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α-synuclein, alcohol use disorders, and Parkinson disease: a case-control study

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Abstract

Collaborative pooled analyses demonstrated that allele length variability of the dinucleotide repeat sequence within the alpha-synuclein gene promoter (*SNCA* REP1) is associated with Parkinson disease (PD) worldwide. Other studies demonstrated that variability in the *SNCA* promoter is also associated with alcohol use disorders, but not consistently. Yet other studies demonstrated that alcohol use disorders are inversely associated with PD, but not consistently. The aim of this study was to clarify the patterns of association between REP1 genotype, alcohol use disorders, and PD. Cases were recruited from the Department of Neurology of the Mayo Clinic in Rochester, MN. The controls included unaffected siblings and unrelated controls. We assessed alcohol use via a structured telephone interview and screened for alcohol use disorders using the CAGE questionnaire. REP1 genotyping was performed using an ABI 3730XL platform. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using conditional logistic regression models. We recruited 893 case-control pairs. There was an increasing risk of PD with increasing *SNCA* REP1 allele length (OR 1.18 for each REP1 genotype score unit, 95% CI 1.02 to 1.35; $p = 0.02$). There was a decreasing risk of PD with increasing CAGE score ($p = 0.01$). The association of REP1 score with PD remained significant after adjusting for CAGE score, and the association of CAGE score with PD remained significant after adjusting for REP1 score. There were no pairwise interactions. Our findings suggest that *SNCA* REP1 genotype and alcohol use disorders are independently associated with PD.

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Keywords

alpha-synuclein; alcohol use disorders; Parkinson disease

1. Introduction

Aggregation and fibrillization of the alpha-synuclein protein (encoded by the *SNCA* gene) have been implicated in the pathogenesis of Parkinson disease (PD) [1]. Increasing length of a dinucleotide repeat sequence within the *SNCA* promoter referred to as REP1 (D4S3481) is associated with an increasing risk of PD [2]. In vitro studies demonstrated that increasing length of REP1 alleles is associated with increasing expression of the *SNCA* gene, and deletion of the REP1 sequence resulted in a 4-fold reduction in expression of the *SNCA* gene [3].

Variability in the *SNCA* promoter and increased *SNCA* expression have been associated also with alcohol preference in animal models [4–6]. Experimental studies have suggested that alpha-synuclein levels modulate dopamine transmission [7,8], which in turn has been suggested as the main mechanism mediating reinforcement, withdrawal, and craving associated with alcohol (and drug) addiction. Bonsch et al. [9] found that alcohol-dependent subjects had longer REP1 alleles and elevated *SNCA* mRNA levels in peripheral blood as compared to controls. Subsequent studies did not confirm the association between variability in the *SNCA* promoter and alcohol dependence [10,11], but Foroud et al. [11] found that some of the studied variants were associated with alcohol craving.

It has been hypothesized that PD patients have a premorbid personality of reduced novelty seeking (consistent with reduced dopamine), and hence they avoid the use of addictive substances and are less prone to addiction [12]. A prior history of heavy alcohol use or alcoholism was found to occur less frequently in PD patients compared to controls in some studies [13,14], whereas a prospective study found that alcoholism was associated with a slightly lower risk of PD in men only [15]. The aim of this study was to clarify the patterns of association between REP1 genotype, alcohol use disorders, and PD.

2. Subjects and methods

The Mayo Clinic Investigational Review Board approved all study methods.

2.1 Subjects

Case subjects were PD patients sequentially referred to the Department of Neurology of the Mayo Clinic in Rochester, MN from June 1996 through February 2006 and who resided in Minnesota or in one of the surroundings four states (Wisconsin, Iowa, South Dakota, or North Dakota). The diagnosis of PD was made by neurologists specializing in movement disorders using previously reported criteria [16]. Control subjects included unaffected siblings of cases or population unrelated controls when there were no available siblings. Potential control subjects were screened for parkinsonism using a validated telephone instrument [17]. Only potential controls who screened negative for PD, or who were confirmed not to have PD via clinical assessment (despite having screened positive by telephone interview), were included in the study. All subjects were screened for cognitive impairment using the Mini Mental State Examination (MMSE) for cases and by telephone using the TICS-m [18] for controls. Cognitive impairment was defined as MMSE<24 in cases and TICS-m ≤27 in controls.

