMPORTANCE Large-scale genome-wide association studies in the European population have identified 90 risk variants associated with Parkinson disease (PD); however, there are limited studies in the largest population worldwide (ie, Asian).

OBJECTIVES To identify novel genome-wide significant loci for PD in Asian individuals and to compare genetic risk between Asian and European cohorts.

DESIGN SETTING, AND PARTICIPANTS Genome-wide association data generated from PD cases and controls in an Asian population (ie, Singapore/Malaysia, Hong Kong, Taiwan, mainland China, and South Korea) were collected from January 1, 2016, to December 31, 2018, as part of an ongoing study. Results were combined with inverse variance meta-analysis, and replication of top loci in European and Japanese samples was performed. Discovery samples of 31 575 individuals passing quality control of 35 994 recruited were used, with a greater than 90% participation rate. A replication cohort of 1 926 361 European-ancestry and 3509 Japanese samples was analyzed. Parkinson disease was diagnosed using UK Parkinson's Disease Society Brain Bank Criteria.

MAIN OUTCOMES AND MEASURES Genotypes of common variants, association with disease status, and polygenic risk scores.

RESULTS Of 31 575 samples identified, 6724 PD cases (mean [SD] age, 64.3 [10] years; age at onset, 58.8 [10.6] years; 3472 [53.2%] men) and 24 851 controls (age, 59.4 [11.4] years; 11 030 [45.0%] men) were analyzed in the discovery study. Eleven genome-wide significant loci were identified; 2 of these loci were novel (*SV2C* and *WBSCR17*) and 9 were previously found in Europeans. Replication in European-ancestry and Japanese samples showed robust association for *SV2C* (rs246814; odds ratio, 1.16; 95% CI, 1.11-1.21; $P = 1.17 \times 10^{-10}$ in meta-analysis of discovery and replication samples) but showed potential genetic heterogeneity at *WBSCR17* (rs9638616; I^2=67.1%; $P = 3.40 \times 10^{-3}$ for hetereogeneity). Polygenic risk score models including variants at these 11 loci were associated with a significant improvement in area under the curve over the model based on 78 European loci alone (63.1% vs 60.2%; $P = 6.81 \times 10^{-12}$).

CONCLUSIONS AND RELEVANCE This study identified 2 apparently novel gene loci and found 9 previously identified European loci to be associated with PD in this large, meta–genome-wide association study in a worldwide population of Asian individuals and reports similarities and differences in genetic risk factors between Asian and European individuals in the risk for PD. These findings may lead to improved stratification of Asian patients and controls based on polygenic risk scores. Our findings have potential academic and clinical importance for risk stratification and precision medicine in Asia.

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Supplemental content

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Parkinson disease (PD) (gene: OMIM 168600) is one of the most common age-related neurodegenerative diseases worldwide and has been a factor in more than 200 000 deaths and 3.2 million disability-adjusted life-years worldwide in 2016.[1,2] Parkinson disease presents as a hypokinetic movement disorder characterized by bradykinesia, postural instability, rigidity, and resting tremors resulting from loss of nigrostriatal dopaminergic neurons and other nondopaminergic structures. Several genes containing rare pathogenic variants have been identified in familial PD, suggesting that, although genetic factors play a role in PD pathogenesis, the disease is heterogeneous and associated with multiple genes and pathways.

Large-scale meta-analyses of genome-wide association studies (GWASs) of approximately 40 000 PD cases and 20 000 proxy cases in the European population have since identified several dozen loci that implicate lysosomal function and other pathways in PD pathogenesis and confirmed the involvement of familial PD genes, such as *SNCA* (OMIM 163890) and *LRRK2* (OMIM 609007), in sporadic PD as well. The Asian population is the largest worldwide and thus makes up a significant fraction of patients with PD globally.[1] Studies have demonstrated both similarities and differences in genetic risk factors underlying PD in Asian and European individuals,[3,4] such as the absence of the *MAPT* (OMIM 157140) H2 protective haplotype and the *LRRK2* G2019S risk variant in Asian individuals and the identification of the Asian-specific *LRRK2* R1628P and G2385R variants. However, the numbers of samples analyzed have been relatively small to date.

To identify novel, potentially Asian-specific loci and conduct a robust comparison between genetic risk for PD in Asian and European individuals, we conducted what was, to our knowledge, the first East Asian meta-GWAS in 31 575 individuals (6724 patients and 24 851 controls) and replicated the top single-nucleotide variants (SNVs) (formerly SNPs) in up to 56 306 cases and 1 417 791 controls from the meta-analyses by the International Parkinson's Disease Genomics Consortium (IPDGC),[5] 1239 cases and 451 025 controls from the UK Biobank,[6] and 988 cases and 2521 controls from Japan.[4]

Key Points

Question What are the genetic risk loci for Parkinson disease in an Asian population?

