

目崎高広, 林明人, 中瀬浩史, 後藤準, 梶龍兒, <u>長谷川一子</u>	ボツリヌス毒素療法の手引き	ジストニア 2012	長谷川一子	中外医学社	東京	2012	278-294
<u>長谷川一子</u>	ドパミンアゴニスト	GP/レジデントのためのパーキンソン病テキストブック	山本光利	アルタ出版社	東京	2012	121-128
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戸田 達史	各種疾患 神経筋疾患 福山型筋ジストロフィーの分子病態と治療(解説)	Annual Review 神経	2013 巻	238-245	2013
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中島健二, ほか	進行性核上性麻痺 (PSP) およびその亜型	Medical Practice	30	60-63	2013
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長谷川一子	パーキンソン病治療ガイドライン 2011	調剤と情報	18	57-64	2012
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長谷川一子	パーキンソン病内科治療の最近の動向	脳神経外科ジャーナル	21	758-7764	2012
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#### IV. 研究成果の刊行物・別刷

# Large-scale replication and heterogeneity in Parkinson disease genetic loci

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Supplemental data at [www.neurology.org](http://www.neurology.org)

Supplemental Data



## ABSTRACT

**Objective:** Eleven genetic loci have reached genome-wide significance in a recent meta-analysis of genome-wide association studies in Parkinson disease (PD) based on populations of Caucasian descent. The extent to which these genetic effects are consistent across different populations is unknown.

**Methods:** Investigators from the Genetic Epidemiology of Parkinson's Disease Consortium were invited to participate in the study. A total of 11 SNPs were genotyped in 8,750 cases and 8,955 controls. Fixed as well as random effects models were used to provide the summary risk estimates for these variants. We evaluated between-study heterogeneity and heterogeneity between populations of different ancestry.

**Results:** In the overall analysis, single nucleotide polymorphisms (SNPs) in 9 loci showed significant associations with protective per-allele odds ratios of 0.78–0.87 (*LAMP3*, *BST1*, and *MAPT*) and susceptibility per-allele odds ratios of 1.14–1.43 (*STK39*, *GAK*, *SNCA*, *LRRK2*, *SYT11*, and *HIP1R*). For 5 of the 9 replicated SNPs there was nominally significant between-site heterogeneity in the effect sizes ( $I^2$  estimates ranged from 39% to 48%). Subgroup analysis by ethnicity showed significantly stronger effects for the *BST1* (rs11724635) in Asian vs Caucasian populations and similar effects for *SNCA*, *LRRK2*, *LAMP3*, *HIP1R*, and *STK39* in Asian and Caucasian populations, while *MAPT* rs2942168 and *SYT11* rs34372695 were monomorphic in the Asian population, highlighting the role of population-specific heterogeneity in PD.

**Conclusion:** Our study allows insight to understand the distribution of newly identified genetic factors contributing to PD and shows that large-scale evaluation in diverse populations is important to understand the role of population-specific heterogeneity. *Neurology*® 2012;79:659–667

## GLOSSARY

CI = confidence interval; **GEO-PD** = Genetic Epidemiology of Parkinson's Disease; **GWAS** = genome-wide association studies; **HWE** = Hardy-Weinberg equilibrium; **MALDI-TOF** = matrix-assisted laser desorption/ionization time-of-flight; **MSA** = multiple system atrophy; **OR** = odds ratio; **PD** = Parkinson disease; **SNP** = single nucleotide polymorphism.

Genome-wide association studies (GWAS) have provided tangible gains in understanding the genetic architecture of complex diseases,<sup>1,2</sup> including Parkinson disease (PD).<sup>3</sup> Several GWAS have been conducted in PD in Caucasian populations and only 1 in the Asian population.<sup>3–11</sup> Consistent and reproducible association signals were confirmed in  $\alpha$ -synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), and microtubule-associated protein tau (*MAPT*), thus underscoring the importance of these 3 genes in the pathophysiology of the common sporadic forms of PD.<sup>3–10,12</sup> In addition to that, different studies have provided some evidence for an association for *BST1*, *GAK*, and *HLA-DRB5* with PD.<sup>6–9,13</sup>

A recently published GWAS meta-analysis in PD increased the number of identified PD genetic loci to 11.<sup>14</sup> This study reported significant between-study heterogeneity for some of the 11 genetic loci<sup>14</sup> even though data were restricted to Caucasian descent populations.

