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REGULAR RESEARCH ARTICLE

Clinical and Clinical-Pharmacogenetic Models for Prediction of the Most Common Psychiatric Complications Due to Dopaminergic Treatment in Parkinson's Disease

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Abstract

Background: The most common psychiatric complications due to dopaminergic treatment in Parkinson's disease are visual hallucinations and impulse control disorders. Their development depends on clinical and genetic factors.
Methods: We evaluated the simultaneous effect of 16 clinical and 34 genetic variables on the occurrence of visual hallucinations and impulse control disorders. Altogether, 214 Parkinson's disease patients were enrolled. Their demographic, clinical, and genotype data were obtained. Clinical and clinical-pharmacogenetic models were built by The Least Absolute Shrinkage and Selection Operator penalized logistic regression. The predictive capacity was evaluated with the cross-validated area under the receiver operating characteristic curve (AUC).
Results: The clinical-pharmacogenetic index for prediction of visual hallucinations encompassed age at diagnosis (OR = 0.99), rapid eye movement (REM) sleep behavior disorder (OR = 2.27), depression (OR = 1.0002), *IL6* rs1800795 (OR = 0.99), *GPX1* s1050450 (OR = 1.07), *COMT* rs165815 (OR = 0.69), *MAOB* rs1799836 (OR = 0.97), *DRD3* rs6280 (OR = 1.32), and *BIRC5* rs8073069 (OR = 0.94). The clinical-pharmacogenetic index for prediction of impulse control disorders encompassed age at diagnosis (OR = 0.95), depression (OR = 1.75), beta-blockers (OR = 0.99), coffee consumption (OR = 0.97), *NOS1* rs2682826 (OR = 1.15), *SLC6A3* rs393795 (OR = 1.27), *SLC22A1* rs628031 (OR = 1.19), *DRD2* rs1799732 (OR = 0.88), *DRD3* rs6280 (OR = 0.88), and *NRG1* rs3924999 (OR = 0.96). The cross-validated AUCs of clinical and clinical-pharmacogenetic models for visual hallucinations were 0.60 and 0.59, respectively. The AUCs of clinical and clinical-pharmacogenetic models for impulse control disorders were 0.72 and 0.71, respectively. The AUCs show that the addition of selected genetic variables to the analysis does not contribute to better prediction of visual hallucinations and impulse control disorders.
Conclusions: Models could be improved by a larger cohort and by addition of other types of Parkinson's disease biomarkers to the analysis.

Keywords: impulse control disorders, Parkinson's disease, pharmacogenetics, polymorphism, predictive model, psychiatric complications, visual hallucinations

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Significance Statement

Parkinson's disease (PD) is a highly multifactorial disorder, which indicates that biomarkers of different types have to be evaluated to properly characterize PD-related phenotypes, including dopaminergic treatment response. Visual hallucinations and impulse control disorders are among the most important psychiatric complications due to treatment of PD. Several clinical and genetic factors influence the occurrence of these 2 adverse events. In the reported study, we evaluated the simultaneous effect of selected clinical and genetic parameters on the occurrence of visual hallucinations and impulse control disorders. This is one of the first studies to construct clinical and clinical-pharmacogenetic models for prediction of these 2 adverse events with potential for translation to clinical practice and personalization of PD treatment. Such predictive models would give us a window of opportunity to avoid the occurrence of the adverse events or at least to increase caution and enable prompt action in at risk patients.

Introduction

The most common psychiatric complications of dopaminergic treatment in patients with Parkinson's disease (PD) are visual hallucinations (VH) and impulse control disorders (ICD) (Wood, 2010). VH affect up to 40% of PD patients treated with dopaminergic drugs (Wood, 2010). They usually present with vision of nonthreatening images of people or animals. They can be either benign with retained insight or may be perceived as threatening without insight (Ceravolo et al., 2016; Marinus et al., 2018). The prevalence rates of ICD vary from 6% to 39% of PD patients treated with dopaminergic therapy (Wood, 2010). The main symptoms of ICD encompass pathological gambling, hyper-sexuality, compulsive buying, and binge eating (Ceravolo et al., 2016). These behaviors represent an important public health problem because they can affect the patients' socioeconomic status and can also lead to illegal acts (Kraemmer et al., 2016).

Not all treated patients are affected by VH or ICD. Several clinical parameters have already been suggested as potential predictors of these AEs. VH may occur either due to dopaminergic treatment and/or due to progression of PD (Connolly and Lang, 2014). It has been reported that older age at onset, longer disease duration, depression, cognitive decline, female sex, excessive daytime sleepiness, and REM sleep behavior disorder (RBD) increase the risk for development of VH (Marinus et al., 2018). ICD mostly develop due to dopaminergic treatment (Ceravolo et al., 2016; Marinus et al., 2018). Several risk factors of ICD have already been reported, such as younger age at disease onset, longer disease duration, male sex, family or personal history of gambling and alcoholism, depression, unmarried status, impulsive or novelty-seeking traits, cigarette smoking, and caffeine use (Ceravolo et al., 2016; Kraemmer et al., 2016). Despite all of the known clinical risk factors, the occurrence of these 2 AEs cannot be predicted in individual patients.

