BRIEF REPORT

Alpha-Synuclein Repeat Variants and Survival in Parkinson's Disease

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ABSTRACT

Objectives: To determine whether α-synuclein dinucleotide repeat (REP1) genotypes are associated with survival in Parkinson's disease (PD).

Methods: Investigators from the Genetic Epidemiology of Parkinson's Disease Consortium provided REP1 genotypes and baseline and follow-up clinical data for cases. The primary outcome was time to death. Cox proportional hazards regression models were used to assess the association of REP1 genotypes with survival.

Results: Twenty-one sites contributed data for 6,154 cases. There was no significant association between α-synuclein REP1 genotypes and survival in PD. However, there was a significant association between REP1 genotypes and age at onset of PD (hazard ratio: 1.06; 95% confidence interval: 1.01-1.10; *P* value = 0.01).

Conclusions: In our large consortium study, α-synuclein REP1 genotypes were not associated with survival in PD. Further studies of α-synuclein's role in disease progression and long-term outcomes are needed. © 2014 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; α-synuclein; gene; survival; association

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Additional Supporting Information may be found in the online version of this article.

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Genetic studies of familial Parkinson's disease (PD) discovered rare pathogenic missense and multiplication mutations in the α-synuclein gene (*SNCA*).[1-4] The mechanism by which multiplication mutations cause familial PD is overexpression.[5,6] Similarly, we observed that polymorphisms in the promoter region of the *SNCA* gene confer susceptibility to PD,[7] presumably by the same overexpression mechanism.[5,6,8-11] Therefore, therapies are being developed to reduce α-synuclein in PD as a method of neuroprotection.[12-14]

However, it is unclear whether reduced *SNCA* expression genotypes or therapies targeting *SNCA* expression slow progression of PD. Our recent genome-wide study found no evidence of *SNCA* single-nucleotide polymorphism (SNP) association with motor and cognitive outcomes of PD at the genome-wide level.[15] By contrast, a recent population-based study of 242 PD cases found that *SNCA* dinucleotide repeat (REP1) allele-length variants are associated with rate of motor progression in PD.[16] Clinical assessments of motor or cognitive outcomes in PD may be confounded by treatment effects.

Here, for the first time, the Genetic Epidemiology of Parkinson's Disease (GEO-PD) consortium conducted a collaborative study to determine whether *SNCA* genotypes are associated with risk of death in PD (a clear outcome measure).

Patients and Methods

Study Subjects

Between June 28, 2010 and November 13, 2011, GEO-PD sites provided the following data for each PD case: *SNCA* REP1 genotype (base pair [bp] length/bp length), genotyping laboratory and platform, diagnostic criteria for PD, date of birth, age at disease onset, age at diagnosis, age at time of study enrollment (baseline), gender, ethnicity, family history of PD, education (years), smoking (ever/never, pack-years), levodopa therapy (ever/never, response), date at last follow-up, method of last follow-up (telephone contact, mail contact, medical records abstraction, death registry, death certificate, or other), vital status at last follow-up, and date of death. Samples were collected at each site for the purpose of conducting genetic association studies. Samples were not collected specifically for the purpose of a survival analysis.

All studies were approved by the local ethical committees after the procedures of each site.

Genotyping

Each participating GEO-PD site measured *SNCA* REP1 genotypes using site-specific genotyping platforms (Supporting Table 1). As in previous studies,[17,18] the REP1 score was calculated as the sum of two allele scores, with each 259-bp allele contributing 0 points, each 261-bp allele contributing 1 point, and each copy of a 263-bp allele contributing 2 points, giving a score (sum of the two allele scores) ranging from 0 to 4. In secondary analyses, genotypes were coded as follows: 259-bp allele count (0, 1, or 2); 263-bp allele count (0, 1, or 2); and 263/263 vs. 259/259 (excluding other genotypes). We evaluated allele frequencies and genotype heterozygosity for each site. We used Pearson's chi-square statistics to assess whether genotype distributions for the *SNCA* REP1 allele-length variants departed from Hardy-Weinberg's equilibrium (HWE). Sites with a significant ($P < 0.005$) deviation from HWE were excluded.