It is important to establish whether the 11 genetic loci that have been postulated to be associated with PD are replicated when tested with direct genotyping in a larger spectrum of diverse populations. The consistency or lack thereof of the genetic effects of these genetic

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variants across different populations may help to determine whether they represent genuine loci for PD susceptibility and whether they can be used for risk prediction across these diverse populations.<sup>15</sup> To gain further insight into genetic factors contributing to PD across different populations and define the implications of between-population heterogeneity, we performed a large-scale replication study within the GEO-PD consortium.

**METHODS Consortium.** Investigators from the Genetic Epidemiology of PD (GEO-PD) Consortium were invited to participate in this study. A total of 21 sites representing 19 countries from 4 continents agreed to contribute DNA samples and clinical data for a total of 17,705 individuals (8,750 cases and 8,955 controls). Healthy individuals matched for age and gender served as controls. They underwent neurologic examination and were excluded from the study whenever there was clinical evidence for any extrapyramidal disorder.

**Genotyping.** We selected 1 SNP per each gene locus, exactly as they were proposed by the recently published GWAS meta-analysis.<sup>14</sup> Genotyping was performed by a central genotyping core (Department of Human Genetics, Helmholtz Zentrum, Munich). Each site provided 100–200 ng of DNA to the laboratory core. In total 11 SNPs located in and around the genes encoding *SYT11*, *ACMSD*, *STK39*, *LAMP3*, *GAK*, *BST1*, *SNCA*, *HLA-DRB5*, *LRRK2*, *HIP1R*, and *MAPT* were genotyped. The genotyping core was blinded to case-control status of each site. Genotyping was performed using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry on a MassArray system (Sequenom, San Diego, CA). Cleaned extension products were analyzed by a mass spectrometer (Bruker Daltonik, USA) and peaks were identified using the MassArray Typer 4.0.2.5 software (Sequenom). Assays were designed by the AssayDesigner software 4.0 (Sequenom) with the default parameters for the iPLEX Gold chemistry and the Human Genotyping Tools ProxSNP and PreXTEND (Sequenom). All variants were genotyped in 1 multiplex assay. An experienced investigator blinded to case or control status of the samples visually checked genotype clustering. The average call rate of the variants was >97%.

In order to further enrich the samples of Asian ancestry populations, we also included GWAS data from a Japanese population (988 cases, 2,521 controls).<sup>6</sup> We used  $r^2$  threshold of 0.8–1.0 to select proxy SNPs from the Japanese GWAS. Using this threshold, we were able to capture only 3 SNPs from *BST1*, *SNCA*, and *LRRK2* genes.

**Standard protocol approvals, registrations, and patient consents.** The local Ethics Committee approved the study. All participants signed an informed consent.

**Analysis.** An exact test was used to assess whether the genotype distributions for each SNP deviated from Hardy-Weinberg equilibrium (HWE) among controls; each site was tested separately and deviation from HWE was considered significant at <0.01. We excluded data from sites where the missing rate was >5%. For our analysis, we adhered to the same allele coding as in the previous GWAS meta-analysis.<sup>14</sup>