It has been reported that VH and ICD have a complex multigene heritability. The interpatient variability in the development of the 2 adverse effects (AEs) can be to some extent assigned to genetic factors. *DRD2* rs1800497, *DRD3* rs6280, *SLC6A3* rs2652511, *APOE* ε4, *ACE* I/D, *CCK* rs1799923, and *HOMER1* rs4704559 polymorphisms were associated with VH in several different populations. On the other hand, *DRD1* rs4867798, *DRD1* rs4532, *DRD2* rs1800497, *DRD3* rs6280, and *GRIN2B* rs7301328 were independently associated with ICD (Lee et al., 2009; Zainal Abidin et al., 2015; Politi et al., 2018). As many clinical and genetic factors may influence the occurrence of different phenotypes, their simultaneous effect should be evaluated. To the best of our knowledge, only 1 clinical-pharmacogenetic model for prediction of ICD has been published so far, which pointed out the importance of *OPRK1*, *HTR2A*, and *DDC* genotypes along with several clinical parameters (Kraemmer et al., 2016). Besides genetic factors from dopaminergic pathway, other pathways affecting the PD pathogenesis, such as inflammation, oxidative stress, and neurodevelopment, may also influence the occurrence of VH and ICD. We have previously reported that *COMT* rs165815 and *DRD3* rs6280 influence the occurrence of VH (Redenšek et al., 2019b), while *NOS1* rs2682826 affects development of ICD (Redenšek et al., 2019a).

Both VH and ICD can be quite troublesome for patients and their caregivers. It would be thus extremely valuable to be able to predict the occurrence of these AEs in an individual patient. The construction of predictive models could be helpful in building clinical algorithms for the identification of patients at higher risk for certain AEs. Appropriate statistical tools are, however, required when numerous clinical and genetic parameters are included in the modelling process. The Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression allows the inclusion of many different covariates when the study group is relatively small. Additionally, it is a variable selection method, which also prevents overfitting to data (Moons et al., 2004; Goeman, 2010; Jenko et al., 2017). Better predictive models would enable clinicians to avoid the occurrence of these AEs or at least to be more cautious and recognize the early presentations of AEs in at-risk patients. The aim of this study was to evaluate the simultaneous effect of demographic and clinical parameters in combination with selected candidate gene variants on the occurrence of VH and ICD in PD patients treated with dopaminergic drugs. The additional aim was to build the predictive models for the development of VH and ICD with as good as possible predictive capacity to be translated into clinical practice.

Methods

Participants and Clinical Data

Patients were enrolled in this study according to the following criteria: (1) diagnosis of PD according to the UK Parkinson Disease Society Brain Bank criteria (Goetz, 2008); (2) available clinical data; (3) at least 1 year of dopaminergic treatment duration either with dopamine agonists, and/or levodopa. The recruitment period lasted from October 2016 to April 2018. Patients were recruited from the Department of Neurology, University Medical Centre Ljubljana. Demographic and clinical data were collected with structured interviews with patients/caregivers and from medical records. Only explanatory variables that are known at the beginning of treatment were included in the analysis to enable future algorithm construction for potential therapy guiding. The primary endpoints of the study were VH and ICD occurring due to dopaminergic treatment. Presence or absence of the AE throughout the course of dopaminergic treatment was recorded.

The study protocol was approved by the Slovenian Ethics Committee for Research in Medicine (KME 42/05/16). All participants gave written informed consent in accordance with the Declaration of Helsinki.

Single Nucleotide Polymorphism (SNP) Selection and Genotyping Analysis

The SNP selection (supplementary Table 1) and genotyping analysis were carried out as described previously (Redensek et al., 2019c). In total, 37 SNPs from 22 genes from the following pathways were evaluated: (1) dopamine metabolism, transport, and signaling; (2) neuroinflammation; (3) oxidative stress; (4) neuron development, proliferation, and differentiation; and (5) apoptosis. We chose SNPs with reported associations with neurodegeneration, PD pathogenesis, and response to dopaminergic treatment (Baratchi et al., 2010; Terzic et al., 2015; Xu et al., 2017; Redenšek et al., 2018, 2019a). Only functional SNPs were selected to enable mechanistic explanations of the possible associations.

Statistical Analysis

Median and first and third interquartile (IQR) ranges were used to describe central tendency and variability of continuous variables. Frequency and percentage were used to describe categorical variables. The agreement of genotype frequencies with Hardy-Weinberg equilibrium (HWE) was evaluated by chi-squared test. The additive genetic model was used in all analyses.

