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BRIEF REPORT

The Interaction between *HLA-DRB1* and Smoking in Parkinson's Disease Revisited

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ABSTRACT: Background: Two studies that examined the interaction between *HLA-DRB1* and smoking in Parkinson's disease (PD) yielded findings in opposite directions.
Objective: To perform a large-scale independent replication of the *HLA-DRB1* × smoking interaction.
Methods: We genotyped 182 single nucleotide polymorphism (SNPs) associated with smoking initiation in 12 424 cases and 9480 controls to perform a Mendelian randomization (MR) analysis in strata defined by *HLA-DRB1*.
Results: At the amino acid level, a valine at position 11 (V11) in *HLA-DRB1* displayed the strongest association with PD. MR showed an inverse association between genetically predicted smoking initiation and PD only in absence of V11 (odds ratio, 0.74, 95% confidence interval, 0.59–0.93, $P_{Interaction} = 0.028$). *In silico* predictions of the influence of V11 and smoking-induced modifications of α-synuclein on binding affinity showed findings consistent with this interaction pattern.
Conclusions: Despite being one of the most robust findings in PD research, the mechanisms underlying the inverse association between smoking and PD remain unknown. Our findings may help better understand this association. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; smoking; gene-environment interaction; HLA

Genome-wide association studies (GWAS) in Parkinson's disease (PD) identified an association with the human leukocyte antigen (*HLA*) region, in particular with *HLA-DRB1*. Hollenbach et al[1] reported an inverse association of PD with the shared epitope (SE), a combination of amino acids (AA) coded by *HLA-DRB1*, only in the presence of a valine at position 11 (V11). The strongest association in a cross-ethnic GWAS meta-analysis was an inverse association with a histidine at position 13 (H13) in *HLA-DRB1*, strongly correlated with V11.[2] The latest study, with some overlap with the previous two, highlighted three AA (V11, H13, and H33) encoded by *HLA-DRB1* inversely associated with PD.[3]

Following studies showing interactions between smoking and *HLA-DRB1* in other conditions,[4-6] Chuang et al[7] genotyped one single nucleotide polymorphism (SNP) in the *HLA-DRB1* region whose minor G allele is inversely associated with PD (2056 cases, 2723 controls) and reported a significant positive interaction between self-reported smoking and rs660895-G: the inverse association between smoking and PD was stronger in carriers of the AA genotype compared to G-allele carriers.[7] Based on a smaller selected sample (837 cases, 918 controls), the study that identified an inverse association of the SE and V11 combination (SE+V11+) with PD also showed an interaction with smoking, but in the opposite direction: the inverse association between smoking and PD was restricted to SE+V11+ carriers.[1] The authors hypothesized that post-translational modifications of α-synuclein induced by smoking (citrullination/homocitrullination) explained this interaction.

We performed a large-scale independent replication of the *HLA-DRB1* × smoking interaction by performing a Mendelian randomization (MR) analysis using smoking predisposing genes as instrumental variables in strata defined by *HLA-DRB1*.

Subjects and Methods

Courage-PD

The Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease (Courage-PD) consortium pooled individual-level data from 35 studies and used the Neurochip array to genotype participants (Supplementary Appendix S1). Analyses are based on 26 studies with at least 50 cases or controls of European descent (12 424 cases, 9480 controls); participants' chracteristics are shown in Supplementary Table S1. Additional methods on genotyping and imputation of *HLA* alleles/haplotypes/AA are available as Supplementary Appendix S1. All studies were approved by local ethical committees following procedures of each country.

Smoking Initiation: Two-Sample Mendelian Randomization

Because self-reported smoking was not available in most studies, we used SNPs associated with smoking initiation to perform two-sample MR.[8] Summary statistics for the association between SNPs and smoking initiation (182 SNPs independently associated at $P < 5 \times 10^{-8}$) came from the GWAS and Sequencing Consortium of Alcohol and Nicotine use (n = 1 232 091, European descent) (Supplementary Appendix S1),[9] and those for associations with PD came from Courage-PD (Supplementary Table S2).

