Short Report

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Association of HLA locus variant in Parkinson's disease

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Abstract

A variant (rs3129882) in the genome-wide association study (GWAS)-linked variant [in the human leukocyte antigen (HLA) gene region] has been reported to associate with an increased risk of Parkinson's disease (PD) in Caucasian population. Studies among Chinese are limited. To address this, we analysed rs3129882 in a total of 1312 subjects of Chinese ethnicity from independent Asian centers comprising of 675 controls and 637 PD cases. The rs3129882 variant was associated with a decreased risk in our ethnic Chinese PD patients. Logistic regression analysis taking into consideration variables of age, gender and race showed that allele A reduced the risk of PD via a dominant model [odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.62, 0.96, p = 0.018]. As HLA is a highly polymorphic region, it is possible that ethnic-specific effect or environmental agents may modulate the effect of this GWAS-linked locus in influencing the risk of PD.

Parkinson's disease (PD) is a progressive neurodegenerative disease which frequently leads to neurological disability. There have been a number of genes that have been associated with familial and sporadic PD, including \textit{LRRK2}, \textit{PINK1}, \textit{Parkin/Park2} [1]. A recent genome-wide association study (GWAS) identified another possible genetic marker that is associated with PD among Caucasians, and this was particularly strong for men and for late-onset PD [2]. This GWAS-linked single nucleotide polymorphism (SNP) is located in the human leukocyte antigen (HLA) gene on chromosome 6p21.3. The SNP rs3129882 in intron 1 of HLA-DRA has been shown to be most robustly associated with PD. HLA-DR is a major histocompatibility complex which has a role in immune responses and inflammation. The identification of rs3129882 highlights the links between PD and human immunity and inflammation, and potentially opens up a new avenue for therapeutic intervention.

Recent replication studies in other Caucasian populations have provided conflicting results [3, 4]. Interestingly, while the Caucasian cohort study examined by Hamza [2] found the minor G allele to be the susceptibility allele, Guo [4] reported the susceptibility allele to be the A allele in their Asian cohort. The HLA region is known to be polymorphic amongst different ethnic groups, and therefore the differences in minor alleles can be attributed to the polymorphic nature of this genomic region.
To address current limited information of this locus among ethnic Chinese and conflicting results among Caucasians, we examined the association between rs3129882 and PD among ethnic Chinese in two independent Asian centers.

Methods

1. Recruitment
   Patients diagnosed to have PD by movement disorders neurologists at three Asian centers (two in Singapore and one in Malaysia) based on the UK Brain Bank criteria were recruited. Controls of similar age, gender and race examined by clinicians and those without any evidence of neurological diseases were also recruited for the study. Effort was taken to match these controls with the patients in terms of geographical region.

2. Genotyping analysis
   A total of 1312 ethnic Chinese subjects comprising of 675 controls and 637 PD cases were included in the study. Eighty cases and 57 controls have participated in a previous GWAS study [5]. Genomic DNA was extracted from blood samples using standard protocols. Genotyping of rs3129882 was performed using TaqMan® SNP Genotyping Assay and TaqMan® genotyping Master Mix according to the manufacturer's standard protocol on a 96-well plate. Fluorescent signals of VIC- and FAM-probes were analysed at end point; allele call and genotypes were generated automatically in Applied Biosystems, Foster City, CA 7500 series Real-Time polymerase chain reaction (PCR) System. The thermal cycling conditions included 50°C for 2 min, 95°C for 10 min and 40 cycles of denaturing and anneal/extension reactions (92°C for 15 s and 60°C for 1 min). Sequencing was carried out to validate representative genotypes in selected samples.

