RESEARCH ARTICLE

Dopamine Pathway and Parkinson's Risk Variants Are Associated with Levodopa-Induced Dyskinesia

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ABSTRACT: Background: Levodopa-induced dyskinesia (LID) is a common adverse effect of levodopa, one of the main therapeutics used to treat the motor symptoms of Parkinson's disease (PD). Previous evidence suggests a connection between LID and a disruption of the dopaminergic system as well as genes implicated in PD, including *GBA1* and *LRRK2*.

Objectives: Our goal was to investigate the effects of genetic variants on risk and time to LID.

Methods: We performed a genome-wide association study (GWAS) and analyses focused on *GBA1* and *LRRK2* variants. We also calculated polygenic risk scores (PRS) including risk variants for PD and variants in genes involved in the dopaminergic transmission pathway. To test the influence of genetics on LID risk we used logistic regression, and to examine its impact on time to LID we performed Cox regression including 1612 PD patients with and 3175 without LID.

Results: We found that *GBA1* variants were associated with LID risk (odds ratio [OR] = 1.65; 95% confidence interval [CI], 1.21–2.26; $P = 0.0017$) and *LRRK2* variants with reduced time to LID onset (hazard ratio [HR] = 1.42; 95% CI, 1.09–1.84; $P = 0.0098$). The fourth quartile of the PD PRS was associated with increased LID risk ($OR_{fourth\_quartile} = 1.27$; 95% CI, 1.03–1.56; $P = 0.0210$). The third and fourth dopamine pathway PRS quartiles were associated with a reduced time to development of LID ($HR_{third\_quartile} = 1.38$; 95% CI, 1.07–1.79; $P = 0.0128$; $HR_{fourth\_quartile} = 1.38$; 95% CI = 1.06–1.78; $P = 0.0147$).

Conclusions: This study suggests that variants implicated in PD and in the dopaminergic transmission pathway play a role in the risk/time to develop LID. Further studies will be necessary to examine how these findings can inform clinical care. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: levodopa-induced dyskinesia; Parkinson's disease; dopamine; *GBA1*; *LRRK2*

Levodopa is one of the most commonly administered therapies for Parkinson's disease (PD), particularly to treat motor symptoms.[1] However, as the disease progresses and patients are exposed to long-term levodopa therapy, a significant proportion develops levodopa-induced dyskinesia (LID), a debilitating side effect characterized by involuntary, uncontrolled, and often choreiform movements.[2] LID is estimated to affect ~40% to 50% of PD patients within 4 to 6 years of initiating levodopa therapy,[3,4] however, a subset of them manifests LID also within the first year of the therapy,[5] demonstrating the broad variability of LID risk and onset. The main pathophysiologic hypothesis behind LID development suggests that the presynaptic nigrostriatal degeneration, in combination with the brief half-life of levodopa, may produce an aberrant pulsatile stimulation of dopamine receptors.[6] The loss of dopaminergic neurons results in reduced dopamine storage capacity, leading to a radical increase in dopamine release for each dose of levodopa.[7] Other mechanisms have also been implicated in LID development, including the involvement of the glutamatergic, serotoninergic, and noradrenergic neural circuits. In particular, as a result of the nigrostriatal degeneration, levodopa might be preferentially metabolized in serotoniergic and noradrenergic terminals, which are unable to regulate effectively dopamine release because of the absence of D2 autoreceptors and appropriate dopamine transporters.[8,9] Another parallel pathophysiologic hypothesis suggests that the development of LID is not only a consequence of an altered dopaminergic transmission but also a reflection of aberrant plastic changes in the corticobasal ganglia system.[10]

Multiple environmental risk factors affecting LID have been identified, including levodopa dosage and duration of the therapy, use of dopamine agonists, PD age at onset (AAO), disease duration and severity, female sex and lower body mass index (BMI).[11-15] Most of the suggested genetic risk factors for LID are related to the dopamine pathway, including genes encoding the dopamine receptors, especially *DRD2* and *DRD3*,[16-18] the dopamine transporter *SLC6A3*,[19,20] or enzymes that metabolize dopamine and are targeted by PD therapeutics,[21,22] catechol-O-methyltransferase (*COMT*)[23-25] and monoamine oxidases A and B (*MAOA*, *MAOB*).[24-26] Interestingly, variants in *GBA1* and *LRRK2*, among the most frequent genetic risk factors for PD,[27,28] have also been identified as potential risk factors for LID,[29-36] and PD patients carrying *LRRK2* variants display preserved to enhanced serotonergic activity compared to idiopathic PD.[37] Carriers of *GBA1* and *LRRK2* variants show distinctive clinical presentations in PD, with *GBA1* variants being associated with a more rapidly progressive PD with earlier onset,[38] and *LRRK2* variants with an overall more benign disease course, but with also more frequent postural instability and gait difficulty as well as slightly earlier AAO compared to sporadic PD.[39] Other variants reported in LID include those in *BDNF*, involved in neural plasticity,[40,41] *GRIN2A*, encoding a glutamatergic receptor,[42] and *ADORA2A*, encoding the adenosine A2a receptor gene.[43] However, the association between LID

and most of the above-mentioned putative genetic risk factors is still controversial, with most findings reported deriving from candidate gene studies that failed to be confirmed in replication studies.[44-49]