For consistency effect estimates based on minor vs major allele contrast were computed. We used an additive model adjusted for age and gender to obtain effect estimates. Results were then synthesized using fixed and random effects models. Fixed effect models assume that the genetic effect is the same in populations from different sites and that observed differences are due to chance alone. For associations showing between-study heterogeneity, fixed effect estimates yield narrower confidence intervals (CIs) and smaller  $p$  values as compared to random effects models, which incorporate between-study heterogeneity.<sup>16–18</sup> Fixed effects analysis tests the null hypothesis of no association in all studied populations that are analyzed. Routinely, this assumption is used in GWAS settings to increase the power of meta-analysis to detect associations that may exist in some (at least 1) population. However, in presence of heterogeneity the effects may differ substantially in different populations and not all populations may show a genetic effect for the variant of interest. Random effects models allow the genetic effects might be different due to genuine heterogeneity that may exist across different sites. Random effects calculations take into account the estimated between-study heterogeneity. We used the inverse variance method for fixed effects models. Cochran Q test of homogeneity and the  $I^2$  metric were used to evaluate the between-site heterogeneity. The Q statistics follows  $\chi^2$ -based distribution with  $k - 1$  degrees of freedom ( $k =$  number of studies).  $I^2$  is estimated by the ratio  $(Q-df)/Q$ , where  $df$  is degrees of freedom. The  $I^2$  metric ranges from 0% to 100% and measures the proportion of variability that is beyond chance. Typically estimates of  $I^2 < 25\%$  are considered to reflect little or no heterogeneity, 25%–50% moderate heterogeneity, 50%–75% large heterogeneity, and >75% very large heterogeneity. It should be acknowledged that  $I^2$  can have large uncertainty in its estimation especially for variants with low minor allele frequency. Therefore, we also estimated the 95% CI of  $I^2$ .<sup>17</sup>

The overall main analysis considered all sites and populations irrespective of ancestry. Then, we separately analyzed Caucasian and Asian sites and we compared the genetic effects in these 2 major ancestry groups.

The SNPs evaluated in the recently published GWAS meta-analysis are common with minor allele frequencies varying from 13% to 46%,<sup>14</sup> except for SNP, rs34372695 (*SYT11*) where the minor allele frequency is 2%. Therefore, based on minor allele frequency and effect estimates obtained in the GWAS meta-analysis,<sup>14</sup> power calculations showed that our study would have at least 99% power to detect an allele-based odds ratio (OR) of 1.2 for minor allele frequencies of 10% or higher for  $\alpha = 0.05$ . Based on genome-wide significance level ( $\alpha = 5 \times 10^{-8}$ ), our study would have 43% power to detect an allele-based OR of 1.2 for minor allele frequency of 10%, but it would be 99% for same minor allele frequency and on OR of 1.4. Power would be only 69% for a minor allele frequency of 2% and OR of 1.2, but it would be 99% for the same minor allele frequency of 2% and an OR of 1.5.

Meta-analyses were performed using STATA 9.0 (Stata Corp., College Station, TX) and Review Manager 4.2.7.  $p$  Values are 2-tailed.

**RESULTS Characteristics of sites and overall database.** Twenty-one sites contributed a total of 8,750 cases and 8,955 controls. Characteristics of all participating sites are shown in table 1. Most sites contributed participants of Caucasian ancestry ( $n = 16$ ); 5 sites (counting also the GWAS performed in the Jap-