Clinical models including only clinical variables and clinical-pharmacogenetic models including clinical and genetic variables were built using logistic regression analysis with LASSO penalization. The method of LASSO penalization was used due to a large amount of explanatory variables relative to the number of events. LASSO penalization prevents overfitting to avoid over-optimistic results and shrinks the estimates of the regression coefficients towards zero. The shrinkage is estimated by the tuning parameter λ, which is obtained by the cross-validation of the (partial) likelihood (Goeman, 2010). If the estimated regression coefficient was not shrunk to zero, the variable was considered statistically significant.

Receiver operating characteristic curves were constructed for both types of models. Sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were assessed. The predictive indexes were estimated by selecting the threshold that provided the maximized sum of the cross-validated true positive and true negative rates. Indexes were defined as the linear predictors obtained from the penalized logistic regression model. Based on the penalized regression equations, multivariate signatures for individual patients were calculated. Cross-validation was applied to all predictive accuracy estimates (AUC, true and false positive rates) to avoid biased and over-optimistic results. The apparent and cross-validated estimates are reported. The model's performance is presented in the confusion matrix, where each row represents the instances in a predicted class while each column represents the instances in an actual class. The positive predictive value (PPV) was calculated based on the number of true and false positives.

The predictive accuracy of the models was ranked as follows: AUC <0.6 was considered as worthless, between 0.6 and 0.7 as poor, between 0.7 and 0.8 as fair, between 0.8 and 0.9 as good, and >0.9 as excellent.

All of the statistical analyses were carried out using the R software (Goeman, 2010; Foucher and Danger, 2012; Team, 2018).

Results

Patient Characteristics

In total, 214 PD patients were included in the analysis; of those, 90 (42.1%) were female. The median age at diagnosis was 61.7 (54.6–70.6) years. Altogether, 54 (25.2%) patients experienced VH, while 32 (15.0%) experienced ICD. Clinical characteristics of included patients accounted for in the construction of the models are presented in Table 1. Additionally, clinical characteristics of patients not accounted for in the construction of the models but are, however, important for a comprehensive description of the patient cohort are presented in Table 2. The continuous data from Table 2 correlated with the age at diagnosis presented in Table 1 and were thus indirectly included and accounted for in the model construction.

All of the patients were genotyped for 37 SNPs. Three SNPs (rs1060253, rs1060257, and rs1787467) deviated from HWE requirements ($P < .05$), so we excluded them from further analysis. Genotype frequencies of the *DDC* rs921451 and rs3837091 did not match the HWE requirements as well. However, frequencies for these 2 SNPs were not significantly different from frequencies reported in the 1000 genomes Utah Residents with Northern and Western European Ancestry population ($P = .730$ and $P = .152$, respectively), which is the population that our patients are the most similar to in terms of ethnicity. These 2 SNPs were thus retained in the analysis. The remaining 32 SNPs were in HWE ($P > .05$; supplementary Table 1).

Table 1. Characteristics of Patients Included in the Constructed Models

Characteristics	All patients (n = 214)	
Female sex	90 (42.1)	
Age at diagnosis (years)	61.7 (54.6–70.6)	
Tremor-predominant PD	174 (81.3)	
Body side of disease initiation	Right	113 (52.8)
	Both	17 (7.9)
	Left	84 (39.3)
REM sleep behavior disorder	105 (49.1)	
Depression	93 (43.5)	
Constipation	90 (42.1)	
Olfactory dysfunction	90 (42.1)	
Beta-blockers	49 (22.9)	
Nonsteroidal anti-inflammatory drugs	40 (18.7)	
Calcium channel blockers	34 (15.9)	
Statins	44 (20.6)	
Tobacco smoking (pack/year*years of smoking)	0 (0–5.7)	
Alcohol consumption (no. of units in a lifetime)	447.2 (0–7033.0)	
Coffee consumption (cups per day)	1 (0–2)	
Visual hallucinations	54 (25.2)	
Impulse control disorders	32 (15.0)	

Abbreviations: PD, Parkinson's disease; REM, rapid eye movement.
Categorical variables are presented as frequencies (percentages), whereas numerical variables are presented in years as median and IQR (first – third quartile).

Table 2. Additional Demographic and Clinical Characteristics of Enrolled Patients

Characteristic	All patients (n = 214)
Disease duration	7.6 (4.3–14.0)
Dopaminergic treatment duration	7.8 (3.9–13.6)
Levodopa treatment duration	6.6 (2.6–11.7)
LED at enrolment	1000.0 (605.0–1415.0)

Abbreviation: LED, levodopa equivalent dose presented as mg/d.
The characteristics are presented in years as median (first-third quartile).