Here, we aimed to systematically evaluate how genetics affect the risk and rate of progression to LID including a total of 4787 PD patients from multiple centers. For this purpose, we performed genome-wide association studies (GWAS) and downstream analyses focused on specific genes previously implicated in LID. In addition, we tested the effect produced by cumulative genetic risk on the occurrence and rate of progression to LID, including risk variants previously associated with PD and variants in genes involved in the dopaminergic transmission pathway.

Methods

Population

The study population included a total of 4787 PD patients, of which 1612 with and 3175 without LID (Supplementary Table S1). PD was diagnosed by movement disorder specialists according to the United Kingdom (UK) Brain Bank or International Parkinson Disease and Movement Disorders Society criteria.[50] In each participating center, LID diagnosis was made by a movement disorder specialist. We collected data about LID based on the specialist clinical evaluation in multiple appointments or the Unified Parkinson's Disease Rating Scale (UPDRS) part IV produced after clinical assessment of the patient. In the McGill cohort, LID was self-reported in a specific questionnaire where the patient was asked if they experienced LID symptoms. The participants were of European ancestry and their clinical and genetic data were collected from 15 different cohorts (Supplementary Table S1), 12 of which were from the International Parkinson's Disease Genomics Consortium (IPDGC) and three from the Accelerating Medicines Partnership Parkinson's Disease (AMP-PD, https://amp-pd.org/). The latter includes the Parkinson's Disease Biomarkers Program (PDBP), Parkinson's Progression Markers Initiative (PPMI), and Harvard Biomarker Study (HBS) cohorts. The cohorts were included in the different analyses depending on data availability. The cohorts included in each analysis are specified in Supplementary Table S2.

Genetic Analyses

The study design included two stages. First, we performed an analysis focused on the *GBA1* and *LRRK2* genes, which are known to affect the risk for PD and have been suggested to affect LID in previous studies. In the second stage of the analysis, we performed a GWAS to examine genome-wide potential associations with risk and time to develop LID, followed by polygenic risk score (PRS) analyses as detailed below. Excluding the AMP-PD cohorts, with whole genome sequencing (WGS) data, the other centers (Supplementary Table S1) were genotyped using the OmniExpress, NeuroX,[51] NeuroChip,[52] or MegaChip GWAS array according to the manufacturer's instructions (Illumina). Quality control was performed following standard pipelines (detailed in https://github.com/neurogenetics/GWAS-pipeline) using Plink 1.9.[53] In brief, we filtered out heterozygosity outliers using an *F*-statistic cutoff of <-0.15 or >0.15. Individuals with a variant call rate <95% and sex mismatch were excluded. Variants missing in >5% of the participants, with disparate missingness between cases and controls ($P < 1e{-}04$), or significantly deviating from Hardy–Weinberg equilibrium in controls ($P < 1e{-}04$) were also removed. We used genome-wide complex trait analysis to check for relatedness closer than first cousins between participants (genome-wide pairwise relatedness [PIHAT] >0.125). We performed imputation using the Michigan imputation server (https://imputationserver.sph.umich.edu/index.html#) with the Haplotype Reference Consortium reference panel r1.1 2016 under default settings. Ancestry outliers were detected using HapMap3 principal component analysis (PCA) data in R version 4.0.1.

After imputation, we selected variants with r2 >0.8 and a minor allele frequency >0.05, while retaining common risk variants in the *GBA1* (p.N370S, p.E326K, and p.T369M) and *LRRK2* (p.G2019S and p.M1646T) regions, to perform specific analyses on these variants (detailed below). These genes were specifically selected given their importance in PD etiology[27,28] and recent clinical trials[54] as well as their previously suggested association with LID.[29-34] The carrier status of *GBA1/LRRK2* risk variants in individuals with and without LID is detailed in Supplementary Tables S3 and S4. Carriers of variants in the same gene were combined, so that the carrier status for *GBA1* and *LRRK2* refers to any aforementioned *GBA1* and *LRRK2* variants, respectively. To examine the association between the *GBA1* and *LRRK2* risk variant carrier status and LID occurrence we performed logistic regression, and to evaluate the association between the carrier status and time to LID onset we performed Cox regression using the R package "survival" (https://cran.r-project.org/web/packages/survival/). The time to LID variable included in the Cox regression was defined as the period between the start of levodopa therapy and LID onset, as previously done.[55] When LID did not manifest, this parameter was right-censored at the last follow-up. To minimize biases because of possible confounders and further harmonize the analyses across the centers, we adjusted the analyses by multiple covariates including principal components (PCs), PD AAO, sex, levodopa dosage, levodopa equivalent daily dose

