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ITPKB and ZNF184 are associated with Parkinson's disease risk in East Asians

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Abstract (144 words)

A recent meta-analysis of Parkinson's disease (PD) genome-wide association studies has identified 17 novel risk loci in the European population. We aim to assess if these reported novel risk loci are similarly implicated in PD risk within the East Asian population by analyzing the reported risk SNP or proxy SNP in 14,006 East Asian samples (779 patients and 13,227 controls). We found that **nine** out of the 17 reported novel PD risk loci showed very similar effects in Europeans and East Asians ($I^2=0$ to 10.7%), out of which two loci *ITPKB* and *ZNF184* were significantly associated with PD in our samples. Two of the reported risk loci, *ANK2/CAMK2D* and *CTSB*, were non-polymorphic in East Asians and therefore not implicated in PD risk in the East Asian population. Given the small effect sizes of these risk loci, further validation is needed in additional Asian samples.

Key words: Parkinson's disease, Genetics, Association, East Asian population

1. Introduction

A recent meta-analysis of Parkinson's disease (PD) genome wide association studies (GWAS) across 20,184 patients and 397,324 controls of European descent, the largest to date, has identified 17 genome-wide significant novel risk loci (Chang et al., 2017). The neuro-centric candidate genes found at these novel loci suggested possible implication of autophagy and lysosomal regulation in PD. We aim to assess if these reported novel risk loci are similarly implicated in PD risk within the East Asian population.

2. Methods

To evaluate if the 17 novel loci reported are implicated in PD risk in the Asian population, we analyzed 14,006 East Asian samples (779 PD cases and 13,227 controls) in a genome-wide association study as previously described (Foo et al., 2017) and analyzed the reported lead risk SNP at the 17 reported novel risk loci or proxy SNPs in high linkage disequilibrium ($r^2 > 0.8$, identified in 1000 Genome phase 3 East Asian populations with LDlink (Machiela and Chanock, 2015)) where the lead risk SNP could not be assessed directly. Given that each of these 17 loci has prior evidence of association with PD in the European population (Chang et al., 2017), we set $P < 0.05$ as the threshold for statistical significance in assessing each SNP. Cochran's Q statistics and heterogeneity index were calculated using PLINK v1.07 (Purcell et al., 2007). Patients were diagnosed using the UK Brain Bank criteria. All patients and controls gave informed written consent and study was approved by the institutional ethics committee (Nanyang Technological University Singapore Institutional Review Board IRB-2016-08-011 and SingHealth Centralized Institutional Review Board CIRB 2002/008/A).

3. Results and Discussion

Of the 17 reported risk loci, we observed significant association ($P < 0.05$) at the *ITPKB* locus (rs4653767, $P = 0.016$) and *ZNF184* locus (rs9468199, $P = 0.018$) although none of the SNPs survived Bonferroni correction for multiple testing (17 tests; $P > 0.003$). Nonetheless, these two loci should be prioritized for further validation in additional East Asian cases. Another seven loci were found to have comparable effects (*IL1R2*, *SCN3A*, *ELOVL7*, *SH3GL2*, *FAM171A1*, *SORBS3/PDLIM2/C8orf58/BIN3* and *ATP6V0A1/PSMC3I/TUBG2*) between the published European samples and our East Asian samples, as shown by same odds ratio (OR) directionality and low heterogeneity index (**Table 1**, $P_{het} > 0.05$, $I^2 = 0$ to 10.7%), even though the associations were not statistically significant.

Two other loci, *ANK2/CAMK2D* and *CTSB* are unlikely to be implicated in PD risk in East Asians as the respective lead risk SNPs, rs78738012 and rs2740594, are non-polymorphic (**Table 1**). Further, the lead risk SNP at the *COQ7* locus is rare in the East Asian population (1000 Genome EAS minor allele frequency = 0.01) and could not be confidently imputed and assessed in our samples.

The last five reported risk SNPs at *SATB1*, *NCKIPSD/CDC71*, *ALAS1/TLR9/DNAH1/BAP1/PHF7/NISCH/STAB1/ITIH3/ITIH4*, *GALC* and *TOX3* appeared to have opposite OR directionality in Europeans compared to East Asians (**Table 1**). We observed potential evidence for heterogeneity at the *ALAS1/TLR9/DNAH1/BAP1/PHF7/NISCH/STAB1/ITIH3/ITIH4* risk locus (lead risk SNP rs143918452, $P_{het} < 0.05$, $I^2 = 83.15\%$). However, given the small effect sizes at the rest of these

loci in both European and East Asian populations and the lack of evidence for heterogeneity in the observed associations ($P_{het} > 0.05$, $I^2 = 39.8$ to 51.5%), further validation in larger samples is required to determine if these loci contribute to PD risk in the Asian population.