In Silico Prediction of Binding Affinity of *HLA-DRB1* Alleles to α-Synuclein

We assessed the binding affinity (nM) of *HLA-DRB1* alleles to α-synuclein derived peptides using NetMHCIIpan 4.0 and predicted whether peptides are strong, weak, or non-binders.[10] After targeting 607 four-digit *HLA-DRB1* alleles, we restricted our analyses to 34 alleles observed in Courage-PD. Of 126 α-synuclein derived peptides,[1] we retained 96 peptides with lysine residues that can be

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homocitrullinated to examine the role of smoking-related post-translational modifications. We also performed analyses restricted to a single peptide (Tyrosine 39, Y39) that induces T cell responses in PD patients[11] and was previously used for binding affinity predictions.[2]

Statistical Analyses

We used SAS9.4 (SAS Institute Inc, Cary, NC, USA), STATA16 (StataCorp LP, College Station, TX, USA), and R packages HIBAG[12] and TwoSampleMR[13] (R Foundation for Statistical Computing, Vienna, Austria).

Interaction between Genetically Predicted Smoking Initiation and HLA-DRB1

To perform an independent replication of the *HLA-DRB1* × smoking interaction, we excluded the French study that contributed to identify the interaction between smoking and rs660895 in PD.[7]

We used the random-effects inverse-variance weighted (IVW)[8] approach to perform MR analyses for genetically predicted smoking initiation in two strata defined by the presence of V11 encoded by *HLA-DRB1* alleles (Supplementary Appendix S1). We compared the two MR estimates using the statistic $(\beta_2-\beta_1)/\sqrt{\left(SE(\beta_2)^2+SE(\beta_1)^2\right.}$, where β_1 and β_2 are MR estimates in the two strata with variances $SE(\beta_1)^2$ and $SE(\beta_2)^2$; this difference represents the interaction between smoking and *HLA-DRB1* and follows a normal distribution. In sensitivity analyses, we used other MR approaches that are less powerful, but more robust to pleiotropy (weighted median-method and mode-based, MR-PRESSO, MR-Lasso)[8]; we also performed analyses after excluding 31 pleiotropic SNPs associated with alcohol drinking and/or body mass index (Supplementary Appendix S1).

As secondary analyses, we ran MR analyses stratified by rs660895[7] and *HLA-DRB1**04,[3] which are both inversely associated with PD and in linkage disequilibrium with V11. Analyses stratified by rs660895 have the advantage that they did not involve *HLA* imputation and are, therefore, based on a larger number of cases and controls than analyses that required *HLA* imputation.

In Silico Prediction of Binding Affinity

To examine the influence of V11 encoded by *HLA-DRB1* alleles and homocitrullination (HC) of α-synuclein derived peptides on binding affinity, we described binding affinity for the four groups defined by the combination of V11 and HC. All 2 × 2 differences were tested using the Wilcoxon non-parametric test corrected for multiple comparisons.[14] We compared the percentage of binding peptides in the four groups using multinomial logistic regression.

Data Availability

Results can be reproduced using the Supplementary Appendix S1.

Results

Supplementary Table S3 shows 19 SNPs from the *HLA* region associated with PD after accounting for multiple comparisons, of which 17 were located near *HLA-DRB1* (including rs660895); none of them was associated with smoking initiation ($P > 0.05$). Among 64 alleles of *HLA* class 2 genes (*HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1*), five were significantly and inversely associated with PD (*HLA-DQA1**03:01, *HLA-DQA1**03:03; *HLA-DQB1**03:02; *HLA-DRB1**04:01, and *HLA-DRB1**04:04) (Supplementary Table S4). The odds ratio (OR) for the association of all *HLA-DRB1**04 alleles combined with PD was of 0.84 (95% confidence interval [CI], 0.78–0.91; $P = 3.9 \times 10^{-6}$). Associations between *DRB1* ~ *HLA-DQB1* haplotypes and PD are shown in Supplementary Table S4.