Clinical and Clinical-Pharmacogenetic Models for Prediction of VH

The LASSO penalized clinical model for prediction of VH included: age at diagnosis (OR = 0.98), RBD (OR = 2.48), depression (OR = 1.12), statins (OR = 0.99), and coffee consumption (OR = 0.98) (Table 3; Figure 1A). The apparent AUC for prediction of VH was 0.80, which decreased to 0.60 after cross-validation (Figure 1B). Sensitivity and specificity were 46.3% and 69.1%, respectively. The PPV was 48.4%. The predictive index was –1.48, which means that patients with a multivariate signature above this threshold had higher odds for development of VH.

The LASSO penalized clinical-pharmacogenetic model for prediction of VH included: age at diagnosis (OR = 0.99), RBD (OR = 2.27), depression (OR = 1.0002), *IL6* rs1800795 (OR = 0.99), *GPX1* rs1050450 (OR = 1.07), *COMT* rs165815 (OR = 0.69), *MAOB* rs1799836 (OR = 0.97), *DRD3* rs6280 (OR = 1.32), and *BIRC5* rs8073069 (OR = 0.94) (Table 3; Figure 1C). The apparent AUC for prediction of VH was 0.81, which decreased to 0.59 after cross-validation (Figure 1D). Sensitivity and specificity were 28.3% and 88.7%, respectively. The PPV was 56.7%. The predictive index was –1.25. The confusion matrices of both models are presented in supplementary Table 2.

Clinical and Clinical-Pharmacogenetic Models for Prediction of ICD

The LASSO penalized clinical model for prediction of ICD included: sex (OR = 0.97), age at diagnosis (OR = 0.95), depression (OR = 2.12), beta-blockers (OR = 0.75), alcohol consumption (OR = 1.00), and coffee consumption (OR = 0.84) (Table 4; Figure 2A). The apparent AUC for prediction of ICD was 0.78, while the cross-validated AUC was 0.72 (Figure 2B). Sensitivity and specificity were 69.0% and 78.2%, respectively. The PPV was 38.5%, and the predictive index was –3.95.

The LASSO penalized clinical-pharmacogenetic model for prediction of ICD included: age at diagnosis (OR = 0.95), depression (OR = 1.75), beta-blockers (OR = 0.99), coffee consumption (OR = 0.97), *NOS1* rs2682826 (OR = 1.15), *SLC6A3* rs393795 (OR = 1.27), *SLC22A1* rs628031 (OR = 1.19), *DRD2* rs1799732 (OR = 0.88), *DRD3* rs6280 (OR = 0.88), and *NRG1* rs3924999 (OR = 0.96) (Table 4; Figure 2C. The apparent AUC for prediction of ICD was 0.79, while the cross-validated AUC was 0.71 (Figure 2D). Sensitivity and specificity were 66.1% and 70.6%, respectively. The PPV was 32.8%, and the predictive index was –4.24.

The confusion matrices of the models are presented in supplementary Table 2.

Discussion

This is the first study, to our knowledge, that evaluated the combined influence of selected 16 clinical parameters and 34 candidate gene variants on the occurrence of VH and ICD in PD patients treated with dopaminergic therapy. LASSO penalized logistic regression was used to build the clinical and clinical-pharmacogenetic models for the prediction of VH and ICD. No clinically important differences in the prediction capacities were observed between clinical and clinical-pharmacogenetic models.

Table 3. Variables Selected by LASSO Penalized Regression for Clinical and Clinical-Pharmacogenetic Models for Prediction of Visual Hallucination Occurrence

Clinical model[a]	OR	Regression coefficient[c]
Age at diagnosis	0.98	–0.019
REM sleep behavior disorder	2.48	0.910
Depression	1.12	0.109
Statins	0.99	–0.008
Coffee consumption	0.98	–0.016
Clinical-pharmacogenetic model[b]		
Age at diagnosis	0.99	–0.015
REM sleep behavior disorder	2.27	0.821
Depression	1.0002	2.19E-4
IL6 rs1800795	0.99	–0.014
GPX1 rs1050450	1.07	0.066
COMT rs165815	0.69	–0.365
MAOB rs1799836	0.97	–0.027
DRD3 rs6280	1.32	0.280
BIRC5 rs8073069	0.94	–0.066

[a]Regression equation: multivariate signature for the patient = –0.48 – 0.019 * age at diagnosis + 0.910 * REM sleep behaviour disorder + 0.109 * depression –0.008 * statins –0.016 * coffee consumption.
[b]Regression equation: multivariate signature for the patient = –0.67 – 0.015 * age at diagnosis + 0.821 * REM sleep behavior disorder + 2.19E-4 * depression –0.014 * *IL6* rs1800795 + 0.066 * *GPX1* rs1050450 –0.365 * *COMT* rs165815 –0.027 * *MAOB* rs1799836 + 0.280 * *DRD3* rs6280 –0.066 * *BIRC5* rs8073069.
[c]Regression coefficient is a natural logarithm of the OR.