4. Conclusion

A recent replication study in Chinese samples (Chen et al., 2018) reported a lack of association with PD and multiple system atrophy risk at the *SCN3A*, *ZNF184*, *BIN3*, *GLAC* and *TOX3* loci. The lack of association at *ZNF184* in the Chinese population (Chen et al., 2018) may be due to a potential population specific effect of the *ZNF184* risk locus, potential interactions with other gene or environmental factors or the lack of statistical power to adequately assess the small effects of this and other risk variants.

Although our study had modest estimated power of 6.9-44.7% at $\alpha=0.05$ to detect associations at the 17 novel loci, we replicated the associations at *ITPKB* and *ZNF184* and conclude that three reported European PD risk alleles are rare or non-polymorphic and therefore are not major genetic risk factors for PD in East Asians. At least **nine** of these 17 PD risk loci, including *ITPKB* and *ZNF184*, are potential genetic risk factors for PD in East Asians which require further validation in more Asian samples. The “druggable” potential of the *ITPKB* protein product (Chang et al., 2017; Hopkins and Groom, 2002) provides greater motivation for further validation of the *ITPKB* risk locus. Overall, further validation and meta-analysis is needed in additional Asian sample collections to determine if these novel reported loci influence PD risk in Asians and other more diverse populations.

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Data Access

GWAS data is available upon request at <https://www.nni.com.sg/research/research-platforms/Genomics/Pages/Home.aspx>

Table 1: Assessment of novel Parkinson's disease loci discovered in Europeans in the East Asian population.

CHR:Bp (Hg19)	SNP	Candidate gene	European PD GWAS meta-analysis					East Asian samples					Meta-analysis _m	
			EAF 1000G EUR _l	EAF case	EAF control	P discovery	OR discovery	EAF 1000G EAS _m	EAF case _n	EAF control _n	P	OR	P _{het}	I ₂
Same direction														
1:226916078	<i>rs4653767_a</i>	<i>ITPKB</i>	31.00%	27.00%	28.30%	2.40×10 ⁻¹⁰	0.92	26.00%	25.55%	28.41%	0.016	0.87	0.349	0
2:102413116	<i>rs34043159_b</i>	<i>IL1R2</i>	35.00%	35.00%	33.20%	3.83×10 ⁻⁸	1.07	49.00%	48.26%	47.83%	0.72	1.02	0.335	0
2:166133632	<i>rs353116_c</i>	<i>SCN3A</i>	38.00%	37.00%	38.90%	9.73×10 ⁻⁷	0.94	60.00%	60.91%	60.99%	0.909	0.99	0.29	10.67
5:60273923	<i>rs2694528</i>	<i>ELOVL7</i>	11.00%	11.00%	9.30%	1.69×10 ⁻¹¹	1.15	5.00%	4.24%	4.20%	0.855	1.02	0.393	0
6:27681215	<i>rs9468199_d</i>	<i>ZNF184</i>	18.00%	20.00%	17.80%	3.44×10 ⁻¹³	1.12	18.00%	21.69%	19.34%	0.018	1.16	0.798	0
8:22525980	<i>rs2280104_e</i>	<i>SORBS3, PDLIM2, C8orf58, BIN3</i>	37.00%	36.00%	35.20%	9.06×10 ⁻⁷	1.06	20.00%	19.06%	17.37%	0.112	1.11	0.512	0
9:17579690	<i>rs13294100_f</i>	<i>SH3GL2</i>	36.00%	33.00%	35.40%	1.99×10 ⁻¹²	0.91	52.00%	50.90%	52.33%	0.297	0.95	0.449	0
10:15569598	<i>rs10906923_g</i>	<i>FAM171A1</i>	30.00%	31.00%	32.60%	2.37×10 ⁻⁸	0.93	56.00%	55.92%	56.47%	0.605	0.97	0.399	0
17:40698158	<i>rs601999</i>	<i>ATP6V0A1, PSMC3I, TUBG2</i>	69.00%	66.00%	67.40%	8.03×10 ⁻⁹	0.93	98.00%	98.00%	98.42%	0.221	0.80	0.412	0
Different direction														
3:18277488	<i>rs4073221</i>	<i>SATB1</i>	13.00%	14.00%	12.90%	3.02×10 ⁻⁹	1.11	6.00%	5.74%	5.90%	0.718	0.96	0.197	39.8
3:48748989	<i>rs12497850_h</i>	<i>NCKIPSD, CDC71</i>	34.00%	34.00%	35.60%	6.80×10 ⁻⁸	0.93	5.00%	2.66%	2.66%	0.972	1.01	0.149	51.94
3:52816840	<i>rs143918452_i</i>	<i>ALAS1, TLR9, DNAH1, BAP1, PHF7, NISCH, STAB1, ITIH3, ITIH4</i>	100.00%	99.00%	99.50%	2.25×10 ⁻⁷	0.68	99.00%	98.85%	98.55%	0.345	1.26	0.015	83.15
14:88472612	<i>rs8005172</i>	<i>GALC</i>	42.00%	45.00%	43.60%	1.20×10 ⁻⁹	1.08	61.00%	65.10%	65.09%	0.971	1.00	0.175	45.59
16:52599188	<i>rs4784227_j</i>	<i>TOX3</i>	25.00%	26.00%	24.70%	8.29×10 ⁻⁸	1.08	25.00%	23.64%	24.05%	0.748	0.98	0.136	55.1
Non-polymorphic/ Rare														
4:114360372	<i>rs78738012</i>	<i>ANK2, CAMK2D</i>	11.00%	11.00%	10.00%	2.11×10 ⁻⁹	1.14	0.00%	NA	NA	NA	NA	NA	NA
8:11707174	<i>rs2740594</i>	<i>CTSB</i>	74.00%	75.00%	73.40%	9.54×10 ⁻¹¹	1.1	100.00%	NA	NA	NA	NA	NA	NA
16:19279464	<i>rs11343_k</i>	<i>COQ7</i>	46.00%	46.00%	44.10%	1.46×10 ⁻⁹	1.07	1.00%	-	-	-	-	-	-

