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Genetic risk scores and hallucinations in patients with Parkinson disease

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Abstract

Objective

We examine the hypothesized overlap of genetic architecture for Alzheimer disease (AD), schizophrenia (SZ), and Parkinson disease (PD) through the use of polygenic risk scores (PRSs) with the occurrence of hallucinations in PD.

Methods

We used 2 population-based studies (ParkWest, Norway, and Parkinson's Environment and Gene, USA) providing us with 399 patients with PD with European ancestry and a PD diagnosis after age 55 years to assess the associations between 4 PRSs and hallucinations after 5 years of mean disease duration. Based on the existing genome-wide association study of other large consortia, 4 PRSs were created: one each using AD, SZ, and PD cohorts and another PRS for height, which served as a negative control.

Results

A higher prevalence of hallucinations was observed with each SD increase of the AD-PRS (odds ratio [OR]: 1.37, 95% confidence interval [CI]: 1.03–1.83). This effect was mainly driven by *APOE* (OR: 1.92, 95% CI: 1.14–3.22). In addition, a suggestive decrease and increase, respectively, in hallucination prevalence were observed with the SZ-PRS and the PD-PRS (OR: 0.77, 95% CI: 0.59–1.01; and OR: 1.29, 95% CI: 0.95–1.76, respectively). No association was observed with the height PRS.

Conclusions

These results suggest that mechanisms for hallucinations in PD may in part be driven by the same genetic architecture that leads to cognitive decline in AD, especially by *APOE*.

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Glossary

AD = Alzheimer disease; **aOR** = adjusted odds ratio; **CI** = confidence interval; **GWAS** = genome-wide association study; **MDS-UPDRS** = Movement Disorder Society–Unified Parkinson Disease Rating Scale; **MMSE** = Mini-Mental State Examination; **PD** = Parkinson disease; **PEG** = Parkinson's Environment and Gene; **PK** = ParkWest; **PRS** = polygenic risk score; **SZ** = schizophrenia.

Parkinson disease (PD) is the second most common neurodegenerative disease worldwide after Alzheimer disease (AD). Associated with a decreased health-related quality of life and increased mortality, hallucinations are an important nonmotor symptom among patients with PD.[1,2]

Prolonged disease duration is a major risk factor for hallucinations, and one hypothesis is that neurodegenerative changes are responsible for the onset of hallucinations. A well-known disease with hallucinations is schizophrenia (SZ), although hallucinations in SZ differ in characteristics from those in PD. Furthermore, hallucinations often co-occur with cognitive decline, and the genetic underpinnings of the pathomechanisms related to AD or SZ may be relevant.[3,4]

Studies aimed to identify genetic risk factors for hallucinations reported conflicting results, as discussed in various review articles.[5–7] However, these studies tested candidate genes, and no study has taken a comprehensive look at the genetic architecture of SZ, AD, or PD using polygenic risk scores (PRSs) and their association with hallucinations among patients with PD.

Here, we used existing genome-wide association study (GWAS) results from large consortia for AD, SZ, or PD to first create PRS. Then, we examined the hypothesized overlap between genetic burdens for AD, SZ, and PD susceptibility and hallucinations among patients with PD using 2 longitudinal studies of PD progression.

Methods

This study combines 2 separate population-based patient cohorts: The Parkinson's Environment and Gene (PEG) study and the Norwegian ParkWest (PW) study.

The PEG study began as a population-based case-control study among residents of the Central Valley of California, United States. The specifics of this study have been described previously.[8] In this article, we used information from the cohort of patients with PD that was followed between 2001 and 2019. These patients with PD were clinically classified by movement disorder neurologists as probable idiopathic PD according to published criteria.[9] See extensive information regarding the patient recruitment in appendix e-1, links.lww.com/NXG/A297. In total, for the PEG study, we followed 434 patients with PD who provided information about the presence or absence of hallucinations.

The PW study is a longitudinal, population-based cohort of patients with PD and noncases in South and West Norway.[10] All patients with incident PD diagnosed between November 2004 and August 2006 were approached for this study. Patients with PD are currently under continued follow-up, and only those with a confirmed diagnosis of PD at their latest or final clinical visit were eligible for this study. Here, we included data from 191 patients at baseline and 159 patients seen at a 5-year follow-up visit.