(LEDD),[56,57] dopamine agonist use, BMI, Hoehn and Yahr score (HY) and, exclusively for logistic regression, disease duration. For logistic regression analyses, we included the cumulative levodopa dosage and LEDD starting from the baseline (ie, levodopa initiation) to the last time point (ie, LID onset or last follow-up when LID was not present). In Cox regression, to avoid collinearity with the time to LID onset dependent variable, we replaced cumulative doses with doses at the last time point. All the covariates were selected using an Akaike Information Criterion (AIC)-based stepwise regression approach, which evaluated the model goodness of fit and selected the most appropriate covariates to include in the model. We performed the analyses separately in each cohort and then meta-analyzed the results using the R package "metafor" (https://cran.r-project.org/web/packages/metafor/index.html). Because variants in these genes have been previously associated with LID, we used a significance threshold of $\alpha = 0.05$.

Similar to the analyses on specific genes, to investigate the impact of common genetic variants on LID risk and time to onset we also performed GWAS with, respectively, logistic and Cox regression adjusted for the above-specified covariates. Cox regression was performed using the SurvivalGWAS_SV software (https://www.liverpool.ac.uk/population-health/research/groups/statistical-genetics/survival-gwas-sv/).[58] We conducted the analyses in each cohort separately, and then meta-analyzed the results using the METAL software (https://genome.sph.umich.edu/wiki/METAL_Documentation) with a fixed effects model weighted by β coefficients and the inverse of the standard errors.

PD Risk Variant-Based PRS

To assess the impact on LID of the cumulative genetic risk for PD we calculated PRS for each PD patient including the 90 variants associated with PD in the most recent GWAS meta-analysis in Europeans.[59] PRS calculation was performed based on the weighted allele dose as implemented in PRSice2 using default clumping (https://choishingwan.github.io/PRSice/).[60] To investigate the association between the PRS and LID risk we performed logistic regression, whereas to evaluate the association between PRS and progression to LID we performed Cox regression. The analyses were adjusted for PCs, PD AAO, sex, HY, and levodopa dosage, cumulative in logistic regression and at the last time point in Cox regression. The covariates were selected to minimize collinearity based on the results of the previous model goodness-of-fit analyses. These analyses were repeated using PRS as a continuous variable and then as a discrete variable by dividing the PRS into quartiles. For the analysis using PRS quartiles, we separately compared the association of individual membership to the second, third, and fourth quartiles versus the first quartile with LID risk/progression.

Dopamine Pathway PRS

To assess the impact of genes involved in the dopaminergic transmission pathway we also constructed a pathway PRS, or polygenic effect score (PES)[61] using the PRSet feature of PRSice2 (https://choishingwan.github.io/PRSice/prset_detail/). Genes involved in this pathway were obtained from Explore the Molecular Signatures Database (MSigDB, version 2023.1), a collection of annotated gene sets for use with Gene Set Enrichment Analysis (GSEA) software (https://www.gsea-msigdb.org/gsea/msigdb/). These genes included *CDK5*, *FLOT1*, *PARK7*, *CHRNB2*, *ADORA2A*, *CRH*, *CRHBP*, *DRD1*, *DRD2*, *DRD3*, *DRD4*, *DRD5*, *TOR1A*, *RASD2*, *PNKD*, *GDNF*, *ARRB2*, *PRKN*, *PTGS2*, *RAB3B*, *PINK1*, *SLC6A2*, *SLC*, *6A3*, *SLC6A4*, *SNCA*, *TH*, and *CNTNAP4* (detailed at http://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GOBP_SYNAPTIC_TRANSMISSION_DOPAMINERGIC). To investigate the role of dopamine genes overall in LID development, we also performed PES analyses including genes more strongly related to multiple dopamine pathways (ie, transmission, transportation, synthesis, and metabolism, including *DRD1*, *DRD2*, *DRD3*, *DRD4*, *SLC6A3*, *ANKK1*, *VMAT*, *DDC*, *TH*, *COMT*, *MAOA*, and *MAOB*). To select the variants in each of the genes to include in the PES analyses we used the LID GWAS meta-analysis summary statistics from the current study, filtering variants with a *P*-value less than or equal to 0.05. In addition, we performed linkage disequilibrium (LD) clumping using the default $r2 = 0.1$ and selecting variants within 250 Kb of distance from the pathway-related genes. A total of 1000 permutations were implemented to generate the empirical *P*-value corresponding to the optimized PES prediction of the dependent variable in the target cohort. We then calculated individual PES for each target cohort. To avoid potential inflation because of the presence of the target cohort in the meta-analysis summary statistics, each time we calculated the PES for a target cohort we excluded such cohort from the meta-analysis using a leave-one-out approach. To investigate the association between the dopamine pathway PES and LID risk we performed logistic regression, whereas to evaluate the association between the PES and progression to LID we performed Cox regression, as specified above for the PRS analyses.