The most prominent clinical predictor of VH was the presence of RBD. RBD increased risk for development of VH, which is in concordance with the previous literature (Diederich et al., 2009). In both models, younger age at diagnosis and depression increased the odds for development of VH. Younger age at diagnosis may predispose patients to VH as the disease should generally last longer in these patients, while depression has already been recognized as risk factor for VH as well (Ceravolo et al., 2016). The clinical model revealed an additional 2 clinical parameters as potential predictors of VH: statins and coffee consumption. They both may protect against VH due to their potential neuroprotective effects (van der Most et al., 2009; Herden and Weissert, 2018). Both parameters were recognized as protective against PD as well (Kalia and Lang, 2015; Yan et al., 2019). However, it was also shown that caffeine increases dopamine signaling in the brain (Volkow et al., 2015), which might indicate an increased risk for VH development rather than protection against this AE.

The largest genetic effect on the occurrence of VH was observed with *COMT* rs165815 and *DRD3* rs6280. *COMT* rs165815 C allele decreased odds for development of VH, while the *DRD3* rs6280 C allele increased odds for this AE, confirming the results of the univariate analysis in the same cohort (Redenšek et al., 2019b). *IL6* rs1800795 was protective against VH. This SNP may lower the expression of IL6, which might lower the chance of VH development (Watkins and Andrews, 2016). Furthermore, *GPX1* rs1050450 may increase the risk for development of VH. This polymorphism decreases the enzyme's activity, weakening the defense against reactive oxygen species, which might further increase VH development (Watkins and Andrews, 2016). Our results suggest a protective effect of *MAOB* rs1799836, which may