Findings In this genetic-association study of 31 575 individuals, 1 novel locus *SV2C* showed robust replication in European and Japanese samples; 11 genome-wide significant loci were identified in an Asian-only meta–genome-wide association study in 6724 individuals with Parkinson disease and 24 851 controls. Substantial overlap in genetic risk factors appeared to exist between Asian and European individuals, with 63 of 78 polymorphic European risk variants displaying a similar direction of association.

Meaning Risk prediction models constructed based on Asian and European risk variants appear to be associated with improvements in stratification of Parkinson disease risk in the worldwide population of Asian individuals.

Methods

Patients and ethnically and regionally matched controls were recruited by 13 independent centers and study groups from 6 regions across East Asia (eMethods, eTable 1 in the Supplement). Patients were diagnosed with PD using the UK Parkinson's Disease Society Brain Bank criteria. Written informed consent was obtained according to the Declaration of Helsinki.[7] This study was approved by the SingHealth Centralized Institutional Review Board and Nanyang Technological University Institutional Review Board. The study was conducted from January 1, 2016, to December 31, 2018. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline.

We analyzed SNVs within the 2 novel loci in 988 cases and 2521 controls from Japan.[4] We also analyzed our top SNVs in the largest European-ancestry PD GWAS from the IPDGC (56 306 cases and 1 417 791 controls).[5,8] Summary statistics of SNVs within the loci of interest were assessed in the UK Biobank study on G20: Parkinson disease (1239 PD cases and 451 025 controls, eMethods in the Supplement).[6]

Statistical Analysis

A total of 34 162 Han Chinese and South Korean samples were genotyped, followed by sample filtering (eMethods, eFigure 1 in the Supplement). Imputation of untyped SNVs and prephasing was conducted using the multiethnic 1000 Genomes Project phase 3 reference panel (released in October 2014), followed by stringent quality-control filtering at the SNV level (eTable 2, eFigure 2 in the Supplement). Logistic regression analyses were conducted on genotype dosages. Results were combined by fixed-effects inverse variance meta-analysis (eMethods in the Supplement).

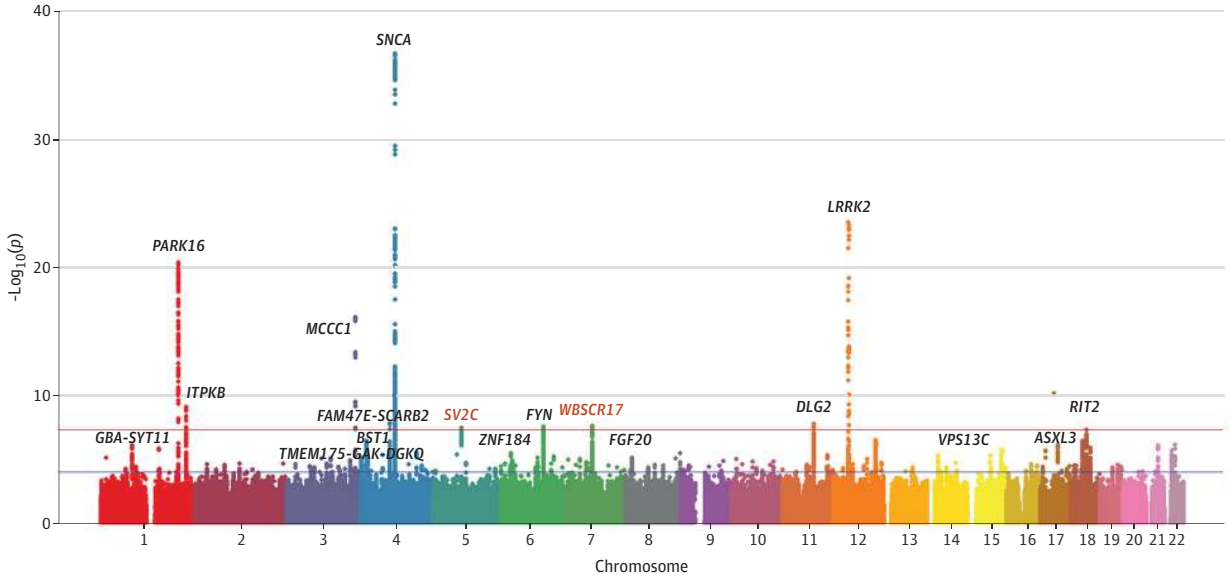
Polygenic risk scores were calculated in 2536 PD cases and 21 840 population-based controls from Singapore/Malaysia based on 11 genome-wide significant Asian SNVs, 78 SNVs from European-ancestry studies,[5,8,9] or a combination of Asian and European SNVs (80 SNVs) (eMethods in the Supplement).

The percentage of the total variance explained was estimated via Nagelkerke pseudo R^2 analysis. Area under the curve (AUC) estimates were conducted to assess receiver operating characteristic curve differences (eMethods in the Supplement). Significance was assessed at genome-wide significance level $P < 5 \times 10^{-8}$ for GWAS and $P < .05$ for other comparisons.