Results

GBA1 and LRRK2 Variants Show Significant Associations with LID Risk and Time to LID

Analyses focusing on *GBA1* showed that *GBA1* variants were significantly associated with LID risk (odds ratio [OR] = 1.65; 95% confidence interval [CI], 1.21–2.26; $P = 0.0017$) (Fig. 1A). No association was found with time to LID (hazard ratio [HR] = 1.25; 95% CI, 0.99–1.58; $P = 0.0635$) (Fig. 1B). In contrast,

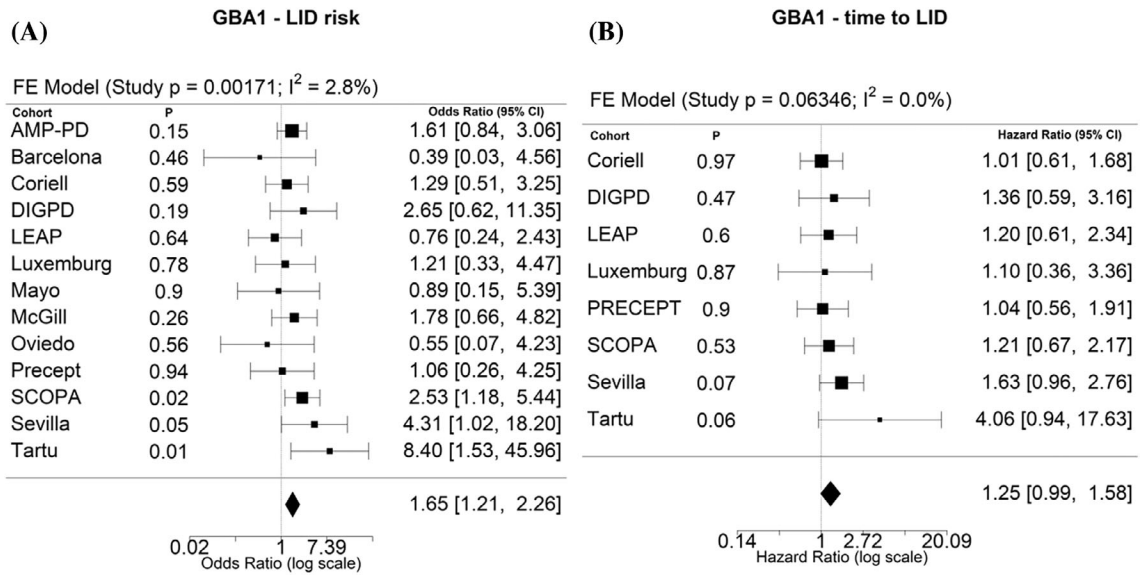

FIG. 1. (**A**,**B**) Association between *GBA1* variants and levodopa-induced dyskinesia (LID). The meta-analysis forest plot shows the coefficient (black squares) and 95% confidence interval (bars) of the analyses in each single cohort. The size of the square is proportional to the weight the cohort had on the overall meta-analysis, based on their single standard error. The black diamond at the bottom represents the overall coefficient and confidence interval. (**A**) Logistic regression between *GBA1* variants and LID risk. (**B**) Cox regression between *GBA1* variants and time to development of LID. FE, fixed effect model; AMP-PD, Accelerating Medicines Partnership Parkinson's disease, including the New Discovery of Biomarkers (BioFIND), the Harvard Biomarker Study (HBS) and the Parkinson's Disease Biomarkers Program (PDBP) cohorts; Barcelona: Hospital Universitari Mutua de Terrassa, Spain; Coriell, National Institute for Neurological Disorders and Stroke (NINDS) Exploratory Trials in PD Long-Term Study 1 (NET-PD LS1), Coriell Institute for Medical Research, USA; DIGPD, Drug Interaction With Genes in Parkinson's Disease, France; LEAP, Levodopa in Early Parkinson's Disease, Netherlands; Luxemburg, Luxembourg Centre for Systems Biomedicine; Mayo, Mayo Clinic, USA; McGill, McGill University, Canada; Oviedo, Central University Hospital of Asturias, Spain; PreCEPT, Parkinson Research Examination of CEP-1347 Trial; SCOPA, Scales for Outcomes in Parkinson's disease; Sevilla, Universidad de Sevilla; Tartu, University of Tartu.