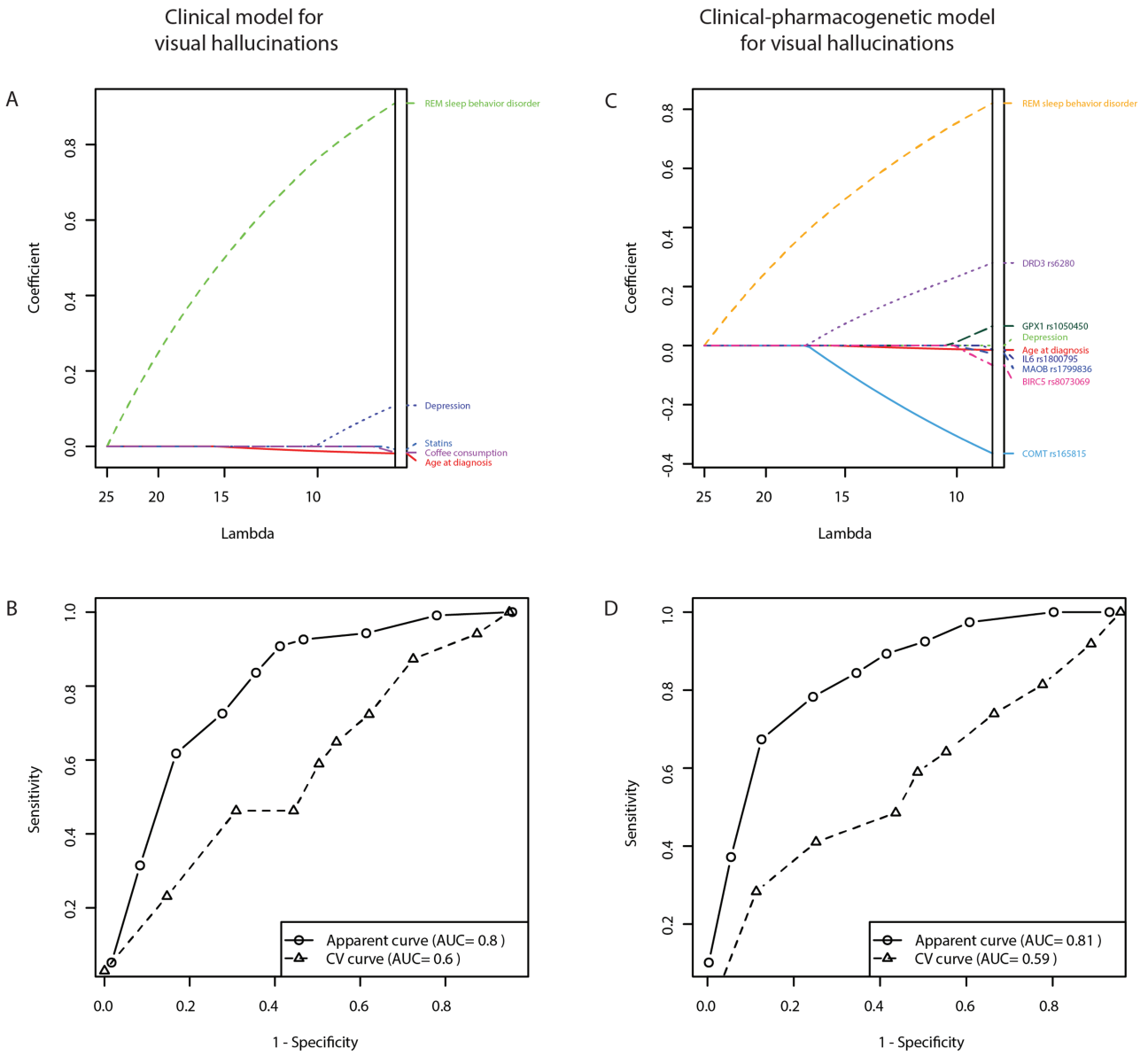

Figure 1. Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression models and receiver operating characteristic (ROC) curves for prediction of the risk for development of visual hallucinations (VH). (A) Clinical model for prediction of VH. The highest predictive quality of the model was estimated at $\lambda = 7.1$. (B) ROC curve of the clinical model for prediction of VH. (C) Clinical-pharmacogenetic model for prediction of VH. The highest predictive quality of the model was estimated at $\lambda = 8.8$. (D) ROC curve of the clinical-pharmacogenetic model for prediction of VH. Only significant variables are presented in the graphs of the LASSO penalization as their regression coefficients were not shrunk to zero by λ. CV, cross-validated.

be due to lowered dopamine turnover in G allele carriers (Lohle et al., 2018). *BIRC5* rs8073069 may protect against VH by increased survivin expression (Jenko et al., 2016), which decreases apoptosis and consequently also decreases inflammation and oxidative stress.

The most prominent clinical predictor of ICD was depression. This common and also prodromal sign of PD has been observed as a risk factor for ICD previously (Gatto and Aldinio, 2019). Younger patients were reported to be more prone to development of impulsive behavior (Ceravolo et al., 2016). We also observed that patients taking beta-blockers have lower odds for development of ICD. Beta-blockers could attenuate levodopa's extra-physiological efflux of dopamine (Bhide et al., 2015) and thus reduce the risk for ICD. Both types of our models showed protective effect of caffeine, although previous studies have indicated the contrary (Ceravolo et al., 2016). Further studies are warranted as higher caffeine intake was also recognized as protective against PD (Kalia and Lang, 2015). Our clinical model suggests an association of alcohol consumption with increased odds for development of ICD, which is in agreement with previously reported data (Ceravolo et al., 2016; Gatto and Aldinio, 2019). Our observation that males develop ICD more often compared with females is in agreement with the previous data as well (Gatto and Aldinio, 2019).

The clinical-pharmacogenetic model for prediction of ICD identified 6 potential genetic biomarkers. The *NOS1* rs2682826 A allele increased odds for development of ICD, which is in agreement with the univariate analysis in the same cohort (Redenšek et al., 2019a). *NOS1* polymorphisms were previously associated with other psychiatric disorders (Topaloglu et al., 2017). *SLC22A1* rs628031 A allele increased risk for ICD as well, which confirms the results of the univariate analysis in the

Table 4. Variables Selected by LASSO Penalized Regression for Clinical and Clinical-Pharmacogenetic Model for Prediction of Impulse Control Disorders Occurrence

Clinical model[a]	OR	Regression coefficient
Sex	0.97	−0.033
Age at diagnosis	0.95	−0.052
Depression	2.12	0.751
Beta-blockers	0.75	−0.282
Alcohol consumption	1.00	6.35E−7
Coffee consumption	0.84	−0.172
Clinical-pharmacogenetic model[b]		
Age at diagnosis	0.95	−0.048
Depression	1.75	0.560
Beta-blockers	0.99	−0.013
Coffee consumption	0.97	−0.033
NOS1 rs2682826	1.15	0.139
SLC6A3 rs393795	1.27	0.242
SLC22A1 rs628031	1.19	0.173
DRD2 rs1799732	0.88	−0.124
DRD3 rs6280	0.88	−0.126
NRG1 rs3924999	0.96	−0.038

[a]Regression equation: multivariate signature for the patient = 1.21 − 0.033 * sex −0.052 * age at diagnosis + 0.751 * depression −0.282 * beta-blockers + 6.35E-7 * alcohol consumption −0.172 * coffee consumption.
[b]Regression equation: multivariate signature for the patient = 0.66 − 0.048 * age at diagnosis + 0.560 * depression −0.013 * beta-blockers −0.033 * coffee consumption + 0.139 * *NOS1* rs2682826 + 0.242 * *SLC6A3* rs393795 + 0.173 * *SLC22A1* rs628031 −0.124 * *DRD2* rs1799732 −0.126 * *DRD3* rs6280 −0.038 * *NRG1* rs3924999.

same cohort (Redenšek et al., 2019b). The latter suggests an important role of this transporter in the occurrence of AEs. As the intronic *SLC6A3* rs393795 is in linkage disequilibrium with SNPs affecting splicing and with SNPs in 3 exons nearby, it could affect the transporter's function and dopamine availability (van Munster et al., 2010) and thus also the occurrence of ICD. Our results indicate that *DRD2* rs1799732 and *DRD3* rs6280 may support prediction of ICD, which might be explained by the reported influence of these 2 SNPs on the expression and splicing, respectively (Xu and Taylor, 2009). The *NRG1* rs3924999 T allele affecting splicing (Xu and Taylor, 2009) lowers risk for ICD development. This SNP has already been associated with schizophrenia and dementia in patients with Alzheimer's disease (He et al., 2016; Shah et al., 2017).