The presence of hallucinations was assessed using the Movement Disorder Society–Unified Parkinson Disease Rating Scale (MDS-UPDRS) in PEG, whereas PW used the UPDRS.[11,12] The presence of hallucinations was considered positive when a patient or caregiver indicated the presence of illusions, hallucinations, and/or psychosis over the past week. To achieve consistency between studies in terms of disease duration for the assessment of hallucination, we used information provided at the first follow-up visit by PEG patients (on average 5.7 years after diagnosis) and from the 5-year disease duration mark for PW patients.

Genetic data

Blood samples from both studies were genotyped using a genome-wide single nucleotide polymorphism (SNP) array. The PEG study used the Global Screening Array (GSA; Illumina, Inc) chip and the PW study the Illumina Infinium OmniExpress. For pre- and post-imputation quality control, see appendix e-1, links.lww.com/NXG/A297. Phasing was performed using ShapeIT v2.r790,[13] and the reference panel was HRC.r1.2016.[14] We imputed SNPs using the Michigan Imputation Server, which uses Minimac3 for imputation.[15] We restricted to 5,400,408 SNPs that were available in both data sets. All quality control was performed using Plink 1.9.[16]

For family members with estimated kinship of 12% or more (reflecting second-degree relatives or more closely related) based on estimated IBD,[16] one individual was randomly selected to remain in the study. Fractional ancestry among all individuals was estimated using hidden Markov modeling and clustering (Structure 2.3.4).[17] We restricted the analysis to individuals classified as the European super-population, and in the analysis, we adjusted using the fractional ancestry.

After quality control, 524 patients with PD, followed longitudinally, had provided both genotyping and hallucination information (390 in PEG and 133 in PW); of these, 447 were of European descent. We then excluded 48 patients with PD

who were diagnosed at or before age 55 years to exclude potential hereditary, nonidiopathic PD leaving 399 patients with PD.

Standard protocol approvals, registrations, and patient consents

All study protocols regarding human subjects have been approved by their local institutional review board, and written consent was given by all participants.

Creation of PRSs

Four weighted sum PRSs were created using PRSice 2.1.8[18] based on 4 distinct sets of the GWAS, i.e., using SNPs and effect sizes found with the GWAS of AD, SZ, PD, and for height as a negative control. Each PRS is described in detail in appendix e-1, links.lww.com/NXG/A297. We clumped the data to take linkage disequilibrium into account, based on an R-squared threshold of 0.5, without a p value threshold. The final PRS included variants that had a p value less than of 5×10^{-8} in the previously performed GWAS. The allelic weights were based on the effect estimates from previous large-scale GWAS data,[19–27] and for AD a large meta-analysis that specifically estimated the effect size for the *APOE* allele.[28] The final score for each individual in the PD progression sample was the sum of the number of risk alleles for that individual weighted by each β-coefficient (log of the odds ratio). Each set of PRS values was then standardized using z-transformations. For specific details of each PRS, please see the additional information in appendix e-1, links.lww.com/NXG/A297.

Analysis

We performed logistic regression analysis using each PRS as a covariate and the presence of hallucinations among patients with PD during follow-up as the outcome. All analyses additionally included sex, fractional ancestry, age at diagnosis, disease duration at the time of assessment for hallucinations, and study as potential confounders through the use of a propensity score. We restricted the analysis to those individuals diagnosed after age 55 years. All analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

Sensitivity analysis

As sensitivity analyses, we also performed logistic regression analyses with the total population, and a subpopulation diagnosed at or after age 60 years. In addition, we performed logistic regression analysis adjusting for various confounders and/or risk factors for hallucinations to further explore the influence of potential confounding.

For the PRS, we used a genome-wide p value threshold of 5×10^{-8}. However, the p values in the GWA studies depend on the sample size, the effect size of the allele, and the type of outcome (continuous vs dichotomous). As this differed between the 4 GWASs, it is difficult to compare the PRSs with each other. Therefore, as part of our sensitivity analyses, we created 4 PRSs with the top 75 SNPs. Furthermore, we created PRSs with different p value thresholds (1×10^{-8}, 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4}).