3. Statistical analysis
   Fisher's exact test was performed to verify the Hardy–Weinberg equilibrium (HWE) of rs3129882 among controls and the gender distribution between cases and controls. Odds ratio (OR) and 95% confidence interval (CI) were estimated to investigate the role of SNP in the development of PD by means of logistic regression. Then, the most suitable model was selected based on the relationship of OR$_1$ (AA vs GG) and OR$_2$ (AG vs GG) to reflect a biological model of gene effect. We assumed the disease allele is in complete linkage disequilibrium with rs3129882 and with the same allele.
A total of 1312 subjects that consisted of 675 controls and 637 cases were included in the analysis. Table 1 shows the demographic features of the cohort. The SNP rs3129882 was in HWE among controls verified by means of Fisher's exact test. The median age, together with range of controls and cases were 60.0 (29, 88) and 62.0 (21, 90) years, respectively. Logistic regression analysis taking variables such as age, gender and race into consideration showed that variant A reduced the risk of PD via a dominant model (OR = 0.77, 95% CI = 0.62, 0.96, p = 0.018; Table 2).

### Table 1. Demographic features of subjects from the two centers

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>67.2 (SD = ±9.80)</td>
<td>61.6 (SD = ±9.56)</td>
</tr>
<tr>
<td>Mean age of onset (years)</td>
<td>61.0 (SD = ±11.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Gender, male %</td>
<td>57.2</td>
<td>51.2</td>
</tr>
<tr>
<td>Chinese</td>
<td>637</td>
<td>675</td>
</tr>
</tbody>
</table>

SD, standard deviation.

### Table 2. Frequency of genotypes and alleles for the rs3129882 variant among Parkinson's disease (PD) and controls
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR(^a)</th>
<th>OR(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>304</td>
<td>278</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>GA</td>
<td>260</td>
<td>321</td>
<td>0.74 (0.59, 0.94)</td>
<td>0.74 (0.58, 0.94)</td>
</tr>
<tr>
<td>AA</td>
<td>73</td>
<td>76</td>
<td>0.88 (0.61, 1.26)</td>
<td>0.87 (0.59, 1.27)</td>
</tr>
<tr>
<td>Common (G) allele</td>
<td>868</td>
<td>877</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Minor (A) allele</td>
<td>406</td>
<td>473</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dominant model</td>
<td>—</td>
<td>—</td>
<td>0.77 (0.62, 0.96)</td>
<td>0.76 (0.61, 0.96)</td>
</tr>
<tr>
<td>p value</td>
<td>—</td>
<td>—</td>
<td>0.018</td>
<td>0.018</td>
</tr>
</tbody>
</table>

OR, odds ratio.

\(^a\) Raw OR.

\(^b\) Adjusted by age, gender and race.

**Discussion**

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The rs3129882 variant at the GWAS-linked locus is the most widely assessed marker at the HLA-DRA region in relation to PD, though other variants have also been examined [6]. Both HLA-DRA and HLA-DRB encode proteins that are referred to as class II HLA-DR antigens. The HLA-DRA expression level is correlated with rs3129882, even though rs3129882 is an intronic marker. The rs3129882 is not in high LD with any variant within the HLA-DRA region (\(r^2 \leq 0.8\%\)) [2]. It is possible that the variant may affect HLA mRNA splicing or gene expression.

The first report of this variant as a susceptibility factor was in PD by Hamza and colleagues, replication studies in Caucasian cohorts have produced inconsistent results (Table 3). It is also interesting to note that the minor alleles are reversed in Caucasians and Chinese. Guo reported the A allele to be a risk factor in late-onset, sporadic Chinese PD

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patients in Mainland China, while the result could not be replicated by Chiang and colleagues in Taiwan. In this study, we showed that the A allele reduces risk of developing PD among ethnic Chinese in Singapore and Malaysia. The minor allele frequency (MAF) of the A allele in the controls in Chiang's study was 0.368, in Guo's study 0.29 and in our dataset was 0.35. The MAF for this allele in the HapMap Han Chinese (China) database was 0.384. Therefore, it is possible that there was a selection bias of controls in the study by Guo. Although the distributions of alleles are different in different populations, the biological effect of each allele (A or G) might be same in different populations. Functional studies will need to be conducted to investigate the effect of the G and A alleles.