Among 131 AA encoded by *HLA-DRB1* and 116 by *HLA-DQB1*, 11 AA were associated (9 inversely, 2 positively) with PD and were all encoded by *HLA-DRB1* (Supplementary Table S5). Two AA, V11, and S37, remained significantly associated with PD after a backward stepwise selection procedure, with a stronger association for V11 (OR, 0.85; 95% CI, 0.79–0.92; $P = 2.2 \times 10^{-5}$) than S37 (OR, 1.07; 95% CI, 1.00–1.14; $P = 0.040$). The association of H13 and H33 with PD was explained by V11 (Supplementary Table S6). We found no significant interaction between SE and V11 ($P = 0.29$); only V11 remained associated with PD (OR, 0.81; 95% CI, 0.74–0.89; $P < 10–3$) when both were included in the model (Supplementary Table S7).

The overall association between genetically predicted smoking initiation and PD was of 0.86 (95% CI, 0.73–1.05; $P = 0.10$) without evidence of heterogeneity between SNPs ($P = 0.40$). Compared with 26% (n = 2212) of the controls, 22% (n = 2531) of the cases carried at least one V11 residue. Genetically predicted smoking initiation was inversely associated with PD in the absence of V11 (OR_{IVW}, 0.74; 95%, 0.59–0.93; $P = 0.0092$), but not in its presence ($OR_{IVW,}$ 1.25; 95% CI, 0.83–1.87; $P = 0.29$), with a positive and significant interaction ($P = 0.03$) (Table 1, Fig. 1). There was no significant heterogeneity across SNPs and MR-Presso did not detect pleiotropy (all $P > 0.10$). Results of pleiotropy-robust approaches were consistent with the IVW method, although CIs were generally larger. Similar conclusions were reached after

TABLE 1 *Mendelian randomization analysis of the relation between genetically predicted smoking initiation (182 SNPs) and PD stratified by* HLA-DRB1

	0 allele or AA residue			1/2 alleles or AA residues				
HLA-DRB1	**OR per 1-SD increase in the prevalence of ever smoking (95% CI)**	***P***	***P*-het.**	**OR per 1-SD increase in the prevalence of ever smoking (95% CI)**	***P***	***P*-het.**	**Interaction OR (95% CI)[a]**	***P***
Valine 11[b]	6383 controls, 8812 cases			2212 controls, 2531 cases				
Inverse variance weighted	0.74 (0.59–0.93)	9.2×10^{-3}	0.73	1.25 (0.83–1.87)	0.29	0.40	1.68 (1.06–2.68)	0.0
Weighted median	0.75 (0.53–1.07)	0.11		1.14 (0.61–2.15)	0.68		1.52 (0.75–3.11)	0.26
Weighted mode	0.63 (0.30–1.31)	0.22		1.72 (0.38–7.82)	0.48		2.74 (0.51–14.77)	0.24
MR-Lasso	No invalid SNP ($\lambda = 0.20$)			1.30 (0.87–1.96)	0.20[c]		1.76 (1.10–2.81)	0.020
MR-PRESSO			0.59			0.47		
rs660895-G[d]	6498 controls, 8903 cases			2982 controls, 3521 cases				
Inverse variance weighted	0.73 (0.59–0.91)	4.8×10^{-3}	0.84	1.33 (0.95–1.87)	0.10	0.41	1.83 (1.22–2.74)	3.5×10^{-3}
Weighted median	0.72 (0.52–1.00)	0.05		1.04 (0.62–1.73)	0.89		1.45 (0.78–2.66)	0.24
Weighted mode	0.68 (0.31–1.48)	0.34		0.99 (0.23–4.26)	0.99		1.46 (0.30–7.08)	0.66
MR-Lasso	No invalid SNP ($\lambda = 0.19$)			1.25 (0.89–1.75)	0.20[e]		1.71 (1.14–2.56)	9.1×10^{-3}
MR-PRESSO			0.83			0.40		
*HLA-DRB1**04[b]	6563 controls, 9014 cases			2032 controls, 2329 cases				
Inverse variance weighted	0.73 (0.59–0.92)	6.8×10^{-3}	0.77	1.29 (0.83–2.00)	0.26	0.47	1.75 (1.07–2.87)	0.03
Weighted median	0.70 (0.50–0.97)	0.03		1.16 (0.59–2.29)	0.66		1.67 (0.81–3.46)	0.18
Weighted mode	0.67 (0.30–1.48)	0.32		1.51 (0.34–6.66)	0.59		2.26 (0.38–13.39)	0.34
MR-Lasso	No invalid SNP ($\lambda = 0.20$)			1.18 (0.76–1.83)	0.46[f]		1.61 (0.98–2.64)	0.06
MR-PRESSO			0.67			0.57		