LRRK2 variants showed no association with LID risk (OR = 1.18; 95% CI, 0.84–1.67; $P = 0.3484$) (Fig. 2A), but were significantly associated with reduced time to development of LID (HR = 1.42; 95% CI, 1.09–1.84; $P = 0.0098$) (Fig. 2B). The *GBA1* and *LRRK2* meta-analyses were not significant for genetic heterogeneity ($I^2 = 2.8\%$, $P = 0.4187$ and $I^2 = 0\%$, $P = 0.7069$ for the *GBA1* logistic and Cox regression, respectively; $I^2 = 0\%$, $P = 0.8315$ and $I^2 = 0\%$, $P = 0.4886$ for the *LRRK2* logistic and Cox regression, respectively), suggesting that heterogeneity does not drive these associations.

In the GWAS, genomic inflation was evaluated using quantile-quantile plots (Q-Q plots) and the lambda factor, showing no inflation and a slight deflation (lambda logistic regression = 0.9709, lambda Cox regression = 0.9555) (Supplementary Figs. S1 and S2). GWAS using both logistic and Cox regression showed no significant association with LID risk or time to development of LID, respectively (Supplementary Figs. S3 and S4). We further examined whether variants previously associated with LID in the literature[16-20,23-26] and from the LIDPD website (http://LiDpd.eurac.edu/) showed associations in the current GWAS, but we found no significant results (Supplementary Tables S5 and S6). A recent GWAS in LID[62] nominated significant signals in a progression GWAS meta-analysis. However, our study failed to confirm these findings and the reported variants did not reach the nominal significance of 0.05 in our GWAS (Supplementary Table S7).

PD Risk Variant-Based PRS Is Associated with Increased Risk for LID

PRS analyses aggregating PD-associated variants showed that higher values of PRS were associated with a very mild increase in LID risk (OR = 1.02; 95% CI, 1.002–1.035; $P = 0.0298$) (Fig. 3B). When dividing the PRS in quartiles, logistic regression showed a significant association between the fourth quartile and LID, with a greater risk compared to the analyses using PRS as a continuous variable ($OR_{fourth\_quartile} = 1.27$; 95% CI, 1.03–1.56; $P = 0.0210$) (Fig. 3A, Supplementary Table S8). Cox regression did not show any significant associations between PRS and time to development of LID (Supplementary Fig. S5A,B, Supplementary Table S9). The PD PRS logistic regression was significant for a moderate heterogeneity ($I^2 = 43.90\%$, $P = 0.0449$) and repeating the meta-analysis using a random-effect model, which accounts for heterogeneity, the results did not show statistically significant associations (OR = 1.02, $P = 0.2038$). PD PRS Cox regression did not show heterogeneity (I2 = 0%, $P = 0.6236$).

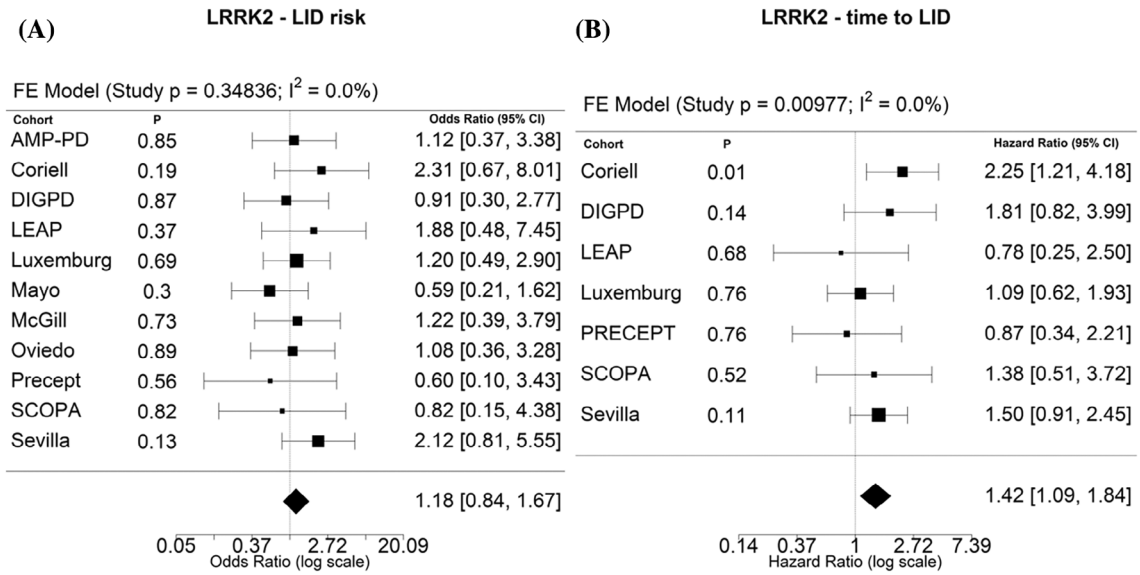

FIG. 2. (**A**,**B**) Association between *LRRK2* variants and levodopa-induced dyskinesia (LID). (**A**) Logistic regression between *LRRK2* variants and LID risk.(**B**) Cox regression between *LRRK2* variants and time to development of LID.