Statistical Analyses

The primary outcome was time to death. A secondary analysis evaluated the association of genotypes with age of onset of PD. Cox proportional hazard regression was used to assess association between genotypes and outcomes. Because the primary outcome investigated in this study is strongly age related, age was used as the time scale and left censoring was accounted for by starting analyses at age at enrollment into the study.[19] All models were adjusted for the contributing GEO-PD site. Because within each site the samples were ethnically homogeneous (after removing minorities), no further adjustment for race or ethnicity was made. To identify relevant covariates, we performed univariate and step-wise Cox regression analyses to identify demographic or clinical variables (including family history) that were associated with outcomes ($P < 0.05$), and the assumption of proportional hazards was evaluated for the covariates using scaled Schoenfeld residuals.[20] For analyses of survival time from age at enrollment into the study until death, the models were adjusted for site, PD duration at baseline, sex, smoking (ever/never), and L-dopa therapy (yes/no). When age at onset was the outcome, site, smoking (pack-years), and education were included as covariates in the models. We performed analyses both unadjusted and adjusted for these covariates. A Woolf's test of homogeneity of hazard ratios (HRs) across sites was performed to assess whether distribution of HRs across sites was compatible with a common HR.[21]

All analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC) and R version 2.13 (www.cran.r-project.org).

Results

Sample

Twenty-one GEO-PD global sites contributed a total of 6,154 PD cases. After data cleaning (excluding 18 duplicate subjects, 28 minority race/ethnicity subjects, and 96 carriers of rare alleles), a total of 6,012 PD

TABLE 1. Demographic and clinical characteristics of subjects by site[a]

Site	Study PI	Country	Continent	No.	Male, n (%)	Age at Onset, Mean (SD)	Age at Study, Mean (SD)	No. Deaths	Follow-up Time, Mean (SD)	Family History, n (%)	Diagnostic Criteria
1	Aasly	Norway	Europe	379	238 (62.8)	58.5 (11.2)	71 (9.1)	167	3.3 (2.8)	48 (12.7)	Gelb
2	Annesi	Italy	Europe	185	106 (57.3)	58.5 (9.9)	66.6 (8.5)	60	10.1 (2.7)	—	Gelb
3	Bentivoglio	Italy	Europe	99	45 (45.5)	57.5 (8)	63.7 (8.9)	17	7.7 (2.3)	15 (15.2)	Gelb
4	Brighina	Italy	Europe	100	58 (58)	57.7 (9.3)	64.9 (9.2)	11	5 (2.5)	6 (6)	Gelb
5	Chartier-Harlin	France	Europe	221	129 (58.4)	51 (10.3)	62.8 (9.4)	49	5.6 (1.8)	21 (9.5)	Gelb
6	Goldwurm	Italy	Europe	821	496 (60.4)	56 (10.9)	63.4 (10.7)	78	3.6 (2)	141 (17.2)	Gibb
7	Hadjigeorgiou	Greece	Europe	357	196 (54.9)	63.5 (9.8)	68.3 (9.9)	77	4 (2.9)	27 (7.6)	Bower
8	Jasinska[b]	Poland	Europe	134	80 (59.7)	51.8 (11)	61 (10.3)	4	4.3 (2.5)	16 (11.9)	Gibb
9	Jeon	Korea	Asia	248	115 (46.4)	52.1 (10.2)	—	18	—	—	Gibb
10	Kim	Korea	Asia	98	41 (41.8)	60.2 (13.9)	64.4 (12.8)	6	3.1 (2.3)	9 (9.2)	Gelb
11	Krüger	Germany	Europe	158	96 (60.8)	56.2 (11.1)	65.4 (9.9)	0	1.4 (0.3)	43 (27.2)	Gibb
12	Lesage	France	Europe	287	177 (61.7)	47.5 (10.1)	57.7 (11.4)	1	1.2 (1.1)	—	Gelb
13	Maraganore	USA	N. America	1,081	695 (64.3)	61.6 (10.7)	66.8 (10.3)	336	6.8 (2.8)	177 (16.8)	Bower
14	Markopoulou	Greece	Europe	59	28 (47.5)	58.6 (11.3)	64.8 (11.4)	7	1.4 (2.2)	19 (32.2)	Gelb
15	Mellick	Australia	Australia	291	145 (49.8)	59.6 (10.9)	68.3 (8.8)	47	4.8 (2.8)	32 (11.3)	Bower
16	Morrison	UK	Europe	574	396 (69)	—	70.1 (9)	111	4.8 (2.2)	94 (16.7)	Gibb
17	Puschmann	Sweden	Europe	102	64 (62.7)	62 (10.1)	70.3 (10)	19	2.7 (0.9)	45 (44.6)	Gibb
18	Tan	Singapore	Asia	182	101 (55.5)	62.3 (11.5)	66.4 (11.1)	0	—	13 (7.1)	Gibb
19	Theuns[c]	Belgium	Europe	429	247 (57.6)	60.4 (11.5)	69.7 (10.2)	136	3.3 (2.4)	74 (19.4)	Gelb
20	Wirdefeldt	Sweden	Europe	94	54 (57.4)	65.3 (11.2)	72.4 (8.4)	60	8.9 (3.2)	9 (9.8)	Gelb
21	Wszolek	USA	N. America	113	69 (61.1)	62 (11.6)	68.7 (11.4)	24	3.4 (3.5)	52 (46)	Gelb
Total				6,012	3,576 (59.5)	58.2 (11.6)	66.5 (10.6)	1,228		841 (14.9)	