Table 1 Description of datasets contributed by each study site

Site	Country	No.	Case	Control	Male (%)	Female (%)	Mean AAO	Mean age at study	Diagnostic criteria
Annesi	Italy	394	197	197	204 (51.7)	190 (48.2)	61.5	63.7	UKPDBB
Brice <sup>a</sup>	France	505	272	233	302 (59.8)	203 (40.1)	47.6	57.8	UKPDBB
Bozi	Greece	222	114	108	107 (48.1)	115 (51.8)	69.9	74.5	UKPDBB
Wszolek	US	1,518	692	826	794 (52.3)	724 (47.6)	64.4	71.7	UKPDBB
Garraux	Belgium	82	68	14	45 (54.8)	37 (45.1)	62.1	69.6	UKPDBB
Hadjigeorgiou	Greece	714	357	357	379 (53.0)	335 (46.9)	63.4	63.7	UKPDBB
Jeon	Korea	749	408	341	314 (41.9)	435 (58.0)	57.6		UKPDBB
Opala	Poland	629	352	277	340 (54.0)	288 (45.7)	50.2	68.1	UKPDBB
Lynch	Ireland	740	368	372	340 (45.9)	400 (54.0)	50.5	70.7	UKPDBB
Lin	Taiwan	320	160	160	160 (50)	160 (50)	62.0	70.8	UKPDBB
Facheris	Italy	181	114	67	86 (47.5)	95 (52.4)	63.0		UKPDBB
Maraganore	US	1,024	801	223	600 (58.5)	361 (35.3)	59	74.7	Bower
Mellick	Australia	2,024	1,012	1,012	1,042 (51.4)	981 (48.4)	59	72.2	Bower
Morrison <sup>a</sup>	England	1,120	766	354	606 (54.1)	514 (45.8)	66.1		UKPDBB
Mok	China	436	260	176	264 (60.5)	170 (38.9)		63.5	UKPDBB
Aasly	Norway	1,278	656	622	721 (56.4)	557 (43.5)	58.8	72.9	UKPDBB
Wirdefeldt	Sweden	299	83	216	147 (49.1)	152 (50.8)	65.8	71.4	Gelb
Van Broeckhoven	Belgium	1,010	501	509	500 (49.5)	509 (50.3)	60.5	66.3	Pals/Gelb
Rogaeva	Canada	560	387	173	303 (54.1)	257 (45.8)	49.7	64.2	UKPDBB
Tan	Singapore	391	194	197	244 (62.4)	147 (37.5)	59.7	54.0	UKPDBB
Toda	Japan	3,509	988	2,521	1,844 (52.6)	1,665 (47.4)	58.7	66.0	UKPDBB
Total		17,705	8,750	8,955			59.5	67.6	

Abbreviations: AAO = age at onset; GWAS = genome-wide association studies; UKPDBB = UK Parkinson's Disease Brain Bank.

<sup>a</sup> Also included in the previously published GWAS.<sup>7,8</sup>

anese population<sup>6</sup>) included participants of Asian ancestry. We excluded 1 site with 114 cases and 67 controls from the analysis due to a plate layout error. The median age at onset was 59 years and median age at examination was 67 years.

We observed that for one site, effect estimates for all SNPs were “inverse” as compared to other Caucasian sites. Allele flipping for one particular site in the same Caucasian descent might reflect error in sampling ascertainment and is unlikely to reflect genuine effects.<sup>19</sup> This site (n = 181) was therefore excluded from further analyses. Overall, genotype call rates were >97%. The genotype distribution for each SNP in the controls of each site showed no departure from HWE, except for rs6599388 (*GAK*) in samples from 4 Asian sites. We therefore excluded this SNP (rs6599388) from analyses in the Asian population.

**Overall data synthesis.** We observed consistent and reproducible associations for *SNCA*, *LRRK2*, *MAPT*, *BST1*, *GAK*, *STK39*, *SYT11*, *LAMP3*, and *HIP1R* loci but not for *ACMSD* (rs10928513) or *HLA-DRB5* (rs3129882) where the per-allele OR was very close to the null (1.02 and 0.95, respectively) and

statistically nonsignificant (table 2). Thus we provide unequivocal support for the involvement of these newly identified genetic loci in the pathogenesis of PD.

Summary effect estimates were generally comparable with the previous GWAS meta-analysis results (table 2), although effect estimates in this study were stronger for *STK39* and somewhat weaker for *LRRK2* compared to the previous GWAS meta-analysis.<sup>14</sup> Exclusion of 1,625 samples that overlap with the previously published GWAS did not change any of the estimates (table e-1 on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org)). The protective per-allele OR ranged from 0.78 to 0.87 (*LAMP3*, *BST1*, and *MAPT*) and the susceptibility per-allele OR ranged from 1.14 to 1.43 (*STK39*, *GAK*, *SNCA*, *LRRK2*, *SYT11*, and *HIP1R*). Cochran Q statistics were nominally significant for *STK39*, *LAMP3*, *BST1*, and *SNCA* with I<sup>2</sup> estimates ranging from 39% to 48%. The heterogeneity reflected primarily differences in the magnitude of the effect sizes across different sites, while the direction of the effect was consistent in all sites, with rare exceptions.