Dopaminergic Transmission Pathway Polygenic Effect Score Is Associated with a Reduced Time to Development of LID

Analyses on the dopaminergic transmission pathway PES showed that higher values of PES were associated with a reduced time to development of LID (HR = 1.10; 95% CI, 1.02–1.18; $P = 0.0088$) (Fig. 4B). In addition, the third and fourth PES quartile were also associated with a reduced time to development of LID with a more elevated effect size compared to the analyses on PES as a continuous variable ($HR_{third\_quartile} = 1.38$; 95% CI, 1.07–1.79; $P = 0.0128$; $HR_{fourth\_quartile} = 1.38$; 95% CI, 1.06–1.78; $P = 0.0147$) (Fig. 4A, Supplementary Table S11). Logistic regression did not show any statistically significant associations between dopaminergic transmission PES and LID risk (Supplementary Fig. S6A,-B, Supplementary Table S10). To ensure that the results were not driven by the *SNCA* variants included in this pathway we also repeated the analyses excluding variants in this gene. We confirmed the previous findings for Cox regression both using the PES as a continuous variable (HR = 1.13; 95% CI, 1.04–1.23; $P = 0.0056$)

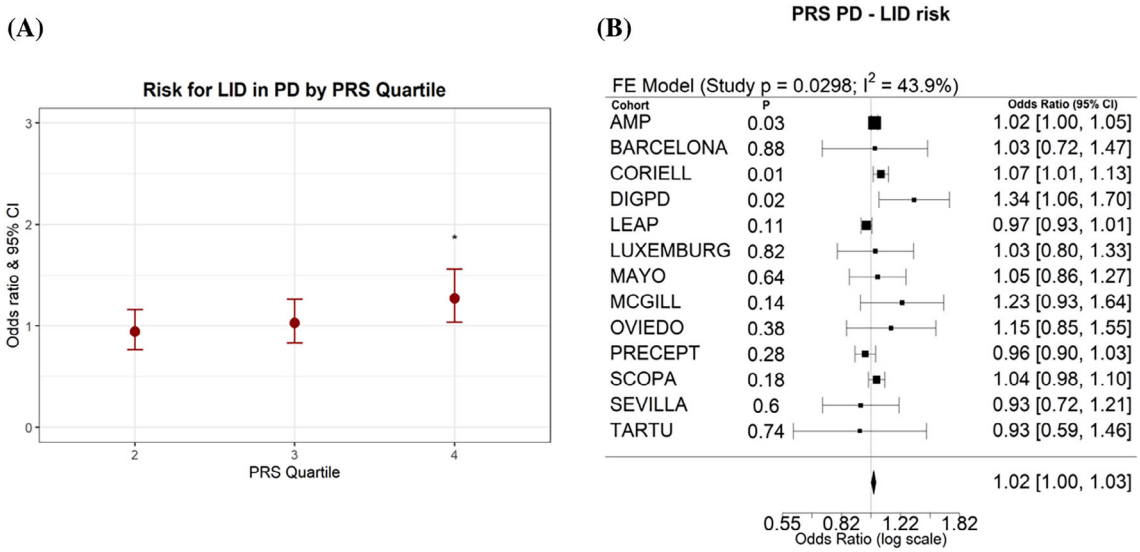

FIG. 3. (**A**,**B**) Logistic regression between polygenic risk scores (PRS) aggregating PD risk variants and levodopa-induced dyskinesia (LID) risk. (**A**) The plot shows the association between each PRS quartile and LID risk compared with the first quartile, meta-analyzing the results across the cohorts. The Y axis represents the PRS quartile, the X axis the odds ratio (red dot) and 95% CI (red bar). The presence of an asterisk indicates a significant association ($P < 0.05$). (**B**) The forest plot shows the association between PRS as a continuous variable and LID risk. CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