Jasinska/Krygowska is shorthand for two investigators, Jasinska-Myga and Krygowska-Wajs; Dr. Krygowska-Wajs contributed 8 cases.
Bower refers to Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. Neurology 1999;52:1214-1220. Gelb refers to Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol 1999;56:33-39. Gibb refers to Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745-752.
[a]Based on n = 6,012 cases with clean data.
[b]The site had two study PIs, Jasinska-Myga and Krygowska-Wajs.
[c] The site had two study PIs, Van Broeckhoven and Theuns.
PI, principal investigator; SD, standard deviation.

cases remained. Clinical characteristics of subjects are summarized in Table 1. Median duration of PD at baseline was 6 years (range, 0-54), and median lag time between baseline and end of follow-up was 4.3 years (range, 0-20.2). The 6,012 PD cases provided 25,453 person-years of follow-up from enrollment to time to event or censoring. There were 1,228 deaths observed (median age at death: 78.6 years; range, 37.8-98.8). Missing data for variables of all sites are summarized in Supporting Table 2. This sample size provided ~80% power to detect HRs as small as 1.4 for a dominant effect of the 259-bp allele.[22]

SNCA and Survival in PD

Results of unadjusted analyses for all sites combined and for all four *SNCA* genotype-coding schemes are illustrated using Kaplan-Meier's curves (Supporting Fig. 1). Results of adjusted analyses for each site separately and combined are illustrated using forest plots (Fig. 1A [REP 1 score] and Supporting Fig. 2 [*SNCA* REP1 259-bp allele count]). No significant associations between *SNCA* genotypes and risk of death were observed for any of the models. In the primary analysis with genotype coded as the REP1 score and with adjustment for site, PD duration at baseline, sex, smoking (ever/never), and L-dopa treatment, the HR was 1.02 (95% confidence interval [CI]: 0.94-1.11; $P = 0.63$). Sensitivity analyses with different covariate adjustments and alternative genotype coding schemes also demonstrated no significant association of REP1 score with risk of death (results not shown). Woolf's test revealed no heterogeneity of HRs between sites.

SNCA and Age at Onset of PD

Results of adjusted analyses for each site separately and combined for *SNCA* REP1 score are illustrated using forest plots (Fig. 1B). There was a significant association between *SNCA* REP1 genotype and age at onset (adjusted analysis), with higher REP1 scores being associated with earlier age at onset (HR, 1.06; 95% CI: 1.01-1.10; $P = 0.01$).

Discussion

In the present study, *SNCA* REP1 genotypes were not associated with survival in PD, but there was some association with age at onset. Multiple studies