Results

A total of 31 575 samples remained after quality-control filtering, consisting of 6724 PD cases (mean [SD] age, 64.3 [10] years; age at onset, 58.8 [10.6] years; 3472 [53.2%] men) and 24 851 controls (age, 59.4 [11.4] years; 11 030 [45.0%] men) from China (2279 cases, 2021 controls), Taiwan (216 cases, 225 controls), Hong Kong (199 cases, 166 controls), South Korea (1494 cases, 599 controls), and Chinese participants from Singapore/

Figure 1. Genome-Wide Association Study of Parkinson Disease in East Asian Individuals



Meta–genome-wide association studies of 5 East Asian sample collections, with novel loci labeled in red, previously reported loci in black, and genome-wide significant loci in bold font. Horizontal lines indicate the thresholds for genome-wide significant association (5×10^{-8}) (red) and suggestive association (1×10^{-4}) (blue).

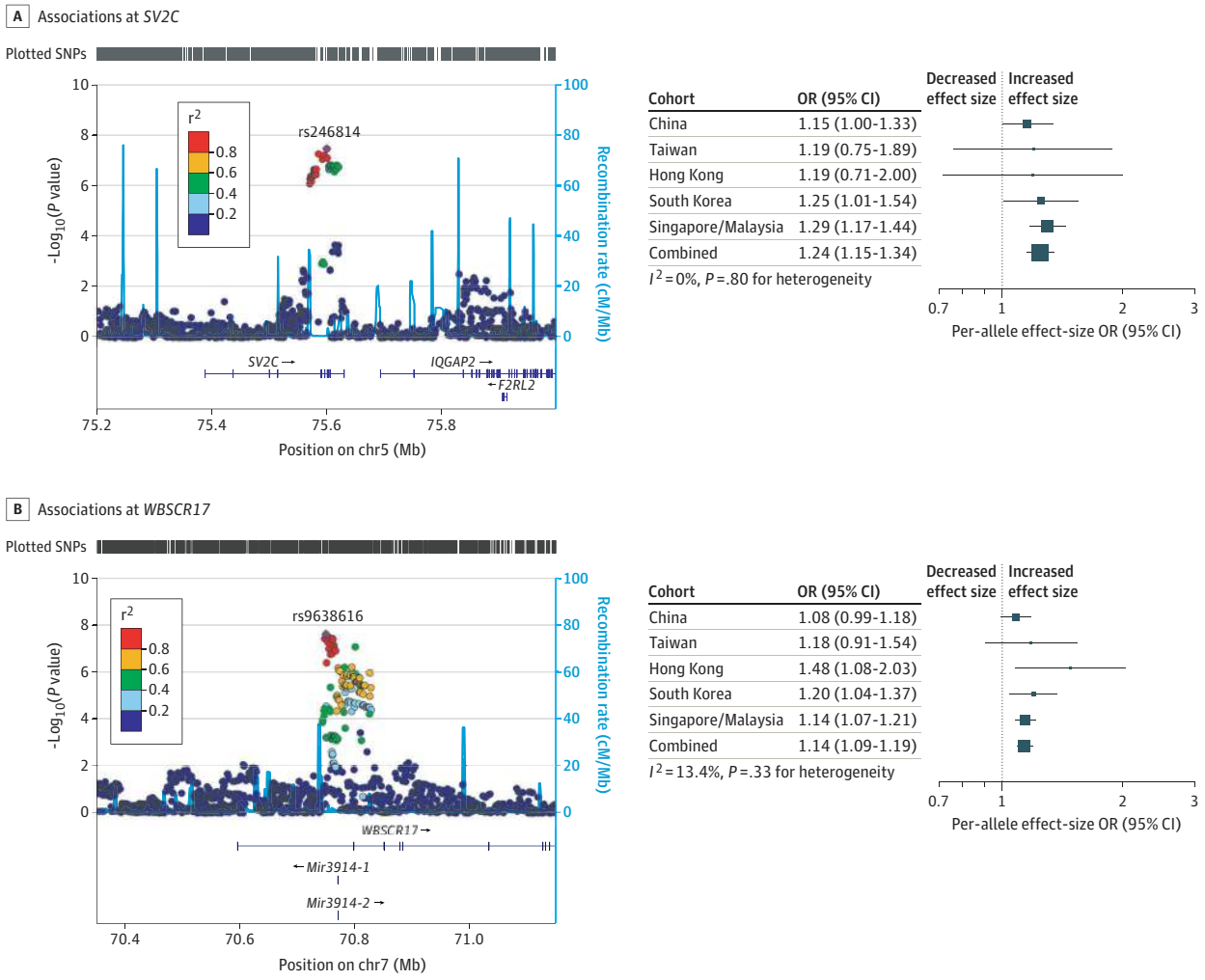
Malaysia (2536 cases, 21 840 controls) (eTable 1B in the Supplement). Association statistics were combined using fixed-effects meta-analysis at a total of 5 843 213 SNVs (minor allele frequency ≥1%; λ genomic control (genomic inflation factor) = 1.082; λ_{1000} = 1.0077; λ genomic control (genomic inflation factor) for minor allele frequency ≥5% = 1.092; λ_{1000} = 1.0087; linkage disequilibrium score intercept = 1.02) that were genotyped or successfully imputed at high quality across all 5 data sets (eFigures 1-3 in the Supplement). Sensitivity analyses using leave-one-out meta-analyses suggested that the effect size estimates were not driven by any single study (eFigure 4, eTable 3 in the Supplement).