Moreover, we removed patients who reported illusions (or slight to mild hallucinations among PW patients as this study did not differentiate between illusions and hallucinations) to examine findings among those with formed hallucinations only. In addition, we performed an ordinal logistic regression to evaluate associations with severity of hallucinations symptoms. Finally, to determine whether these PRSs were associated with PD susceptibility as well as hallucinations, we performed logistic regression analysis to assess the association between the PRS with PD status among PEG patients and controls (restricted to European ancestry only and those diagnosed at or after age 56 years).

Data availability

Access to deidentified data related to this study will be made available on agreement and material transfer agreements. Requests can be made to B.R. for clinical data of PEG, to C.L. and B.R. for genetic data of PEG, and to J. M-G. for clinical and genetic data of the PW study.

Results

There were 281 patients with PD of European descent in PEG and 118 in the PW study, totaling 399 patients with PD of European ancestry. After on average 5.5 years of disease duration, hallucinations were prevalent in 53 patients (13%) during the past week at the time of their follow-up visit (table 1). Among those with hallucinations, 38 patients (72%) reported illusions or hallucinations with insight, whereas 15 patients (28%) had severe hallucinations with loss of insight, psychosis, or delusions.

The results of the PRS associations with hallucinations are provided in table 2. An increase in 1 SD in the AD-PRS was associated with a 37% increase in the odds of hallucinations (95% confidence interval [CI]: 1.03–1.83, table 2). The *APOE*-PRS of hallucinations based on *APOE* status alone (summing the risks for *e4* or *e2* alleles) showed strong effect estimates, i.e., we estimated a 92% increase in odds of hallucinations for an increase in 1 point of the *APOE*-PRS (which is equivalent to 1 *APOE-e4* allele, 95% CI: 1.14–3.22). However, the AD-PRS on exclusion of the *APOE* signal also showed an association with hallucinations (adjusted odds ratio [aOR]: 1.34, 95% CI: 1.00–1.79).

The SZ-PRS was associated with a 23% decrease in odds (95% CI: 0.59–1.01), and every SD increase in the PD-PRS was associated with a 29% increase in the odds for the presence of hallucinations, but the 95% CI is wide (95% CI: 0.95–1.76). The height PRS was not associated with hallucinations in any of our analyses.

There was no collinearity between the 4 PRSs. When we combined all 3 PRSs (AD, SZ, and PD-PRS) in the same model, the effect estimates and CIs were very similar (table 2).

Table 1 Characteristics of patients with PD of European ancestry, diagnosed after age 55 years, stratified by study

	Study					
	PEG		PW		Total	
	No.	%/SD	No.	%/SD	No.	%/SD
No. of patients with PD	281		118		399	
At baseline						
Age at diagnosis	69.0	7.2	68.7	7.1	69.0	7.2
Male sex	165	58.7	73	61.9	238	59.7
Smoking status						
Never smoker	159	56.6	60	50.9	219	54.9
Former smoker	120	42.7	46	39.0	166	41.6
Current smoker	2	0.7	12	10.2	14	3.5
Years of schooling	15.1	3.7	11.3	3.2	13.9	4.0
Disease characteristics at baseline						
UPDRS motor score	19.2	9.9	21.5	9.3	19.9	9.8
Motor phenotype						
PIGD	155	55.2	47	39.8	202	50.6
TD	80	28.5	57	48.3	137	34.3
Intermittent/combination	46	16.4	14	11.9	60	15.0
Hoehn and Yahr ≥3	32	11.6	8	6.8	40	10.1
Total levodopa dosage in mg	372	303	NA		372	303
MMSE	28.3	1.9	27.8	2.3	28.2	2.0
RBD	47	18.0	13	11.0	60	15.8
At first follow-up (PEG study) or 5-year follow-up (PW study)						
Hallucinations[a]	38	13.5	15	12.7	53	13.3
Hallucinations[a]—severity						
None	243	86.5	103	87.3	346	86.7
Slight—illusions without loss of insight	19	6.8	0	0.0	19	4.8
Mild—formed hallucinations without loss insight	14	5.0	0	0.0	14	3.5
Mild or slight[b]	0	0.0	5	4.2	5	1.3
Moderate—formed hallucinations with loss insight	5	1.8	9	7.6	14	3.5
Severe—delusions or paranoia	0	0.0	1	0.9	1	0.3
Disease duration	5.7	2.4	5.0	0.1	5.5	2.0
Hoehn and Yahr ≥3	72	26.8	31	26.3	103	26.6
Total levodopa dosage in mg	624	540	568	326	607	486
UPDRS motor score	24.0	12.0	27.1	13.2	24.9	12.4
MMSE score	27.9	2.5	26.2	4.4	27.4	3.2
Depression[a]	112	39.9	44	37.3	156	39.1
Cognitive impairment[a]	148	52.7	54	45.8	202	50.6
Anxiety[a]	95	33.8	NA		95	33.8
Apathy[a]	92	32.7	75	63.6	167	41.9