**Table 2 Overall analysis irrespective of ethnicity and influence of between-study heterogeneity**

Gene	SNP	Q test p value	I <sup>2</sup> (95% CI)	Odds ratio (95% CI) by random effects	Fixed effects p value	Random effects p value	IPDGC study odds ratio (fixed effects p values)
ACMSD	rs10928513	0.71	0 (0-54)	1.02 (0.96-1.08)	0.479	0.479	1.07 (0.003)
STK39	rs2102808	0.02	46 (0-68)	1.21 (1.08-1.35)	0.0001	0.001	1.12 (0.0016)
LAMP3	rs11711441	0.04	39 (0-64)	0.85 (0.77-0.94)	3.01 × 10 <sup>-5</sup>	0.002	0.87 (6.92 × 10 <sup>-5</sup> )
GAK	rs6599388	0.06	39 (0-64)	1.19 (1.10-1.28)	3 × 10 <sup>-6</sup>	0.001	1.14 (7.46 × 10 <sup>-8</sup> )
HLA-DRB5	rs3129882	0.23	18 (0-53)	0.95 (0.90-1.01)	0.12	0.15	0.80 (9.3 × 10 <sup>-9</sup> )
BST1	rs11724635	0.02	43 (0-65)	0.87 (0.83-0.91)	2.01 × 10 <sup>-6</sup>	0.00001	0.87 (2.43 × 10 <sup>-9</sup> )
SNCA	rs356219	0.02	48 (0-69)	1.30 (1.21-1.40)	4.23 × 10 <sup>-23</sup>	4.23 × 10 <sup>-23</sup>	1.27 (4.23 × 10 <sup>-23</sup> )
SYT11	rs34372695	0.38	6 (0-50)	1.43 (1.15-1.78)	0.001	0.001	1.44 (1.18 × 10 <sup>-6</sup> )
LRRK2	rs1491942	0.75	0 (0-50)	1.14 (1.07-1.21)	1.06 × 10 <sup>-8</sup>	1.06 × 10 <sup>-8</sup>	1.30 (1.06 × 10 <sup>-8</sup> )
HIP1R	rs10847864	0.90	0 (0-44)	1.15 (1.09-1.21)	9.06 × 10 <sup>-7</sup>	9.06 × 10 <sup>-7</sup>	1.13 (9.06 × 10 <sup>-7</sup> )
MAPT	rs2942168	0.14	29 (0-62)	0.78 (0.71-0.85)	1.37 × 10 <sup>-13</sup>	1.37 × 10 <sup>-13</sup>	0.80 (1.37 × 10 <sup>-13</sup> )

Abbreviations: CI = confidence interval; IPDGC = International Parkinson disease Genomics Consortium; SNP = single nucleotide polymorphism.

**Analysis including only Caucasian sites.** Restricting the analysis to Caucasian sites only resulted in per-allele ORs that ranged from 0.78 to 0.90 for the 3 replicated protective loci (*BST1*, *LAMP3*, and *MAPT*) and from 1.14 to 1.43 for the 6 replicated susceptibility loci (*STK39*, *GAK*, *SNCA*, *LRRK2*, *SYT11*, and *HIP1R*), while *ACMSD* and *HLA-DRB5* still had no significant effect (table 3 and figure e-1).

Summary effect estimates were generally comparable to those of the previous GWAS meta-analysis,<sup>14</sup> except for modest differences in *STK39* and *LRRK2* effect sizes, as noted above also for the overall analysis. There was nominally significant heterogeneity only for *SNCA* and *LAMP3* (I<sup>2</sup> estimates 51% and 46%, respectively), but this reflected primarily differences in the magnitude of the effect size estimates rather than direction of effects across sites (figure e-1).

**Analysis including only Asian sites.** In the Asian series, not only the *SYT11* SNP, but also the *ACMSD* and *MAPT* SNPs were monomorphic (table e-2). Summary effect estimates for the remaining SNPs are shown in table 4. We again observed consistent nominally significant evidence of association for all loci except for *STK39* (which still had an effect size estimate consistent with what was seen in the overall analysis) and *HLA-DRB5* (which had a point estimate very close to the null), which still had an effect size estimate consistent with what was seen in the overall analysis. Results were generally consistent across sites, with the exception of *STK39* that showed very large heterogeneity (I<sup>2</sup> = 73%) (figure e-2).