When comparing the predictive capacity parameters of both models for both analyzed AEs, we did not observe any clinically significant advantages of the clinical-pharmacogenetic models over the clinical models. Regarding predictive capacities for VH, both cross-validated AUCs were on the border between worthless and poor. The specificity improved after the addition of genetic variables to the model, but the sensitivity decreased. The PPV was higher in the clinical-pharmacogenetic model compared with the clinical model, which indicates that genetic factors may have a role in the occurrence of VH.

The clinical and clinical-pharmacogenetic models for prediction of ICD displayed very similar cross-validated AUCs, and their predictive capacities were classified as fair. Both specificity and sensitivity decreased after adding genetic variables to the analysis. The PPV of the clinical-pharmacogenetic model was worse compared with the clinical model. This indicates that the selected genetic variables do not contribute to better prediction of the ICD development in a multivariate analysis, although some of them were significantly associated with the AE in the univariate analysis.

We hypothesize that the selected clinical variables had a greater impact on the occurrence of VH and ICD compared with the selected genetic variables. Therefore, an addition of genetic variables did not increase the predictive capacity. Among clinical variables, RBD and depression contributed the most to prediction of VH and ICD, respectively. As discussed above, RBD and depression were already detected as important in increasing the chance of occurrence of studied AEs. It was hypothesized previously that VH are intrusions of REM into wakefulness (Diederich et al., 2009), which indicates a great link between these 2 phenomena. Additionally, depression and ICD have been recognized as comorbidities in many PD patients (Marques et al., 2018). Although several genetic factors significantly influence the occurrence of VH and ICD independently and also in a group, the effect of selected clinical variables, especially RBD and depression, surpasses the effect of selected genetic factors. Consequently, predictive powers of clinical models compared with clinical-pharmacogenetic models do not differ significantly.

The thresholds for preemptive identification of patients at higher risk for development of VH and ICD were calculated. In the case of VH, the fraction of correctly classified patients decreased after inclusion of genetic variables in the model. On the other hand, in the case of ICD, the fraction of correctly classified patients increased in the clinical-pharmacogenetic model, although this improvement was probably not clinically relevant.

The group of patients analyzed in this study was of moderate size although comparable with other pharmacogenetic studies of PD. The sample was also genetically and ethnically uniform. All of the patients were enrolled at the same hospital, which means they were treated according to the same guidelines. Due to the small sample size, the study might have inadequate power to detect subtler associations. However, the method of LASSO penalization allows analysis of a relatively large set of variables that might also correlate between each other even in small cohorts. We used cross-validation to prevent overfitting and over-optimistic results as well. We considered VH and ICD as dichotomous variables due to lack of data regarding the type of these AEs and standardized questionnaires. Information on disease severity at the time of drug prescription would be valuable information and a relevant covariate in the prediction of the studied AEs, too. However, patients' clinical status was not evaluated by any quantitative scales in our study. A longer observation period would probably result in a more comprehensive dataset as the group of cases would presumably get bigger. Nonetheless, the analyzed AEs tend to occur in the first years of treatment (Gatto and Aldinio, 2019). Additionally, we used a pathway-based approach to include several genetic parameters from 5 different pathways included in the PD pathogenesis to capture as much genetic variability as possible. Although it is only partially understood which of the genes and genetic variants contribute to PD and PD related phenotypes, broader knowledge is available about cellular pathways contributing to PD pathogenesis, suggesting that the selection of SNPs on the basis of affected pathways may be an appropriate and efficient way to grasp the key parameters contributing to studied phenotypes. However, additional validation and functional studies are warranted to get a full insight into the exact functions and roles of the important genetic variants in PD-related phenotypes.