Our meta-analysis revealed 11 genome-wide significant loci, of which 9 were previously described (*PARK16* [OMIM 613164], *ITPKB* [OMIM 147522], *MCCC1* [OMIM 609010], *SNCA* [OMIM 163890], *FAM47E-SCARB2* [OMIM 602257], *DLG2* [OMIM 603583], *LRRK2* [OMIM 609007)], *RIT2* [OMIM 609592], and *FYN* [OMIM 137025]) (**Figure 1**). We identified 2 new associations at *SV2C* (OMIM 610291) and *WBSCR17* (OMIM 615137). We also observed a strong association ($P < 1 \times 10^{-5}$) at 7 other loci that have previously (*GBA* [OMIM 606463]-*SYT11* [OMIM 163890], *BST1* [OMIM 600387], *TMEM175* [OMIM 616660]-*GAK* [OMIM 602052])]-*DGKQ* [OMIM 601207], *ZNF184* [OMIM 602277], *FGF20* [OMIM 605558], *VPS13C* [OMIM 608879], and *ASXL3* [OMIM 615115]) been reported to be associated with PD in European individuals (Figure 1). Of the 16 previously reported loci with $P < 1 \times 10^{-5}$, the top-associated SNV was in high linkage disequilibrium (r^2>0.75) with the reported European SNV within 7 loci. We observed allelic heterogeneity at *LRRK2*, *ITPKB*, *ZNF184*, *FAM47E-SCARB2* and *GBA/SYT11* in which the top Asian SNV was independent of the reported European SNV, and LD differences at *SNCA*, *FYN*, *VPS13C*, and *ASXL3* (eTable 4 in the Supplement), thus demonstrating differences in the underlying genetic architecture between Asian and European individuals at overlapping loci.

We observed genome-wide significant association at rs246814 (odds ratio [OR], 1.24; 95% CI, 1.15-1.34; $P = 3.48 \times 10^{-8}$) located within an intron of the *SV2C* gene (**Figure 2A, Table 1**). Consistent association was observed across all 5 East Asian data sets ($I^2 = 0, P = .80$ for heterogeneity). This SNV is in complete LD (r^2 = 1 in 1000 Genomes Project data and >0.96 in our samples) with a missense variant p.Asp543Asn (rs31244) within *SV2C* (OR, 1.24; 95% CI, 1.14-1.33; $P = 6.22 \times 10^{-8}$). Although this nonsynonymous change is predicted by SIFT and PolyPhen to be tolerated and benign, respectively, the change occurs within an extracellular or luminal domain of SV2C and may affect N-linked glycosylation of this domain[10] via the creation of a new glycosylation site (Asn543-Asp544-Thr545). The SNV rs246814 also tags SNVs located within potential transcription factor binding motifs and DNase hypersensitivity sites (eTables 5 and 6 in the Supplement). *SV2C* is expressed in the basal ganglia and dopaminergic neurons and has previously been evaluated as a functional PD candidate gene because of its restricted expression in brain regions relevant to PD.[11]

Genome-wide significant association was also observed at a second novel locus tagged by rs9638616 (OR, 1.14; 95% CI, 1.09-1.19; $P = 2.53 \times 10^{-8}$) (Figure 2B, Table 1). This SNV is located within an intron of the *WBSCR17* gene and near genes encoding microRNAs mir-3914-1 and mir3914-2. Similarly, consistent association was observed across the 5 data sets (I^2 = 13.4%, P = .33 for heterogeneity). To our knowledge, neither of these 2 genes has previously been implicated in PD.

Figure 2. Two Novel Parkinson Disease Risk Loci



Associations at *SV2C* (A) and *WBSCR17* (B) in the Asian meta–genome-wide association studies. chr Indicates chromosome; cM/Mb, centimorgan/megabase (genomic location in reference build 37 [Hg19]); OR, odds ratio; and SNV, single-nucleotide variant (formerly SNP).

We then evaluated the association evidence at SNVs and loci previously reported to show genome-wide significant association with PD in European populations[5,8,9] in our GWAS meta-analysis results (**Table 2**; eTable 7 in the Supplement). Of the 78 SNVs polymorphic in Asian samples, only 3 showed genome-wide significant association in Asian individuals, and another 6 SNVs were associated at $P < 1 \times 10^{-5}$ (Table 2). A total of 63 SNVs had ORs in same direction (38 with $P < .05$), 15 had ORs in the opposite direction (all $P > .05$ except *MEX3C* [OMIM: 611005]) (eFigure 5 in the Supplement). We recognize that our Asian sample set is smaller than the largest European GWAS and has limited statistical power to validate these loci. However, the fraction of polymorphic SNVs showing same direction of association (63/78 = 80.8%) and the strong enrichment for significant SNVs (38/78 = 48.7% at $P < .05$; median $P = .055$, $\lambda = 8.08$) (eFigure 5 in the Supplement) suggest a substantial but incomplete overlap in genetic risk between Asian and European populations. At the locus level, SNVs with $P < 1 \times 10^{-5}$ were observed in 16 of the previously reported loci (eTable 4, eFigure 6 in the Supplement), while there was no evidence of linked or independent signals crossing $P < 1 \times 10^{-5}$ at the remaining loci (eFigure 6 in the Supplement).