Abbreviations: MDS-UPDRS = Movement Disorder Society–Unified Parkinson Disease Rating Scale; MMSE = Mini-Mental State Examination; NA = not available; PD = Parkinson disease; PEG = Parkinson's Environment and Gene; PIGD = postural instability and gait disturbance; PW = ParkWest; RBD = REM sleep behavior disorder; TD = tremor dominant.

[a] These characteristics were evaluated with the (MDS)-UPDRS questionnaire. The UPDRS score was recoded to the MDS-UPDRS score, when possible.[12] Patients with PD who recorded slight to moderate symptoms of each neuropsychiatric characteristic are combined in this table.

[b] In contrast to the MDS-UPDRS, the UPDRS questionnaire did not differentiate between illusion and hallucinations without a loss of insight.

However, the 95% CIs for the SZ- and PD-PRS (but not the AD-PRS) included the null.

Results sensitivity analyses

Using different subpopulation samples, the results remained similar (table 3). The estimated effect sizes for the AD-PRS, SZ-PRS, and *APOE*-PRS appeared slightly weaker in the total sample and stronger in the subsample diagnosed at or after age 60 years. The effect estimates for the PD-PRS and hallucinations were slightly stronger in the total population.

Adjusting for cognitive status, measured with the Mini-Mental State Examination (MMSE) and assessed at the time collecting hallucination information, strengthened the effect estimate for the AD-PRS and the PD-PRS with hallucinations (AD-PRS: aOR 1.50, 95% CI: 1.10–2.05; PD-PRS: aOR 1.42, 95% CI: 1.01–2.00). Restricting to a population without cognitive decline (MMSE score ≥25) limits the sample size to only 37 patients with PD with hallucinations, but the effect estimates were similar to those after adjustment for MMSE (AD-PRS: aOR 1.45, 95% CI: 1.03–2.05; PD-PRS: aOR 1.56, 95% CI: 1.04–2.33). Adjusting for other risk factors did not change the effect estimates, although adjusting for UPDRS motor score widened the CI slightly (see table e-1, links.lww.com/NXG/A293). In addition, when adjusting for additional variables, especially rapid eye movement sleep behavior disorder and the neuropsychiatric characteristics, such as cognitive decline, depression, apathy, or anxiety scores (see table e-1), the associations between the PD-PRS and hallucinations remained similar, but the CIs narrowed.

As another sensitivity test, we also created multiple PRSs with various p value thresholds (table 4). Point estimates and SDs varied only slightly for the AD-PRS, PD-PRS, SZ-PRS, and height PRS, respectively, suggesting that a relatively small number of SNPs selected according to genome-wide statistically significant p value thresholds suffices. Specifically, adding SNPs by increasing the p value threshold appears to add precision for some (e.g., AD-PRS), but not all, PRSs. In addition, when we created PRSs with the top 75 SNPs from GWAS data, the AD-, SZ-, and PD-PRS effect estimates remained essentially the same—albeit CIs widened—and the height PRS remained unassociated with hallucinations (table 4).

After removing patients with PD who reported illusions, only 29 patients with PD reported formed hallucinations. Although this decreased statistical power, the effect estimates and CIs remained very similar (see table e-2, links.lww.com/NXG/A294). The effect estimates also remained very similar when modeling the severity of hallucinations with the PRS in an ordinal logistic regression analysis (see table e-3, links.lww.com/NXG/A295).