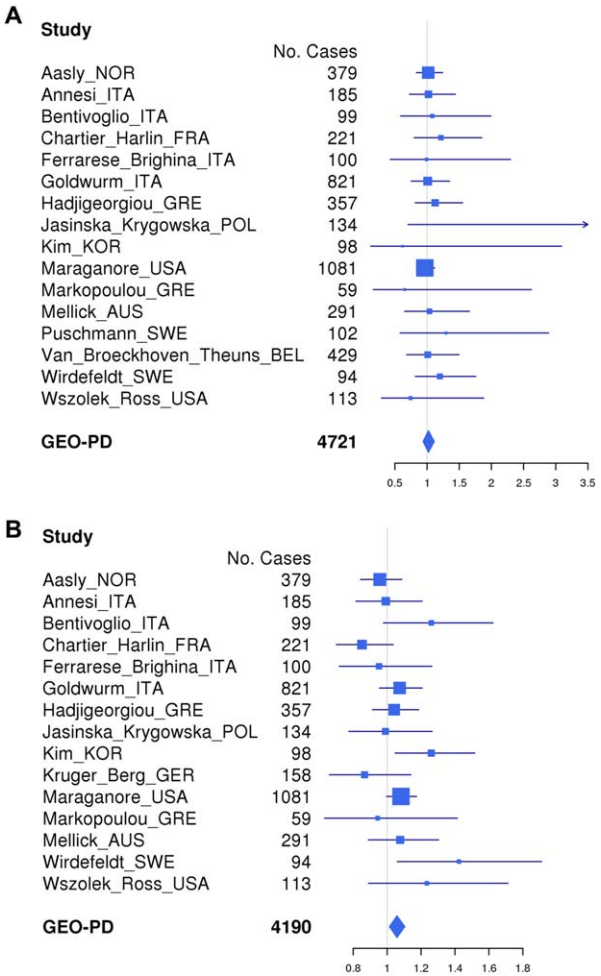

FIG. 1. (A) Forest plot of association HRs between *SNCA* REP1 score and survival in PD. Age at study was considered as "Time 0" (T_0), and we accounted for left truncation using the start-stop counting process style of input within the Cox regression framework. These analyses assumed a log additive effect and were adjusted for disease duration at baseline, sex, smoking (ever/never), and L-dopa treatment. There were no significant associations between *SNCA* REP1 score and survival in PD. Four sites were excluded from analysis because of missing time to event or covariates information. One site was excluded in per-site analysis because of none or few deaths, but it was included in the overall pooled analysis. (B) Forest plot of association HRs between *SNCA* REP1 score and age at onset. These analyses assumed a log additive effect and were adjusted for education and cigarette smoking (pack-years). There was a significant association between *SNCA* REP1 score and age at onset of PD (HR, 1.06; 95% CI: 1.01-1.10; $P = 0.01$). Jasinska_Krygowska refers to two investigators, Jasinska-Myga and Krygowska-Wajs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

have demonstrated that *SNCA* REP1 genotypes are associated with α-synuclein messenger RNA and protein expression levels; specifically, longer *SNCA* REP1 alleles are associated with higher expression levels, and shorter REP1 alleles are associated with lower expression levels.[5,6,8-11] Moreover, in our previously published collaborative pooled analysis of >5,000 GEO-PD cases and controls, REP1 alleles conferring increased expression (263 bp) were associated with a significantly higher PD risk, whereas REP1 alleles conferring reduced expression (259 bp) were associated with a significantly lower PD risk.[7] Consistent with that study, this present study observed an association between overexpression genotypes and earlier age at onset of PD.[23] In aggregate, these studies indicate that the *SNCA* REP1 genotypes, which are associated with α-synuclein expression levels, are associated with PD susceptibility and onset age, but that they do not associate with survival in PD. Though we did not observe an association between *SNCA* REP1 and survival in PD, we cannot exclude an association of the genetic variants with disease progression or other outcomes (such as survival free of H & Y stages 4 or 5 or survival free of dementia).

This seemingly paradoxical dissociation between susceptibility, age at onset, and survival suggests that α-synuclein's role in PD may be complex. In another neurodegenerative disorder, Alzheimer's disease, a similar dissociation is observed, whereby the inciting pathogenic protein, beta-amyloid$_{42}$, is associated with susceptibility and age at onset, but not disease progression.[24,25] However, our results are contrary to the observations of more rapidly progressing motor and cognitive impairments in families with triplication mutations versus duplication mutations.[26,27] It is possible that the level of α-synuclein overexpression in families with multiplication mutations overwhelms cellular systems combating the pathogenic process of α-synuclein aggregation. Our results are also contrary to a recent population-based study reporting that *SNCA* REP1 overexpression genotypes are associated with faster motor decline in PD.[16] However, the sample in that study was small and the duration of follow-up was brief, by contrast to our study.

Our study has strengths. Multiple sites from the GEO-PD consortium amassed a large sample size and with follow-up in the tens of thousands of person-years. We assessed a discreet outcome: death. Our study also has limitations. First, whereas PD cases have a higher risk of death than controls, the median difference in survival is small (approximately 3 years).[28] Therefore, our study may have been underpowered to detect genetic associations underlying limited variability in the death outcome. Second, we considered death from all causes. It was not within the scope of this study to discern causes of death. Third, we did not perform genetic testing to exclude cases with gene mutations known to cause familial parkinsonism ("Mendelian forms"). However, for the three sites with a high frequency of familial PD cases (Markopoulou, 32.2%; Puschmann, 44.6%; Wszolek, 46%), the number of cases that they contributed to the study was small (n = 274 or 4.6% of 6,012 subjects in total). Fourth, the proportion of European sites participating in the study was greater than for other continents. However, the inclusion of additional African, Asian, Australian,

North American, or South American sites may have introduced population stratification biases in the pooled analyses. Fifth, we only considered REP1 variability in the 5' core promoter region of the *SNCA* gene. However, the effects of *SNCA* REP1 variability on expression levels are well defined,[5,6,8-11] by contrast to 3' SNP variability. We have previously shown that REP1 and 3' SNPs have separate and equal effects on PD susceptibility (no additive or multiplicative effects).[18]

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