To determine whether the 2 novel SNVs are associated with PD risk in other populations, we evaluated summary statistics from the largest European-ancestry data sets available online: the UK Biobank (1239 cases, 451 025 controls) and the most recent meta-GWAS by the IPDGC[5] (up to 56 306 cases, 1 417 791 controls). Given that the IPDGC data set includes proxy cases and web-based diagnosed cases and controls, we also analyzed only the subset of clinically diagnosed PD cases consisting of 15 056 cases and 12 637 controls (Table 1). In addition, we analyzed SNVs within these 2 loci in 988 cases and 2521 controls from Japan.[4] Both risk variants were present at lower frequencies in European populations compared with Asian populations (Table 1).

We observed consistent association at *SV2C* in samples of Japanese (OR, 1.11; 95% CI, 0.94-1.31; $P = .24$)[4] and European ancestry populations, including IPDGC full (OR, 1.07; 95% CI,

Table 1. Association and Meta-analysis Results at *SV2C* and *WBSCR17*

Study	MAF, %		OR (95% CI)	*P* value	I^2, %	*P* value for heterogeneity
	Cases	Controls				
***SV2C* rs246814: C**						
China	10.32	9.13	1.15 (1.00-1.33)	.054		
Taiwan	10.51	8.74	1.19 (0.75-1.89)	.45		
Hong Kong	9.79	8.67	1.19 (0.71-2.00)	.51		
Korea	11.92	9.63	1.25 (1.01-1.54)	.04		
Singapore/Malaysia	10.45	8.29	1.29 (1.17-1.44)	1.44×10^{-6}		
Combined discovery			1.24 (1.15-1.34)	3.48×10^{-8}	0	.80
Japan[a]	11.08	10.13	1.11 (0.94-1.31)	.2		
UK Biobank	7.75[b]		1.09 (0.94-1.26)	.25		
IPDGC						
All	8.23[b]		1.07 (1.04-1.11)	3.62×10^{-5}		
Clinical	8.42[b]		1.13 (1.06-1.21)	2.95×10^{-4}		
Combined replication (IPDGC all)[c]			1.07 (1.04-1.11)	9.74×10^{-6}	0	.92
Combined discovery plus replication (all)			1.11 (1.07-1.13)	6.02×10^{-10}	48	.06
Combined replication (IPDGC clinical)			1.12 (1.06-1.19)	7.80×10^{-5}	0	.90
Combined discovery plus replication (clinical)			1.16 (1.11-1.21)	1.17×10^{-10}	0	.50
***WBSCR17* rs9638616:T**						
China	49.24	47.22	1.08 (0.99-1.18)	.08		
Taiwan	48.13	44.17	1.18 (0.91-1.54)	.21		
Hong Kong	47.26	38.39	1.48 (1.08-2.03)	.01		
Korea	56.68	52.29	1.20 (1.04-1.37)	9.50×10^{-3}		
Singapore/Malaysia	47.06	43.27	1.14 (1.07-1.21)	1.93×10^{-5}		
Combined discovery			1.14 (1.09-1.19)	2.53×10^{-8}	13.4	.33
Japan[a]	41.19	40.16	1.04 (0.94-1.16)	.43		
UK Biobank	31.43[b]		0.97 (0.89-1.06)	.53		
IPDGC						
All	32.44[b]		1.00 (0.98-1.02)	.76		
Clinical	31.81[b]		1.01 (0.95-1.06)	.85		
Combined replication (IPDGC all)[c]			1.00 (0.98-1.02)	.77	0	.59
Combined discovery plus replication (all)			1.02 (1.00-1.04)	.04	78.5	3.16×10^{-5}
Combined replication (IPDGC clinical)			1.00 (0.96-1.05)	.89	0	.591
Combined discovery plus replication (clinical)			1.06 (1.03-1.10)	8.37×10^{-5}	67.1	3.40×10^{-3}

Abbreviations: IPDGC, International Parkinson's Disease Genomics Consortium; MAF, minor allele frequency; OR, odds ratio.

[a] rs246813 was used as a proxy for rs246814 (r^2 = 0.99) and rs1317290 was used as a proxy for rs9638616 (r^2 = 0.90) in data from Japan.[4]

[b] Number represents the mean minor allele frequency in percentage across combined cases and controls.

[c] Replication was performed using either the full IPDGC data set of 56 306 cases, 1 417 791 controls (all), or the IPDGC clinically diagnosed subset of 15 056 cases and 12 637 controls (clinical) in which there is no overlap with the UK Biobank samples. The Japan and UK Biobank data sets were included in both analyses.