2.2 Genotyping

Venous blood samples were obtained from all cases and controls who signed a written informed consent. Genomic DNA was extracted from leukocytes using the Puregene procedure (Gentra Systems, Minneapolis, MN). *SNCA* REP1 (D4S3481) allele lengths were measured using previously described genotyping methods [2]. Genotyping was performed on an ABI 3730XL platform and allelic sizes were assessed using the GeneMapper version 4.0 software (Applied Biosytems, Inc., Foster City, California, USA).

2.3 Ascertainment of alcohol use

Both cases and controls underwent a telephone interview using a structured risk factors questionnaire that assessed demographic, social, occupational, medical, and lifestyle characteristics (including alcohol use). Subjects were asked separately whether they ever drank at least once a month for six months or more in their life beer, wine, or liquor. Subjects who responded “yes” were asked additional questions for each alcohol type separately, including the age that they started drinking, and the age they stopped drinking (if applicable). A drink was defined as a 12-ounce can (or bottle) for beer, a 5-ounce glass for wine, and a 1-ounce shot or cocktail for liquors. Subjects were asked whether they always drank the same quantity of drinks or whether there were years in which they drank more or less (the choices were “always the same” or “major changes”). If subjects reported always the same use, we recorded the number of beverages usually drunk per unit of time (the choices were yearly, monthly, weekly, or daily). For subjects who reported major changes, we recorded the number of beverages drunk per unit of time for different life periods. Subjects who ever drank beer, wine, or liquor, were also screened for alcohol use disorders using the CAGE questionnaire [19]. We also asked subjects whether they had ever received medical treatment because of their alcohol use, whether they ever had liver problems because of their alcohol use, and whether they had ever been hospitalized because of their alcohol use.

We assessed the reliability of alcohol exposures as measured via telephone interview. Specifically, we randomly selected from our sample 20 patients with PD, 20 unaffected siblings, and 20 unrelated controls and we conducted a second risk factor assessment via telephone interview. The second interview was performed by an interviewer other than the one who performed the initial one (by design). We calculated kappa statistics for the dichotomous variables, and the intraclass correlation coefficient for polychotomous variables.

2.4 Statistical analysis

To study the associations of *SNCA* REP1 variability and alcohol use with PD, we first matched cases to a single unaffected sibling of the same sex (when possible) and then of closest age at study. For cases without an available unaffected sibling, we matched an unrelated control by sex, age (±2 years), and geographic region of residence (120-mile radius centered in Rochester, MN; remainder of Minnesota; remainder of Iowa; remainder of Wisconsin; and North and South Dakota combined).

Hardy-Weinberg equilibrium was estimated for the *SNCA* REP1 genotypes among controls. We calculated a *SNCA* REP1 genotype score for each subject as previously described [2,9]. We then studied the association of *SNCA* REP1 genotype score (from 0 to 4) with PD susceptibility using conditional logistic regression analyses.

Similarly, we studied the association of PD with alcohol use using conditional logistic regression analyses. We coded alcohol use overall and by beverage type (beer, wine, and liquor) ever/never. In addition, we coded the frequency of use (drinks per day), duration of

use (in years), and cumulative use (drink-years, calculated from the frequency and duration of use) for beer, wine, and liquor separately. Since a CAGE score of at least 2 is the common cut-off score for detecting alcohol use disorders [20], we coded persons with a score ≥2 as screening positive for alcohol use disorders. Finally, we coded alcohol related medical treatment, liver problems, or hospitalizations ever/never.

All analyses of main effects were adjusted for age and sex, education (quartiles), smoking (ever smoked more than 100 cigarettes versus never), and coffee use (ever versus never). Analyses were performed for subjects overall and stratified by family history of PD (defined as at least one first-degree relative with PD), age at study (divided in quartiles), sex, type of controls (unaffected siblings versus unrelated controls), and geographic region (within 120 miles of Rochester, Minnesota or from the greater five state region). We calculated odds ratios (ORs), 95% confidence intervals (CIs), and *p* values (two-tailed tests, $\alpha = 0.05$).