Finally, we also assessed the association between each PRS and a PD diagnosis in the PEG study, using 1,000 individuals (484 patients with PD and 516 controls) with a diagnosis (or interview age for controls) at or after age 56 years. The only PRS we found to be associated with an increased risk for a PD diagnosis was—as expected—the PD-PRS (see table e-4, links.lww.com/NXG/A296).

Table 2 Logistic regression for the association between schizophrenia–PRS, Alzheimer disease–PRS, PD-PRS, and the height PRS and hallucinations among 399 patients with Parkinson disease from the 2 cohorts combined (Parkinson's Environment and Gene and ParkWest)

	No. of SNPs	aOR	95% CI	
Each PRS separately				
Alzheimer disease	92	1.37	1.03	1.83
APOE	2	1.92	1.14	3.22
Schizophrenia	328	0.77	0.59	1.01
Parkinson disease	181	1.29	0.95	1.76
Height	12,688	1.00	0.74	1.35
Joint analysis of the 3 PRSs				
Alzheimer disease	92	1.39	1.04	1.86
Schizophrenia	328	0.79	0.60	1.05
Parkinson disease	181	1.29	0.94	1.78

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; PRS = polygenic risk score.
Fifty-three patients reported hallucinations (13.3%).
PRSs were created using a p value threshold of 5×10^{-8}.
The *APOE*-PRS is based on rs429358 and rs7412, where each apoe4 allele increases risk (β: 1.327), whereas each apoe2 allele decreases risk (β: −0.598) compared with apoe3.
The logistic regression analyses were adjusted for sex, fractional ethnicity, age at diagnosis, disease duration, and study through the use of a propensity score.

Table 3 Logistic regression for the association between schizophrenia–PRS, Alzheimer disease–PRS, PD-PRS, and the height PRS and hallucinations among the total population (including those diagnosed at or before age 55 years) and the subpopulation that was diagnosed at or after age 60 years

		Total population (N = 448)			60+ years (N = 354)		
	No of SNPs	aOR	95% CI		aOR	95% CI	
Alzheimer disease	92	1.23	0.93	1.61	1.47	1.09	1.99
APOE	2	1.62	0.98	2.67	2.08	1.20	3.61
Schizophrenia	328	0.79	0.61	1.02	0.74	0.55	0.99
Parkinson disease	181	1.33	0.99	1.78	1.33	0.96	1.86
Height	12,688	1.07	0.80	1.42	0.97	0.70	1.33

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; PD = Parkinson disease; PRS = polygenic risk score.
The total population consists of 448 patients with PD, with 58 patients reporting hallucinations (13.0%). The subpopulation diagnosed at or after age 60 years consists of 354 patients; 47 patients report hallucinations (13.2%). The PRSs were created using a p value threshold of 5×10^{-8}.
The *APOE*-PRS is based on rs429358 and rs7412, where each apoe4 allele increases risk (β: 1.327), whereas each apoe2 allele decreases risk (β: −0.598) compared with apoe3.
The logistic regression analyses were adjusted for sex, fractional ethnicity, age at diagnosis, disease duration, and study through the use of a propensity score.

Discussion

We studied whether genetic risk architecture of AD, SZ, and PD is associated with hallucinations in patients with PD. We identified an increase of hallucinations within the first 6 years after a PD diagnosis that is associated with higher AD-PRS.

The AD-PRS included a strong *APOE* status component. *APOE* regulates amyloid-beta aggregation and clearance in the brain, as well as brain lipid transport, glucose metabolism, neuronal signaling, neuroinflammation, and mitochondrial function.[29] An association between *APOE* and cognitive decline among patients with PD has been established previously.[30] Previous studies of genetic risk factors related to cognitive decline, such as *APOE*, and hallucinations among patients with PD have not been consistent.[5–7] In our study, the AD-PRS without *APOE* still shows an association with hallucinations, suggesting that other AD-related genetic risk variants also play a role in the occurrence of hallucinations. Finally, when adjusting for cognitive decline, the association between the AD-PRS and hallucinations remained and became stronger, suggesting that the AD-PRS plays an independent role in the development of hallucinations.