1.04-1.11; $P = 3.62 \times 10^{-5}$)[5,8] and IPDGC clinically diagnosed subdata set (OR,1.13; 95% CI, 1.06-1.21; $P = 2.95 \times 10^{-4}$)[5] and UK Biobank data (OR, 1.09; 95% CI, 0.94-1.26; P = .25).[6] Based on the full replication data sets, significant replication was observed at the *SV2C* locus (replication meta-analysis: OR, 1.07; 95% CI, 1.04-1.11; $P = 9.74 \times 10^{-6}$; I^2 = 0%; P = .92 for heterogeneity; combined meta-analysis: OR, 1.11; 95% CI, 1.07-1.13; $P = 6.02 \times 10^{-10}$; I^2 = 48%; P = .06 for heterogeneity) (Table 1). Meta-analysis of Asian consortium discovery samples with the European and Japanese clinically diagnosed PD replication samples[5] provided support for the association at both the lead SNV *SV2C* rs246814 (OR, 1.16; 95% CI, 1.11-1.21; $P = 1.17 \times 10^{-10}$; I^2 = 0%; P = .50 for heterogeneity) (Table 1) and the missense variant p.Asp543Asn rs31244 (OR, 1.16; 95% CI, 1.11-1.21; $P = 1.80 \times 10^{-10}$; I^2 = 0%; P = .53 for heterogeneity) with low intercohort and interethnic heterogeneity.

The *WBSCR17* SNV rs9638616 did not appear to be associated with PD risk in European data, IPDGC full (OR, 1.00; 95% CI, 0.98-1.02; P = .76) and clinically diagnosed data sets (OR, 1.01; 95% CI, 0.95-1.06; P = .85), UK BioBank (OR, 0.97; 95% CI, 0.89-1.06; P = .53), or Japan (OR, 1.04; 95% CI, 0.94-1.16; P = .43) PD GWAS. This SNV (OR, 1.06; 95% CI, 1.03-1.10; $P = 8.37 \times 10^{-5}$; I^2 = 67.1%; $P = 3.40 \times 10^{-3}$ for heterogeneity) and locus did not reach genome-wide significance in a meta-analysis between the discovery, Japanese,[4] and European clinically diagnosed PD samples (Table 1).[5]

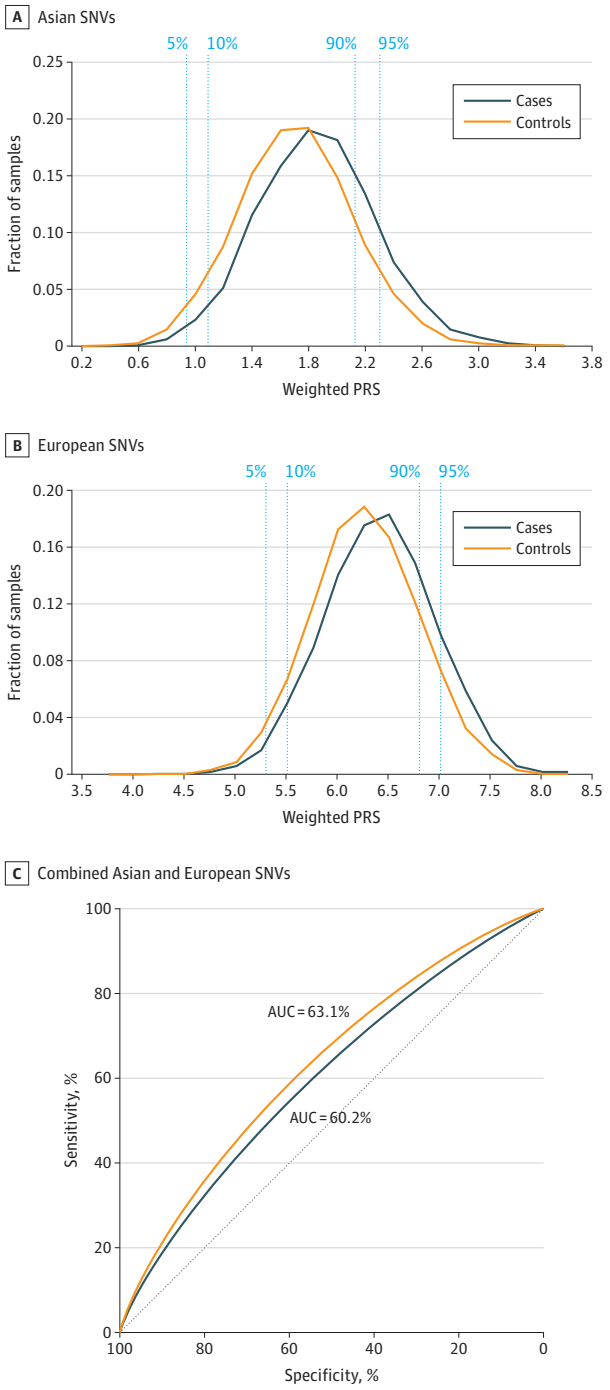
Table 2. Variants at Reported PD Risk Loci With $P < .01$ in Asian Discovery Samples[5,8,9,a]