**Comparison of effect size estimates.** Five gene loci (*HIP1R*, *LAMP3*, *LRRK2*, *SNCA*, and *STK39*)

**Table 3 Caucasian specific effect estimates and influence of between-study heterogeneity**

Gene	SNP	Q test p value	I <sup>2</sup> (95% CI)	Odds ratio (95% CI) by random effects	Fixed effects p value	Random effects p value
ACMSD	rs10928513	0.71	0 (0-54)	1.02 (0.96-1.08)	0.479	0.479
STK39	rs2102808	0.10	37 (0-65)	1.21 (1.08-1.35)	0.000	0.001
LAMP3	rs11711441	0.02	46 (0-70)	0.86 (0.76-0.97)	0.001	0.025
GAK	rs6599388	0.27	17 (0-57)	1.14 (1.06-1.23)	1.01 × 10 <sup>-4</sup>	0.001
HLA-DRB5	rs3129882	0.10	32 (0-63)	0.95 (0.88-1.02)	0.11	0.16
BST1	rs11724635	0.14	29 (0-62)	0.90 (0.85-0.95)	0.001	0.003
SNCA	rs356219	0.01	51 (0-72)	1.30 (1.19-1.42)	4.23 × 10 <sup>-23</sup>	4.23 × 10 <sup>-23</sup>
SYT11	rs34372695	0.38	6 (0-50)	1.43 (1.15-1.78)	0.001	0.001
LRRK2	rs1491942	0.80	0 (0-47)	1.15 (1.07-1.23)	1.06 × 10 <sup>-8</sup>	1.06 × 10 <sup>-8</sup>
HIP1R	rs10847864	0.90	0 (0-47)	1.15 (1.08-1.22)	9.06 × 10 <sup>-7</sup>	9.06 × 10 <sup>-7</sup>
MAPT	rs2942168	0.14	29 (0-62)	0.78 (0.71-0.85)	1.37 × 10 <sup>-13</sup>	1.37 × 10 <sup>-13</sup>

Abbreviations: CI = confidence interval; SNP = single nucleotide polymorphism.

Table 4 Asian specific effects and influence of between-study heterogeneity

Gene <sup>a</sup>	SNP	Q test p value	I <sup>2</sup> (95% CI)	Odds ratio (95% CI) by random effects	Fixed effects p value	Random effects p value
<i>STK39</i>	rs2102808	0.01	73 (0-88)	1.14 (0.85-1.52)	0.28	0.37
<i>LAMP3</i>	rs11711441	0.33	12 (0-72)	0.81 (0.67-0.97)	0.01	0.03
<i>BST1</i>	rs11724635	0.07	53 (0-81)	0.74 (0.68-0.81)	1.2 × 10 <sup>-6</sup>	0.001
<i>HLA-DRB5</i>	rs3129882	0.81	0 (0-68)	0.98 (0.85-1.13)	0.85	0.85
<i>SNCA</i>	rs356219	0.49	0 (0-68)	1.24 (1.08-1.43)	0.002	0.002
<i>LRRK2</i>	rs1491942	0.31	16 (0-73)	1.13 (1.02-1.24)	0.005	0.01
<i>HIP1R</i>	rs10847864	0.36	6 (0-70)	1.14 (0.99-1.32)	0.05	0.06