Table 3. Summary of published literature (Jan 2010–Jun 2012) on rs3129882

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamza et al. [2]</td>
<td>Caucasians (American of European ancestry)</td>
<td>Minor allele G</td>
<td>G allele increases risk of PD OR 1.32 p = 2.9 × 10^{-8}</td>
</tr>
<tr>
<td></td>
<td>2000 PD</td>
<td>G allele</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1986 controls</td>
<td>0.46 PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.40 controls</td>
<td></td>
</tr>
<tr>
<td>Edwards et al. [8]</td>
<td>Caucasian</td>
<td>Minor allele G</td>
<td>Borderline association OR 1.17 p = 0.06 (as mentioned in Mata et al. [3])</td>
</tr>
<tr>
<td></td>
<td>604 PD</td>
<td>G allele</td>
<td></td>
</tr>
<tr>
<td></td>
<td>619 controls</td>
<td>0.46 PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.40 controls</td>
<td></td>
</tr>
<tr>
<td>Mata et al. [3]</td>
<td>Spanish</td>
<td>Minor allele G</td>
<td>No association OR 1.01 p = 0.88</td>
</tr>
<tr>
<td></td>
<td>1445 PD</td>
<td>G allele</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1161 controls</td>
<td>0.43 PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.42 controls</td>
<td></td>
</tr>
<tr>
<td>Simon-Sanchez et al. [6]</td>
<td>Caucasian (Dutch)</td>
<td>Not indicated</td>
<td>No association OR 1.07 p = 0.312</td>
</tr>
<tr>
<td></td>
<td>772 PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2024 controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; PD, Parkinson's disease.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiang et al. [7]</td>
<td>Taiwanese</td>
<td>G allele</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>538 PD</td>
<td>0.647 PD</td>
<td>OR 0.94 for A allele</td>
</tr>
<tr>
<td></td>
<td>532 controls</td>
<td>0.632</td>
<td>p = 0.446</td>
</tr>
<tr>
<td>Guo et al. [4]</td>
<td>Chinese</td>
<td>G allele</td>
<td>A allele confers increased risk of PD, OR 1.37</td>
</tr>
<tr>
<td></td>
<td>284 PD</td>
<td>0.641 PD</td>
<td>controls</td>
</tr>
<tr>
<td></td>
<td>258 controls</td>
<td>0.709</td>
<td>No OR value reported</td>
</tr>
<tr>
<td></td>
<td>A allele</td>
<td>0.359 PD</td>
<td>p = 0.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.291</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>Chinese (Mainland and Taiwan)</td>
<td>G allele</td>
<td>No association</td>
</tr>
<tr>
<td>Chiang et al. [7] and Guo et al. [4] (as in Chiang et al. paper)</td>
<td>822 PD</td>
<td>0.645 PD</td>
<td>OR 1.06</td>
</tr>
<tr>
<td></td>
<td>790 Controls</td>
<td>0.355</td>
<td>p = 0.47</td>
</tr>
<tr>
<td></td>
<td>A allele</td>
<td>0.653 PD</td>
<td>controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.343</td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>Chinese</td>
<td>G allele</td>
<td>A allele reduces risk of PD</td>
</tr>
<tr>
<td></td>
<td>637 PD</td>
<td>0.68 PD</td>
<td>OR 0.76, p = 0.018</td>
</tr>
<tr>
<td></td>
<td>675 controls</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A allele</td>
<td>0.32 PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.35</td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; PD, Parkinson's disease.
Although Chiang's study in Taiwan did not find any significant association with rs3129882, there was a trend toward a protective effect (OR = 0.94, p = 0.446), similar to our study findings [7]. It is likely that the discrepant associations and minor/major allele differences among the same race are due to the highly polymorphic region of the HLA locus which may result in genetic variability that can be influenced by environmental or other gene–gene effects.

In conclusion, our case–control study showed a decreased risk of rs3129882 in our ethnic Chinese PD patients, instead of an increased risk. Our findings add to the understanding of the significance of the HLA region in association with PD in this ethnic group. With continued research into the HLA region and PD in ethnic Han Chinese communities throughout the world, it will become clear whether the protective effect is restricted to certain geographical regions or it represents the association in the Han Chinese as a whole. Our results will also provide impetus for further independent studies in other Chinese populations and comparisons with other Asian races to determine the exact modulating effect of this locus in PD.

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**Ethics approval**

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The study has received approval from the relevant ethics committees and informed consent has been taken from every
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