P value	No. of variants	Locus names
$P < 5 \times 10^{-8}$	3	*SNCA, MCCC1, PARK16*
$P < 1 \times 10^{-5}$	9	*BST1, GAK, ITPKB, RIT2, DLG2, FYN*
$P < 1 \times 10^{-4}$	12	*ASXL3, VPS13C, FGF20*
$P < 1 \times 10^{-3}$	13	*RPS12*
$P < .01$	25	*ZNF184, SH3GL2, CCDC62, RCORL, RIMS1, UBAP2, RNF141, SCAF11, FBRSL1, RPS6KL1, UBTF, STK39*
$P < .05$	39	38 In same direction, 1 in opposite direction (*MEX3C*)

Abbreviation: PD, Parkinson disease.

[a] Full single-nucleotide variant (formerly SNP) identifiers and association statistics are listed in eTable 7 in the Supplement.

Figure 3. Polygenic Risk Score (PRS) Analysis in Asian Samples



Polygenic risk score distribution using 11 genome-wide significant Asian single-nucleotide variant (SNVs) (formerly, SNP) (A) and 90 known Parkinson disease SNVs (78 polymorphic) (B) identified in European samples and receiver operator curve based on polygenic risk prediction of Parkinson disease with previously reported SNVs (black) (area under the curve [AUC], 60.2%) vs combined European and Asian SNVs (orange) (AUC, 63.1%) (C).

Functional annotation and gene set analyses confirmed the enrichment of brain-expressed genes among the 22 genes mapped to the 11 genome-wide significant loci (eFigures 7-9 in the Supplement). Most of the 22 genes are expressed in the human brain throughout childhood and adulthood (eFigure 9 in the Supplement). Higher *SV2C* expression was found in the substantia nigra, striatum, and hypothalamus compared with other brain regions based on GTEX v7 data.[12] *WBSCR17* showed increased expression throughout multiple regions of the brain, similar to other known PD GWAS genes (eFigures 7-9 in the Supplement). There was no evidence for an association of the 2 novel SNVs (rs246814 and rs9638616) with gene expression levels in the brain or other relevant tissues.[12]

We calculated polygenic risk scores based on the 11 genome-wide significant SNVs identified in this Asian PD study. To evaluate the utility of SNVs identified by European GWASs in estimating risk in the Asian population, we calculated separate scores using 90 risk variants (78 polymorphic) from previously reported European loci using effect sizes derived from the GWAS in which they were first reported. We then evaluated the polygenic risk score distribution in the largest Asian subset of 2536 PD cases and 21 840 controls from Singapore/Malaysia (**Figure 3**).

In the weighted polygenic risk score distribution based on the 11 Asian SNVs, we observed a 4.0- and 3.5-fold difference in risk between the top and bottom 5% and 10% of the polygenic risk score distribution in controls (Figure 3A), respectively. We also observed that higher polygenic risk scores are significantly correlated with a younger age at onset in patients with PD ($\beta = -1.784$, $P = 5.17 \times 10^{-4}$), consistent with previous observations.[13] In contrast, there was no correlation between the age of the controls and polygenic risk scores ($\beta = 0.16$, $P = .21$). We estimated a 0.29-year decrease in age at onset for every additional copy of risk allele present among the 11 loci. Assessment within our Asian PD data set of weighted PRS scores based on the 78 European SNVs revealed a 2.9- and 2.2-fold difference in risk between the top and bottom 5% and 10% of polygenic risk score distribution in controls, respectively (Figure 3B).

These 11 Asian SNVs were estimated to account for 2.61% of the variance in PD risk in this data set (AUC, 60.4%; 95% CI, 59.5%-61.8%), while the 78 polymorphic European SNVs explained 2.57% of the variance in the same data set (AUC, 60.2%;

95% CI, 59.0%-61.2%). The AUCs were not significantly different between the 2 models (P = .83). Although the European PD SNVs are still able to discriminate Asian cases and controls, their utility is limited by allelic heterogeneity, LD differences, and variability in effect sizes because of gene-gene or gene-environment interactions. Combining the European and Asian loci, we observed a significant improvement in AUC (63.1%; 95% CI, 62.1%-64.4%) over the model based on European loci alone ($P = 6.81 \times 10^{-12}$) (Figure 3C), and similar to that in European samples (AUC, 65.1%).[5] Similar improvements were observed in the China (66.2% vs 64.7%, P = .005) and South Korea (69.5% vs 68.0%; P = .04) data sets. These analyses suggest that the data resolution conferred by polygenic risk score modeling will progressively improve as further research in Asian samples reveal additional PD risk loci.

Discussion

To our knowledge, we have conducted the largest multicenter Asian GWAS on PD to date, analyzing 31 575 individuals (6724 cases and 24 851 controls) from 6 regions across East Asia. We observed genome-wide significant association signals at 11 loci and consistent association at nominal significance (P < .05) at 51 other previously reported loci. Of the 2 novel loci we identified, we observed replication of the association at *SV2C* across 3 independent sample collections from European-ancestry and Japanese populations.