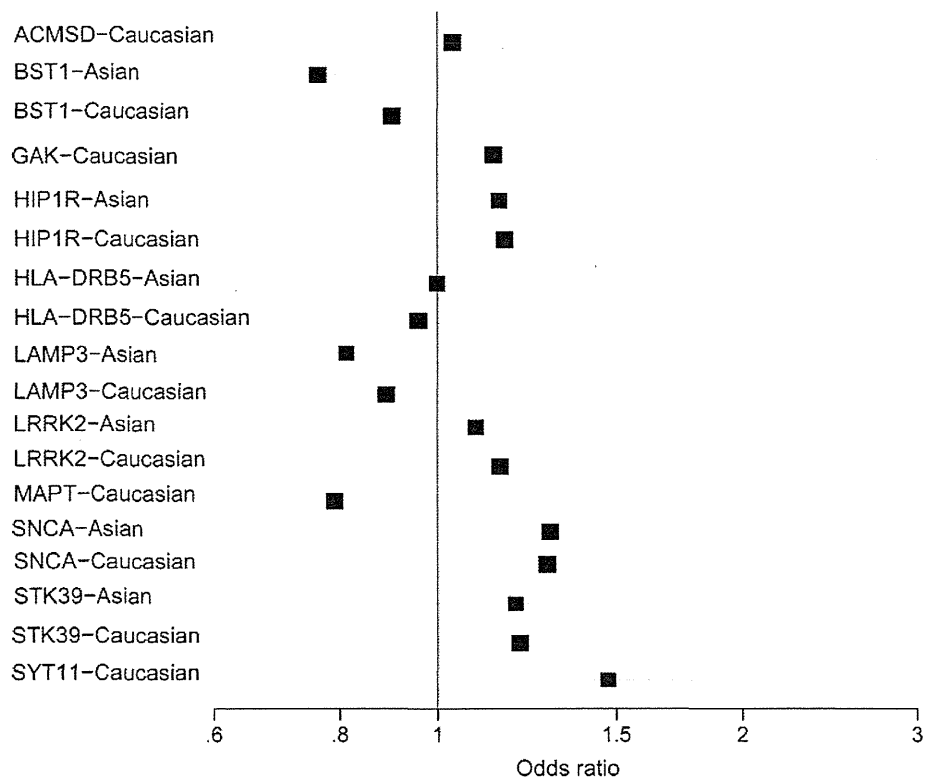
Abbreviations: CI = confidence interval; HWE = Hardy-Weinberg equilibrium; SNP = single nucleotide polymorphism.  
<sup>a</sup> ACMSD, SYT11, MAPT SNPs were monomorphic; GAK SNP showed departure from HWE and thus is not included in the table.

where both Caucasians and Asian populations were represented showed no difference in effect size estimates that were different beyond chance (figure 1). Conversely for *BST1*, the effects were different beyond chance for Asian and Caucasian populations with stronger genetic effects in the former.

**DISCUSSION** We performed a large-scale evaluation to assess the role of recently discovered genetic risk variants in the pathogenesis of PD in different

populations. Our study confirms 9 of the 11 postulated susceptibility SNPs for PD. The confirmed SNPs include the previously well documented *LRRK2*, *SNCA*, *BST1*, *GAK*, and *MAPT* associations,<sup>3,6-8,10,20</sup> and 4 of the 5 more recently proposed associations in *STK39*, *SYT11*, *LAMP3*, and *HIP1R* SNPs that might act as risk factors for PD. Conversely, we were unable to confirm the association between PD risk and SNPs rs10928513, rs3129882 in *ACMSD* and *HLA-DRB5*, respec-

Figure 1 Forest plot showing the comparison of effect of each single nucleotide polymorphism (SNP) in Caucasian and Asian population



Boxes indicate the summary effect estimate. SNPs in 3 loci (MAPT, SYT11, and ACMSD) were monomorphic in the Asian population and thus are not included in the graph. GAK SNP showed deviation from Hardy-Weinberg equilibrium in Asian series and thus excluded from the graph.

tively. Three SNPs were monomorphic in the Asian datasets.

The recently proposed *ACMSD* locus is likely to have represented a spurious association. The OR is very close to the null and 95% CI also excludes an OR larger than 1.08. Of note, even in GWAS meta-analysis, the OR estimate was only 1.07 in the replication phase, as compared with 1.38 in the discovery phase. Our results are in agreement with a recently published study.<sup>21</sup> This finding suggests that large-scale replication with direct genotyping is useful even for SNPs that pass conventional genome-wide significance thresholds. It is possible that with the use of the more extended imputation platforms using the 1,000 Genomes Project, the number of comparisons made is larger than what was done in the past with more limited imputation platforms and this may thus require more stringent levels of significance to claim genome-wide significance.