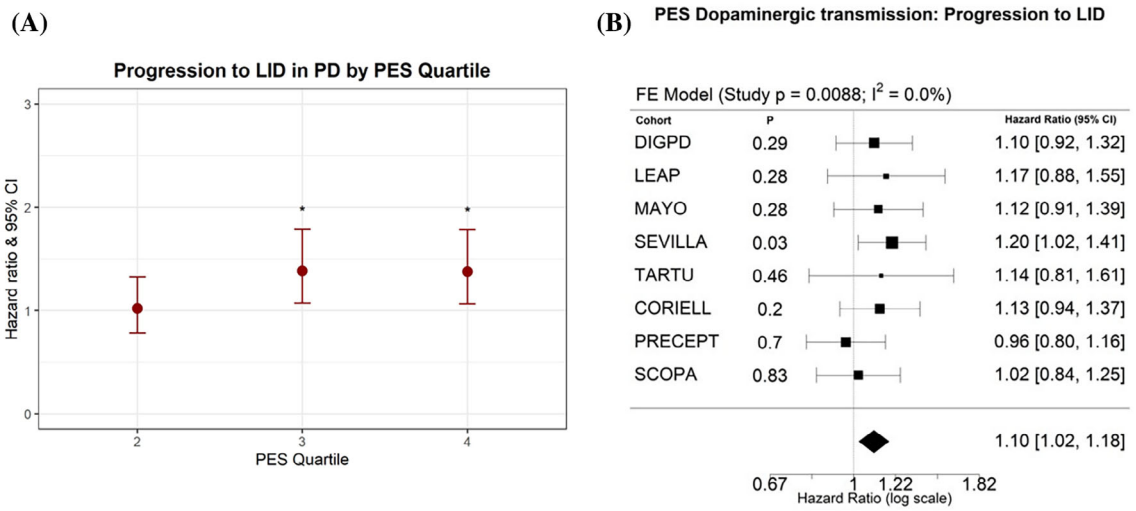

FIG. 4. (**A**,**B**) Cox regression between the dopaminergic transmission pathway polygenic effect score (PES) and time to development of levodopa-induced dyskinesia (LID). (**A**) The plot shows the association between each PES quartile and time to development of LID compared with the first quartile, meta-analyzing the results across the cohorts. The Y axis represents the polygenic risk score (PRS) quartile, the X axis the hazard ratio (red dot) and 95% confidence interval (red bar). (**B**) The forest plot shows the association between PES as a continuous variable and time to development of LID. [Color figure can be viewed at wileyonlinelibrary.com]

(Supplementary Fig. S7B) and divided in quartiles ($HR_{third\_quartile} = 1.32$; 95% CI, 1.01–1.73; $P = 0.0429$; $HR_{fourth\_quartile} = 1.31$; 95% CI, 1.004–1.71; $P = 0.0465$) (Supplementary Fig. S7A, Supplementary Table S12). Logistic regression showed a significant association between the fourth quartile of the dopamine transmission pathway PES and LID risk ($OR_{fourth\_quartile} = 1.33$; 95% CI, 1.04–1.72; $P = 0.0249$) (Supplementary Fig. S8A, Supplementary Table S12), which, however, did not emerge when treating the PES as a continuous variable (OR = 1.01; 95% CI, 0.97–1.06; $P = 0.6099$) (Supplementary Fig. S8B, Supplementary Table S12). Finally, Cox regression for the dopamine PES including multiple pathways did not show any statistically significant results (Supplementary Fig. S9A,B, Supplementary Table S13), whereas it was significantly associated with increased LID risk (OR = 1.12; 95% CI, 1.02–1.22; $P = 0.0142$) (Supplementary Fig. S10B). This association also emerged between the fourth PES quartile and LID risk ($OR_{fourth\_quartile} = 1.63$; 95% CI, 1.003–2.65; $P = 0.0483$) (Supplementary Fig. S10A, Supplementary Table S13). The dopamine transmission PES meta-analyses were not significant for genetic heterogeneity ($I^2 = 30.8\%$, $P = 0.1450$ dopamine transmission PES logistic regression; $I^2 = 0\%$, $P = 0.7934$ dopamine transmission PES Cox regression), suggesting that heterogeneity is not the driver of these associations.

Discussion

In this study, we confirmed that *GBA1* variants were associated with increased risk for LID and demonstrated that *LRRK2* variants were associated with a reduced time to development of LID from the initiation of levodopa treatment. Additionally, we found that PD PRS was associated with mildly increased risk for LID and that the dopaminergic transmission pathway PES is associated with a reduced time to development of LID.

Albeit some studies found contradictory results on the association between the *GBA1* and *LRRK2* variants and LID,[44-47] many others have shown that these variants play a role in LID development,[29-34] and in this study we also demonstrated that *LRRK2* variants might also affect the time to development of LID. The power for the association analyses was optimal (99%, as calculated on https://csg.sph.umich.edu/abecasis/cats/gas_power_calculator/ using the following parameters: cases = 1612, controls = 3175, significance threshold = 5e−8, prevalence in the general population = 0.5, allele frequency = 0.1, and genotype relative risk [as inferred by the power calculator] = 1.3). The absence of significant signals in the risk and progression GWAS and, in general, the difficulty finding congruent results between different genetic studies investigating LID, as also reflected by the divergent results between the recent LID progression GWAS[62] and our study, may be because of the stronger contribution in LID development of environmental factors, especially pharmacologic- (dosage of dopaminergic drugs, use of amantadine) and disease-related factors.[11-15] Our results suggest that *GBA1* variants affect risk for LID, but not LID onset, whereas *LRRK2* variants affect LID onset, but not risk. These results should be replicated by additional

studies in other populations, and the potential mechanisms behind these observations should be studied experimentally.