Strengths and Limitations

Our study had both strengths and limitations. The top-associated haplotype at *SV2C* is consistent between Asian and European-ancestry samples (eFigure 10A in the Supplement). Despite differences in LD patterns, the top SNV rs246814 is in near perfect LD with p.Asp543Asn (rs31244) and 2 other flanking SNVs (rs246813 and rs246815) in both Asian and European populations (eFigure 10B in the Supplement), suggesting that the functional variant likely resides on this common haplotype. The lack of significant replication at *WBSCR17* in the Japanese data set may be attributed to the small effect sizes observed at this locus (68.5% power to detect an association at α = .05). There is no significant genetic heterogeneity between the Japanese replication samples and our East Asian discovery GWAS samples (P = .24 for heterogeneity, I^2 = 25.6%). Future validation in larger collections of Asian samples will be needed to determine whether *WBSCR17* is an Asian-specific PD risk variant.

The Asian population is the largest worldwide and also one of the most ethnically diverse.[1] Our study aimed to identify loci common to 2 major East Asian populations (Han Chinese and South Koreans), with a significant proportion of our GWAS samples (1494 cases and 599 controls) being South Korean. We note that ethnic differences in allele frequencies and effect sizes are known to exist between Han Chinese, South Korean, and Japanese individuals that our study may not have identified. Further differences may exist between these and other unrepresented Asian populations in this study (eg, South Asian).[1] Future collections should include substantial numbers of these samples that will allow further evaluation of the differences in genetic risk between various ethnic Asian subgroups.

Although we have analyzed what is, to our knowledge, the largest Asian sample collection to date, the study still has limited statistical power to analyze rare alleles (minor allele frequency <5%) or common alleles with smaller effects (OR, <1.15) (eFigure 11 in the Supplement). Future GWASs of larger collections (>20 000) of PD cases in the Asian population are expected to lead to identification of multiple novel PD loci, some of which are likely to be population-specific. While the polygenic risk score calculated using common GWAS SNVs appear to be applicable, albeit with limited predictive value, across different populations, we expect more accurate estimates when population-specific risk loci and effect sizes along with rarer alleles are taken into consideration.

Conclusions

We believe our study is notable in several aspects. First, we provide evidence for the association of genetic variants, including a nonsynonymous variant, in *SV2C* with PD risk in humans. *SV2C* has been evaluated for a role in synaptic function and neurotransmitter release in the basal ganglia. SV2C and other synaptic vesicle 2 proteins, SV2A and SV2B, localize to the surface of synaptic vesicles of neurons. Unlike the other 2 proteins, SV2C showed restricted expression, primarily to phylogenetically old brain regions, such as the pallidum, brainstem, substantia nigra, and olfactory bulb, which are regions directly affected by PD pathologic changes.[14] Dardou et al[15] estimated that over 70% of dopaminergic neurons in the substantia nigra and ventral tegmentum and about 45% of cholinergic striatal interneurons in mice express *SV2C*. The investigators subsequently demonstrated increased *SV2C* expression in dopamine-depleted mouse models and increased tyrosine hydroxylase expression in *SV2C* knockout mice.[16] Dunn et al[11] later observed a significant reduction in synaptic striatal dopamine release in *SV2C* knockout mice, which causes mild motor deficits in the animals. The investigators further demonstrated altered expression of SV2C in postmortem brain tissue from human patients with PD with an *SNCA* mutation, but not from patients with other neurodegenerative conditions.[11] The SV2C protein appears to mediate dopamine homeostasis and motor function and may therefore serve as a therapeutic candidate for such deficits in PD. The missense variant Asp543Asn (rs31244) occurs within an extracellular/luminal domain containing multiple N-linked glycosylation sites. The presence of an additional asparagine residue on the risk haplotype may affect glycosylation of SV2C within this domain through introduction of a new glycosylation site matching the consensus sequence Asn-X-Ser/Thr and therefore alter its function and interaction with other proteins.[10] The association we now report between this naturally occurring *SV2C* missense allele and increased risk of PD lends further credence to *SV2C* being a potential therapeutic target, although further fine-mapping efforts and functional work will be needed to elucidate the biologic mechanisms underlying the association at this locus.

In addition, although our results demonstrate similarities in PD genetic risk between European and East Asian individuals with clear overlap in risk loci and consistency in effect sizes, there are some differences in the overall underlying genetic architecture involving allele frequency and LD patterns and allelic heterogeneity, leading to an improvement in the polygenic risk score model on inclusion of SNVs identified in Asian individuals. The newly observed association at *SV2C* underpins this point and suggests that future, larger studies focused on the Asian population will be important to reveal novel loci that are Asian specific or Han Chinese specific. Furthermore, future trans-ethnic meta-analysis with the European samples will help to fine-map these shared loci and further contribute to our understanding of similarities and differences in the genetic risk underlying PD.

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