The SZ-PRS showed a suggestive decrease in prevalence of hallucinations. Possible explanations for this finding include, first, that this is a chance finding; second, that we efficiently selected out of our study all SZ-related patients with parkinsonism; and third, that an underlying genetically determined SZ pathobiology leads to these opposing results. In support of this third hypothesis, SZ and PD both involve dopaminergic dysfunction. In SZ, one of the main hypotheses for the occurrence of hallucinations is an increased dopaminergic activity in the mesolimbic system. Conversely, in patients with PD, there is a depletion of striatal dopamine due to a loss of dopaminergic neurons in the substantia nigra. PD treatment aims at replacing dopaminergic activity at synapses. As neurodegeneration progresses, dopaminergic dysfunction may create imbalances in the circuitry that may lead to hallucinations, similar to the increased dopaminergic tone in the mesolimbic pathway that leads to hallucinations in SZ.[31] We did not see any association between the SZ-PRS and a PD diagnosis. Together, our data suggest that the biology related to the SZ-PRS is not related to vulnerability of dopaminergic neurons in the SN; however, the effect of dopaminergic treatment in the mesolimbic pathway among patients with PD with an increased genetic risk for SZ may differ from those without a genetic risk for SZ.

Although not formally statistically significant in the primary analysis, when analyzing the association adjusting for rapid eye movement sleep behavior disorder, or neuropsychiatric characteristics (such as depression or anxiety), there appears to be an increased prevalence of hallucinations with increasing PD-PRS. Overall, this initial finding suggests that genetic risk factors for PD and the neurodegenerative processes underlying PD might also increase the risk for developing hallucinations among patients with PD.

When studying hallucinations among patients with PD, it is important to take PD disease duration into account because longer duration is known to be associated with an increase in hallucinations. Therefore, we decided to analyze the prevalence of hallucinations within on average about 5 years of disease duration, when the prevalence both in the PEG and PW study was 13%. Mortality and loss-to-follow-up in longitudinal PD studies have been shown to increase substantially after 5 years, further justifying this cutoff to minimize survival bias.

It is difficult to assess the prevalence and onset of hallucinations in PD accurately, and we had to rely on the UPDRS or MDS-UPDRS. More extensive instruments for measuring

Table 4 Logistic regression for the association between the 4 PRS sets and hallucinations, using various *p* value thresholds and using 75 SNPs for the PRS sets among the patients with Parkinson disease from the Parkinson's Environment and Gene study and ParkWest study that were diagnosed after age 55 years (N = 399)

	p Value threshold	No of SNPs	aOR	95% CI	
Different *p* value thresholds					
Alzheimer disease	1×10^{-8}	81	1.36	1.02	1.82
	1×10^{-7}	99	1.36	1.02	1.81
	1×10^{-6}	128	1.40	1.05	1.87
	1×10^{-5}	218	1.45	1.09	1.94
	1×10^{-4}	444	1.36	1.01	1.82
Schizophrenia	1×10^{-8}	243	0.78	0.59	1.02
	1×10^{-7}	374	0.78	0.59	1.03
	1×10^{-6}	632	0.80	0.61	1.06
	1×10^{-5}	1,169	0.82	0.62	1.09
	1×10^{-4}	2,519	0.84	0.63	1.12
Parkinson disease	1×10^{-8}	152	1.29	0.94	1.76
	1×10^{-7}	195	1.28	0.94	1.74
	1×10^{-6}	253	1.25	0.92	1.70
	1×10^{-5}	323	1.25	0.92	1.70
	1×10^{-4}	408	1.22	0.90	1.65
Height	1×10^{-8}	11,282	1.01	0.75	1.36
	1×10^{-7}	13,417	1.01	0.75	1.37
	1×10^{-6}	16,351	1.04	0.77	1.40
	1×10^{-5}	20,478	1.06	0.78	1.43
	1×10^{-4}	27,284	1.06	0.78	1.44
Using the top 75 SNPs from each GWAS					
Alzheimer disease		75	1.36	1.02	1.82
Schizophrenia		75	0.81	0.61	1.06
Parkinson disease		75	1.18	0.87	1.61
Height		75	0.90	0.66	1.21