Conclusions

The reported study presents some new associations between clinical and genetic variables and VH or ICD. More importantly,

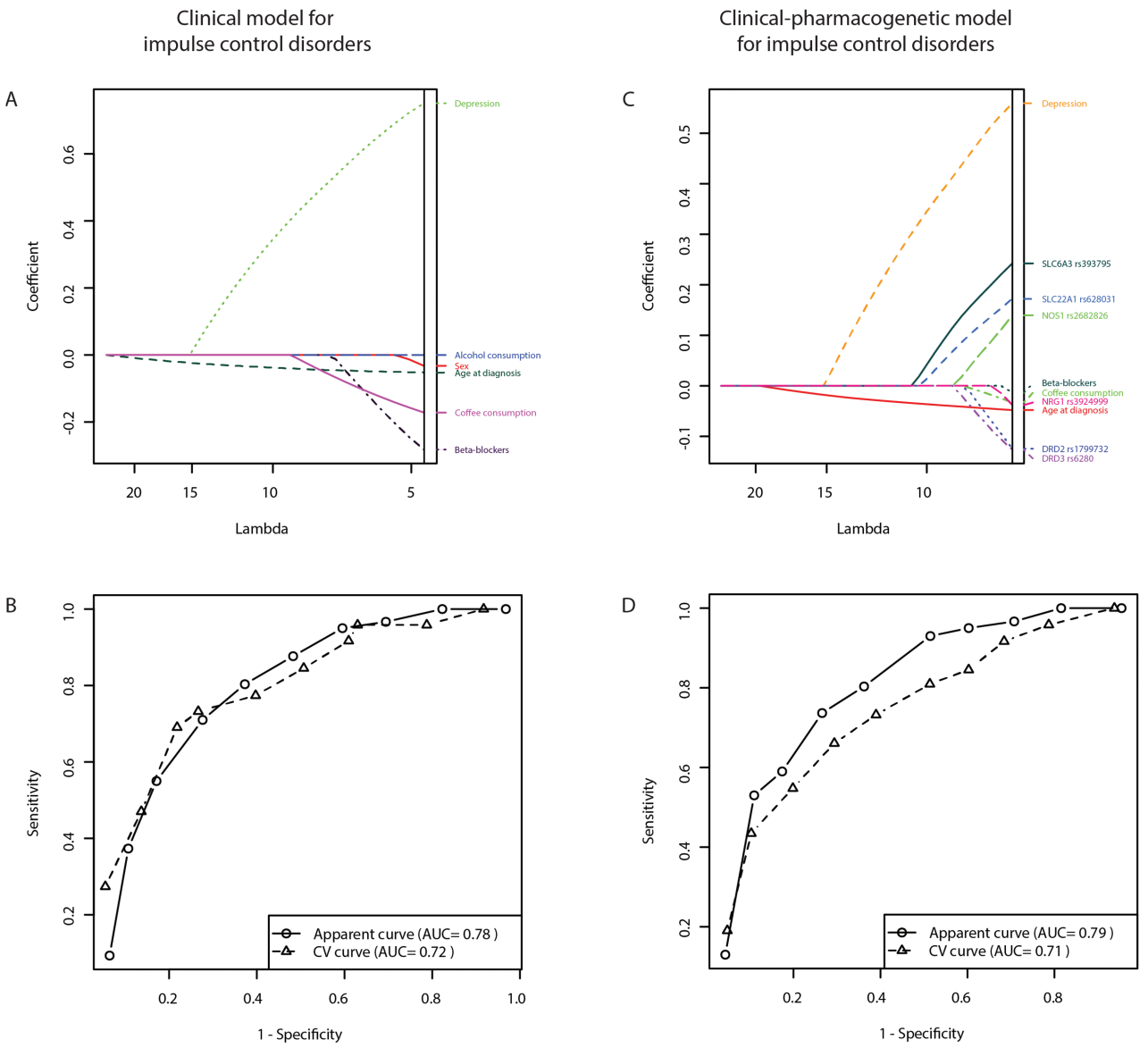

Figure 2. Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression models and receiver operating characteristic (ROC) curves for prediction of the risk for development of impulse control disorders. (A) Clinical model for prediction of impulse control disorders. The highest predictive quality of the model was estimated at $\lambda = 4.7$. (B) ROC curve of the clinical model for prediction of impulse control disorders. (C) Clinical-pharmacogenetic model for prediction of impulse control disorders. The highest predictive quality of the model was estimated at $\lambda = 7.1$. (D) ROC curve of the clinical-pharmacogenetic model for prediction of impulse control disorders). Only significant variables are presented in the graphs of the LASSO penalization as their regression coefficients were not shrunk to zero by λ. CV, cross-validated.

this study presents clinical and clinical-pharmacogenetic models determining the joint effect of selected clinical and genetic variables on the occurrence of VH and ICD. These models could be translated to clinical practice to enable prediction of the occurrence of analyzed AEs. We developed them to facilitate construction of clinically useful algorithms for informed decision-making about the treatment plan for each individual PD patient. The investigated genetic factors did not contribute to clinically relevant better prediction of the VH and ICD in our group of patients. Further analyses on a larger population of PD patients are warranted to determine the simultaneous effect of selected genetic variants on the occurrence of VH and ICD. Additionally, genetic variants from other pathways important in PD could improve predictive capacities of the clinical-pharmacogenetic models.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Statement of Interest

None.

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