Note: EAF -- Effect allele frequency; OR -- Odds ratio; a -- Statistics in East Asian samples based on proxy SNP rs10495249 in high linkage equilibrium ($r_2 = 1$, $D' = 1$) but with lower imputation quality to reported lead SNP; b -- Statistics in East Asian samples based on proxy SNP rs7569169 in high linkage equilibrium ($r_2 = 1$, $D' = 1$) to reported lead SNP; c -- Statistics in East Asian samples based on proxy SNP rs353128 in high linkage equilibrium ($r_2 = 0.811$, $D' = 0.982$) but with lower imputation quality to reported lead SNP; **d** -- Statistics in East Asian samples based on proxy SNP rs9393848 in high linkage equilibrium ($r_2 = 0.922$, $D' = 1$) to reported lead SNP; **e** -- Statistics in East Asian samples based on proxy SNP rs4872531 in high linkage equilibrium ($r_2 = 0.9876$, $D' = 0.9938$) but with lower imputation quality to reported lead SNP; **f** -- Statistics in East Asian samples based on proxy SNP rs10810812 in high linkage equilibrium ($r_2 = 0.892$, $D' = 0.948$) to reported lead SNP; **g** -- Statistics in East Asian samples based on proxy SNP rs4750665 in high linkage equilibrium ($r_2 = 0.988$, $D' = 1$) to reported lead SNP; **h** -- Statistics in East Asian samples based on proxy SNP rs9883469 in high linkage equilibrium ($r_2 = 0.7846$, $D' = 0.9139$) to reported lead SNP; **i** -- Statistics in East Asian samples based on proxy SNP rs60309163 in high linkage equilibrium ($r_2 = 1$, $D' = 1$) but with lower imputation quality to reported lead SNP; j -- Statistics in East Asian samples based on proxy SNP rs4784226 in high linkage equilibrium ($r_2 = 0.9077$, $D' = 0.973$) but with lower imputation quality to reported lead SNP; k -- SNP is rare in EAS and was not confidently imputed; l -- EAF in European population based on 1000 Genome Phase 3; m -- EAF in East Asian population based on 1000 Genome Phase 3; **n -- EAF in East Asian cases and controls are rounded to 2 decimal places;** m -- Meta-analysis was carried out on reported risk SNPs or proxy SNPs, P_{het} refers to p-value for Cochran's Q statistics, I₂ refers to heterogeneity index.

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