Valine 11 amino acids and *HLA-DRB1**04 alleles were determined using imputation of *HLA* alleles and amino acids based on SNPs from the *HLA* region.
[a]The interaction OR represents the OR in carriers of 1/2 alleles or AA residues divided by the OR in carriers of 0 allele or AA residue.
[b]Total number: 8595 controls, 11,343 cases.
[c]Number of invalid SNPs = 4; $\lambda = 0.17$.
[d]Total number: 9480 controls, 12,424 cases.
[e]Number of invalid SNPs = 4; $\lambda = 0.19$.
[f]Number of invalid SNPs = 11; $\lambda = 0.19$.
SNPs, single nucleotide polymorphism; PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; AA, amino acid; *P*-het., *P* for heterogeneity; λ, tuning parameter for MR-Lasso.

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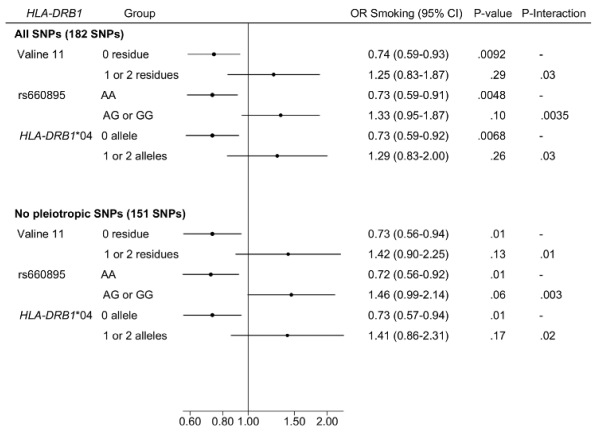

FIG. 1. Forest plot of the association between genetically predicted smoking initiation (inverse variance weighted estimate) and Parkinson's disease stratified by *HLA-DRB1*.