We explored the joint effects of the *SNCA* REP1 genotype score and CAGE score on PD susceptibility using conditional logistic regression models. We included age at study and sex in all of the models. For each interaction term in the models, we calculated ORs, 95% CIs, and *p* values.

All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC) or S-Plus version 7 (Insightful Corporation, Seattle, Washington, USA).

3. Results

There were 893 case-control pairs (514 case-unaffected sibling pairs and 379 case-unrelated control pairs) included in the analyses. A summary of the demographic and clinical characteristics of the cases and controls is provided in Table 1. Overall, the cases included more men than the controls (62.4% vs. 54.9%). However, the cases and controls had a similar median age at study (67.9 vs. 67.2 years). Overall, the median age at onset of PD in the cases was 62.1 years. Cases and controls were primarily Caucasian and of European descent.

The frequencies of *SNCA* REP1 genotypes did not deviate significantly from Hardy-Weinberg equilibrium in controls. In the overall sample, we noted a trend toward increasing risk of PD with increasing *SNCA* REP1 genotype score (OR = 1.18 for each score unit, 95% CI 1.02 to 1.35, $p = 0.02$).

In the overall sample, alcohol use of any type was reported by 68.7% of cases and 72.9% of controls. Specifically, 51.4% of cases and 53.1% of controls reported ever drinking beer, 29.5% of cases and 28.3% of controls reported ever drinking wine, and 41.7% of cases and 47.8% of controls reported ever drinking liquor. Alcohol use (ever vs. never) was not associated with PD after adjustment for age at study, sex, education, smoking, and coffee (OR = 0.88, 95% CI 0.68 to 1.12, $p = 0.29$). Similarly, specific types of alcohol use (beer, wine, and liquor; ever vs. never) were not associated with PD (Table 3), or when coded ever versus never or when coded for frequency of use, duration of use, or cumulative use (data not shown). In the samples stratified by age at study, sex, type of controls, geographic region, or family history of PD, all results were non-significant (data not shown).

In the overall sample, a CAGE score of two or more (screening positive for alcohol use disorders) was reported by 7.2% of cases and 11% of controls, and was associated with PD (reduced risk; OR = 0.63, 95% CI 0.43 to 0.93, $p = 0.02$, adjusted for age at study, sex, education, smoking, and coffee). In addition, there was a trend of decreasing risk of PD with increasing CAGE score (OR = 0.83 for each score unit, 95% CI 0.71 to 0.96; $p = 0.01$). The

association of CAGE score and PD was similar in men and women and in analyses adjusted for interview type and cognitive impairment (data not shown).

In the overall sample, 1.4% of cases and 3.1% of controls reported at least one medical indicator of alcoholism (treatment, liver problem, or hospitalization). These indicators were associated with PD after adjustment for age and gender (reduced risk; OR = 0.41, 95% CI 0.20 to 0.84, $p = 0.01$) but no longer significant after adjusting for education, smoking, and coffee (Table 3).

For our reliability study, the median lag time between the first and the second interview was 4.8 months (range 2.3 to 14.6). We detected percent agreements for ever or never drinking of 93.3% (kappa = 0.87, 95% CI 0.74 to 0.99) for beer, 86.7% (kappa = 0.68, 95% CI 0.48 to 0.88) for wine, and 86.7% (kappa = 0.72, 95% CI 0.54 to 0.90) for liquor. The intraclass correlation coefficients for ages started drinking were 0.93 for beer, 0.85 for wine, and 0.76 for liquor.

In light of the significant main effect findings for REP1genotype score and CAGE score, we explored possible joint effects in multivariate models (Table 4). Both REP1 genotype score and CAGE score were significant (model 3; no confounding). However, the pairwise interaction term was not significant (model 4; no interaction). Finally, we observed no correlation between REP1 score and CAGE score in unrelated controls ($r^2 = 0.0002$).

4. Discussion

In this case-control study we observed an association of *SNCA* (as measured by REP1 genotype score) and alcohol use disorders (as measured by CAGE score) with PD. The two main effects were independent (no confounding, and no interactions).