The significant association between the two PRS analyses suggests that aggregating multiple common variants that might have a scarce effect on LID individually could contribute to uncovering the overall genetic impact on LID. In particular, the association between the PRS including PD risk variants suggests that patients with a stronger genetic risk profile for PD are also more at risk for LID, a factor to consider for patient counselling and potential clinical trials, although the magnitude of the increased risk was small.

We demonstrated that the dopaminergic synaptic transmission pathway PES was associated with an increased rate of LID development, which is in line with previous pathophysiologic hypotheses[8,9,63] and studies suggesting an implication of dopamine pathway genes in the development of LID.[16-20,23-26] When excluding the *SNCA* variants from the dopaminergic transmission PES analyses, we observe that the dopamine transmission PES conserves the significant association with time to LID, suggesting that this association is not driven by the *SNCA* variants. We also observed that the PES including dopamine genes is associated with a mild increase in LID risk, suggesting that, whereas dopamine transmission is more strongly implicated in LID onset, other genes related to dopamine might play a role in LID risk. Additional studies will be necessary to further investigate the association between the PD and dopamine PRS and LID.

Unravelling the etiologic bases of LID is crucial to implementing a tailored therapy for PD patients taking levodopa, adapting the therapeutic choices, dosage, and management depending on the individual risk factors of each patient. Over time, it could be beneficial to define a risk profile accounting for the single genetic and environmental factors associated with LID as well as the cumulative genetic risk provided by the PRS. This might be used to stratify patients for LID prevention clinical trials and lead to a more refined and personalized therapeutic approach for each individual. In addition to the benefits of the current symptomatic therapies, uncovering and confirming genetic factors affecting the risk and time of development of LID could also have important implications for targeted therapies. In particular, *GBA1* and *LRRK2* pathways are already candidate targets for newly developing drugs in clinical trials.[54] A LRRK2 inhibitor, BIIB122/DNL151, reached already experimental phase 3 (https://www.denalitherapeutics.com, 2021).[64] In addition, ambroxol, a pharmacological chaperone for glucocerebrosidase (GCase) capable of increasing its enzymatic levels, completed phase 2 and LTI-291, an activator of GCase, reached phase 1B.[65-67] Because these drugs would likely be used in conjunction with symptomatic therapies, knowing that these pathways can be targeted to reduce the risk or delay the time of LID development could considerably improve the compliance and quality of life of PD patients taking dopaminergic treatments.

The current study has several limitations. First, the subjects were all of European ancestry and, therefore, the results in other populations might be different. Despite an overall large sample size, most of the individual cohorts included a limited number of participants, especially those having longitudinal data necessary for Cox regression, this impacted the power of the study and could have contributed to the lack of association in the GWAS. Similarly, in the analyses focused on *GBA1* some cohorts showed a small number of carriers, however, this did not substantially affect the results as demonstrated by the optimal statistical power. NeuroX and NeuroChip can be limited in the detection of *GBA1* variants, however, any potential errors would be present in both the case and control groups, producing arguably a minimal impact on the results. Some studies suggested that LID is influenced more by the disease duration than by the therapy duration,[68] on this line PD AAO would represent a better baseline than levodopa initiation for the time to LID onset. However, this parameter was chosen in accordance with what was previously done with LID GWAS[55] and accounting for the recall bias that PD AAO suffers from, compared to levodopa initiation, which represents a report made by the physicians. In addition, understanding the genetic basis of the time to LID from levodopa initiation can be of considerable relevance for patient counselling at the time of treatment administration. Finally, we also accounted for the disease duration in each of our analyses with appropriate adjustments. The association between the PD PRS and LID risk is very mild, therefore, the impact of this finding in the clinical practice might be limited. Additionally, we found a moderate heterogeneity in the PD PRS logistic regression meta-analysis. Therefore, the effect of the PRS on LID risk in the fixed effect model could be affected by this slight heterogeneity, which is supported by the lack of statistical significance in the random effect model. Another limitation of this study was that not all the cohorts had the same amount of data available, which limited in part the design of the analytical model. An interesting future line of research could be to investigate the influence of genetics on specific features of LID, such as LID subtypes (ie, peak-dose, wearing-off-state, and diphasic LID) and progression (ie, severity over time), by collecting these data in a large group of patients.

In conclusion, in the current study, we demonstrated that PD risk variants and the dopaminergic transmission PRS are associated with risk of LID/time to development of LID. A better understanding of the role of genetics in LID development could reduce the impact of this adverse effect and enhance therapeutic management in PD.

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Ethics Statement

IRB study number A11-M60-21A (21-11-023) was reviewed and approved by the research ethics offices (REOs). Informed written patient consent was provided in each center before the inclusion of each in the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Data Availability Statement

The LID GWAS summary statistics are publicly available on GWAS catalog (https://www.ebi.ac.uk/gwas/). All codes used for the analyses are available at https://github.com/gan-orlab.

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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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