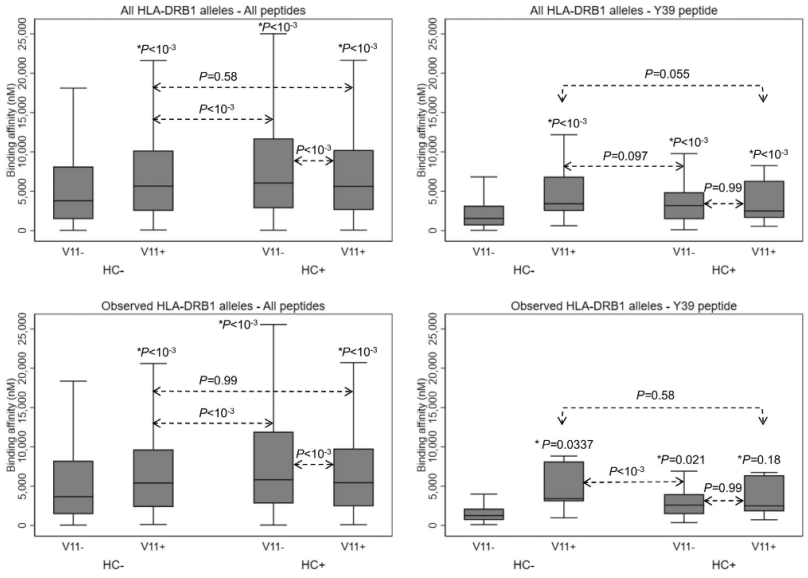

FIG. 2. Prediction of binding affinity (nM) according to the presence of a valine at position 11 (V11) coded by *HLA-DRB1* alleles and homocitrullination (HC) of α-synuclein derived peptides. **P* values for the comparison versus the reference group (V11−HC−).

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excluding 31 pleiotropic SNPs (Fig. 1, Supplementary - Table S8). Results were similar in analyses stratified by rs660895 or *HLA-DRB1**04.

Compared to V11−HC−, V11+HC− and V11−HC+ were both associated with decreased binding affinity, with a stronger effect of HC+ than V11+ (Fig. 2, Supplementary - Table S9). Alternatively, in the presence of HC+, V11+ increased binding affinity (all peptides) or had no effect (Y39); HC+ had no effect on binding affinity in the presence of V11+. Analyses of binding and non-binding peptides paralleled these results (Supplementary Table S10).

Discussion

We replicate an interaction between *HLA-DRB1* and smoking,[7] according to which the inverse association between smoking and PD is only present in participants without protective *HLA-DRB1* AA/alleles. *In silico* predictions of binding affinity are consistent with an interaction between V11 and post-translational smoking-induced modifications of α-synuclein derived peptides.

Recent MR studies showed an inverse association between genetically predicted smoking and PD.[15-18] These findings are in favor of a causal role of smoking in PD, but the underlying mechanisms remain unknown and gene–environment interactions analyses may contribute to their understanding. The interaction pattern we found is similar to the interaction between self-reported smoking and rs660895 reported by Chuang et al.[7] Our study represents a fully independent replication using a different approach to define smoking (MR) and SNP-based imputation of *HLA* amino acids that allowed us to examine this interaction at the AA level. Therefore, our findings contradict those from Hollenbach et al[1] who reported an interaction in the opposite direction based on a selected sample of smaller size.

Lower binding affinity for α-synuclein derived peptides is associated with a weaker immune response that may explain decreased PD risk.[19] Our binding affinity analyses are consistent with the interaction pattern we identified. Although V11 and HC both decreased binding affinity for α-synuclein derived peptides in the absence of each other, consistent with the inverse association of V11 and smoking with PD, there was a positive interaction between V11 and HC, whereby both V11 and HC had a weaker or no effect in the presence of each other; this pattern is consistent with the lack of association between smoking and PD in V11 carriers that we found.

We used MR to define genetically predicted smoking initiation, rather than self-reported smoking; MR has the advantage that, provided that a set of assumptions are met, smoking-PD association estimates are less likely to be biased by confounding or reverse causation than association estimates based on self-reported smoking.[8] Another strength of our study compared to Chuang et al[7] is that rather than using a single SNP, we used genome-wide data to impute AA encoded by *HLA-DRB1*. Finally, using an independent dataset, we report similar associations with *HLA* alleles and AA as previous studies.[2,3] One limitation of our *HLA-DRB1* × smoking interaction analyses is that the approach we used allowed us to estimate the association between smoking initiation and PD stratified by *HLA-DRB1*, but did not allow us to estimate the association between *HLA-DRB1* and PD stratified by smoking.

Despite being one of the most robust findings in PD, the mechanisms underlying its inverse association with smoking remain unknown. This work represents the first example of large-scale replication of a gene–environment interaction in PD, and allows proposing a biological mechanism to explain the inverse smoking-PD association, in the context of a larger body of work on the relationship between the immune system and PD.[19]

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Data Availability Statement

Results can be reproduced using the Supplementary material

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the FIRST DRAFT, B. Review and Critique.

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