As observed in a recently published study,<sup>9</sup> the frequency of the *HLA-DRB5* SNP, rs3129882, varies considerably even within seemingly homogenous Caucasian populations; the frequency of risk allele is low in subjects of Northern European descent as compared to subjects from Southern European descent. Therefore, the observed lack of association for the *HLA-DRB5*-specific SNP rs3129882 should be interpreted with caution. Moreover, directionality as well as the magnitude of effect estimates obtained in our study for the *HLA-DRB5* locus specific SNP are comparable with previously published studies.<sup>9,22</sup>

Our study shed light on the role of heterogeneity in PD genetics. Detection of heterogeneity could provide new insight to understand the genetic architecture of the disease.<sup>17,23,24</sup> A number of factors can be attributed to the observed heterogeneity. First, clinically overlapping pathologies may lead to heterogeneity. Indeed the presence of distinct subgroups of patients during early clinical stages of PD could contribute to clinical heterogeneity.<sup>25</sup> Therefore, it is worth it to consider that genetic variants may exert different pathologic processes that eventually lead to complex clinical phenotypes.<sup>26</sup> For example, it has been shown that multiplications of *SNCA* gene lead to clinical phenotype, which clinically overlap with multiple system atrophy (MSA).<sup>27</sup> Moreover, SNPs in the 3'UTR of *SNCA* were shown to be associated with PD as well as MSA.<sup>3,6–8,28</sup> The most significant SNPs in both diseases clustered around 3'UTR of *SNCA*; SNP rs11931074, that was significantly associated with MSA in contrast to rs356219 in the PD meta-analysis.<sup>14,28</sup> The  $r^2$  between these 2 markers was only 0.16 in the Caucasian population. These 2 distinct signals in different yet overlapping pathologies therefore might reflect one cause of genetic heterogeneity. Second, heterogeneity might reflect that

different tagging polymorphisms were used in previously published GWAS. Of note, a recently published GWAS from United Kingdom, France, and Netherlands provided weak (as they did not surpass genome-wide significant threshold) yet consistent association signals for the *BST1* and *GAK* gene.<sup>7,8,13</sup> This probably reflects that the investigated markers were not causal variants but in linkage disequilibrium with a potential causal variant across different studies.

Our study helps to understand the role of population-specific heterogeneity in PD risk loci. Some risk variants exist only in populations of specific ancestry. For example, it is known that an ancient inversion (~900 kb) in the *MAPT* region occurred, which led to the formation of 2 nonrecombining haplotypes, H1 and H2.<sup>29</sup> The H2 haplotype is absent in East Asian populations as has been shown also by a recently published Asian GWAS that revealed no association for the *MAPT* locus.<sup>6</sup> This is in contrast to previously published candidate gene studies and GWAS in Caucasian populations that have shown consistent association with the *MAPT* locus.<sup>3,7,8,13</sup>

Some other variants may have a different magnitude of effect in populations of different ancestry. In our data, this is well exemplified by *BST1*, where the OR was significantly larger in populations of Asian than those of Caucasian ancestry. Conversely, we found that associations in 5 loci (*SNCA*, *LRRK2*, *LAMP3*, *HIP1R*, and *STK39*) had similar effects in these 2 ancestries.

The consistency or diversity of effect sizes in identified associations may reflect different patterns of linkage disequilibrium in these loci in diverse populations. It may also reflect differences in the susceptibility to develop PD and perhaps also differences in age at onset in different ancestry groups. The diversity in the magnitude of effects is important to take into account when considering the use of such information for personalized risk modeling.<sup>30</sup> Therefore caution should be used in extrapolating risks across different populations.

Our study provides strong and independent support for the role of 9 loci in the pathogenesis of PD in different populations. The detection and documentation of heterogeneity across different populations is useful in understanding the genetic architecture of this complex disease and in properly framing our ability to use this information in different clinical populations.

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## DISCLOSURE

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