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; GWAS = genome-wide association study; PRS = polygenic risk score.
The logistic regression analyses were adjusted for sex, fractional ethnicity, age at diagnosis, disease duration, and study through the use of a propensity score.

hallucinations have been developed,[32] but were unavailable to us at the time we collected our data. Thus, the number of patients with hallucinations in our studies may have been underestimated. Also, patients might have developed hallucinations after the end of our follow-up, and some patients may have been reluctant to acknowledge the presence of hallucinations. Because there is no indication that the genetic score would influence this mismeasurement of the outcome differentially, outcome misclassification is probably nondifferential, and we would expect our estimates to be biased toward the null.

Using existing GWAS data for the creation of a PRS has several benefits. One benefit is the large size of these studies allowing for estimates to be precise and ensuring that the measurement errors for the weights in the PRS are minimized. Another benefit is that there is no need for validation of the PRS in a separate, independent data set, as the scores are created based on independent populations. Previous studies have provided validation for both the AD-PRS and SZ-PRS, whereas we validated the association between PD-PRS and PD diagnosis in our study.[33–36]

In genetic studies, genetic ancestry (population stratification) is a potentially large and commonly observed confounder. We restricted to individuals genetically identified as from European descent, and additionally adjusted for fractional ancestry, limiting any potential confounding in our findings. The SZ-PRS was generated in a mixed population, whereas the AD-PRS and PD-PRS were created with individuals from European ancestry only. Although the SZ-PRS was based on a mixed population, it consisted mainly of European ancestry individuals. Unfortunately, until large GWASs in diverse ethnic populations become available, it is impossible to develop ethnicity-stratified PRS, and it remains open whether the associations we report are generalizable to other ethnicities.

Hallucinations in PD appear to be associated with the genetic architecture of AD, especially as represented by *APOE*. There is some indication for potential associations between hallucinations and the genetic architecture of SZ and also with genetic susceptibility for PD in late-onset patients.

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Appendix Authors

Name	Location	Contribution
Cynthia D.J. Kusters, MD, PhD	University of California, Los Angeles	Design and conceptualization of the study; analysis and interpretation; statistical analysis; and drafting and revision of the manuscript for intellectual content
Kimberly C. Paul, MPH, PhD	University of California, Los Angeles	Guidance for the genetic analysis; interpretation analysis; and revised the manuscript for intellectual content
Aline Duarte Folle, MS, PhD	University of California, Los Angeles	Data acquisition for the PEG study; interpretation analysis; and revised the manuscript for intellectual content
Adrienne M. Keener, MD	University of California, Los Angeles	Data acquisition for the PEG study; interpretation analysis; and revised the manuscript for intellectual content
Jeff M. Bronstein, MD, PhD	University of California, Los Angeles	Data acquisition for the PEG study; interpretation analysis; and revised the manuscript for intellectual content
Valerija Dobricic, PhD	University of Lübeck, Lübeck, Germany	Performing GWAS analysis among the PEG PD patients; interpretation analysis; and revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Ole-Bjørn Tysnes, MD	University of Bergen, Norway	Interpretation analysis and revised the manuscript for intellectual content
Lars Bertram, MD, PhD	University of Lübeck, Lübeck, Germany	Interpretation analysis and revised the manuscript for intellectual content
Guido Alves, MD, PhD	University of Stavenger, Norway	Interpretation analysis and revised the manuscript for intellectual content
Janet S. Sinsheimer, PhD	University of California, Los Angeles	Design and guidance for the genetic analysis; interpretation analysis; and revised the manuscript for intellectual content
Christina M. Lill, MD, PhD	University of Lübeck, Lübeck, Germany	Supervising role for the GWAS analysis among the PEG PD patients; interpretation analysis; and revised the manuscript for intellectual content
Jodi Maple-Grødem, PhD	University of Stavenger, Norway	Major role in data acquisition for the ParkWest study; design and conceptualization of the study; interpretation analysis data; and revised the manuscript for intellectual content
Beate R. Ritz, MD, PhD	University of California, Los Angeles	Design and conceptualization of the study; interpretation analysis; and revised the manuscript for intellectual content

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