Our findings for *SNCA* REP1 and PD are consistent with those reported by a global genetics consortium [2], as expected in part due to the partial overlapping of study subjects. We found no association of ever using alcohol (of any type or by specific type) with PD, consistent with previous studies [15,21–23]. However, we observed an inverse association between CAGE score (a screening measure of alcohol use disorders) and PD, consistent with our findings from a population-based and medical records-based case-control study [14]. In that study, we observed an inverse association of medically diagnosed alcoholism and PD. The overlap of subjects between that study and this study was small (only 57 subjects, all cases), because most of those subjects were deceased at the time of this study. Exclusion of those subjects did not change the results (data not shown). Our findings for CAGE score in this study and our findings for medically diagnosed alcoholism in our previous study suggest that alcohol use disorders, rather than alcohol use per se, are associated with a reduced risk for PD [14]. CAGE scores may be a more sensitive measure of problem drinking because subjects may under-report alcohol use or may be unaware of medical diagnoses. Our findings for CAGE score and PD were similar in men and women. By contrast, two other studies observed an inverse association of heavy alcohol use or medically diagnosed alcoholism with PD in men only [13,15].

There is a strong association between novelty seeking personality and alcohol use disorders [24]. A pre-morbid personality of reduced novelty seeking may precede the onset of the motor symptoms of PD by decades, presumably due to dopamine deficiency within the mesocorticolimbic system [12,25,26]. It is therefore possible that a lower frequency of alcohol use disorders is an early non-motor manifestation of dopamine deficiency (cause-effect inversion).

On the other hand, *SNCA* may be an alcoholism susceptibility locus as well as a PD susceptibility locus. Bonsch et al. [9] demonstrated that *SNCA* REP1 genotype scores were associated with alcohol-dependence and longer REP1 alleles were correlated with increased alpha-synuclein mRNA levels in alcoholics. By contrast, in our study, *SNCA* REP1 score and CAGE score were not correlated. Our findings for REP1 and CAGE score in Caucasian subjects of European descent is similar to the findings of Clarimon et al. [10], who did not observe an association of *SNCA* variants (including REP1) with alcohol dependence in two American Indians populations. However, our sample size was small (379 unrelated controls) and hence our study may have been underpowered to detect an association of REP1 and alcohol use disorders. Moreover, previous studies [11,27,28] reported an association between *SNCA* variability or *SNCA* overexpression and craving for alcohol, which is a common, although not constant, feature of alcohol dependence. Alcohol craving was not specifically addressed by our study, although some CAGE items may partly address craving.

A limitation of our study is that we only measured REP1 variability. It is possible that other common variants in the *SNCA* gene (e.g. SNPs) are associated with PD, alcohol use disorders, or both. Indeed, published studies have recently reported associations of other *SNCA* variants with PD or alcohol use disorders, including SNPs in the 3' untranslated region [11,29].

Another possible limitation of our study is that we measured alcohol exposures via interview. Nevertheless, self-reported drinking has been shown by other studies to be reliable and valid [30]. We used beverage-specific questions, with a close-ended response format to measure alcohol exposures, which are believed to yield better quality data than overall questions with an open-ended response format [31–34]. The CAGE questionnaire is one of the most widely employed of all alcohol screening tools used to detect alcohol use disorders [35,36]. A cutoff of 2 is recommended to provide the best combination of sensitivity, specificity, and positive predictive value to detect alcohol use disorders [38]. The literature reports a sensitivity ranging from 43% to 77% and a specificity ranging from 70% to 86% [39,40]. CAGE has demonstrated high test-retest reliability (0.80–0.95), and good correlations with other instruments (0.48–0.70) [38]. We assessed the reliability of several alcohol exposures measured by our telephone interview and determined that our data were reliable.

Similarly, because we measured alcohol exposures by interview, we cannot exclude some degree of recall bias. However, both study participants and interviewers were blinded to the study hypotheses, and the interviewers were blinded to the case-control status of the participants. It is possible that older subjects and in particular PD patients under-reported alcohol exposures as compared to younger subjects, due to a greater frequency of cognitive impairment. However, we screened all subjects for cognitive impairment and employed a proxy informant when subjects were incapacitated. Furthermore, we performed analyses adjusted for interview type and cognitive impairment that yielded similar results for alcohol use overall and by type, and for indicators of alcohol use disorders.

Finally, we acknowledge that we may have had limited statistical power to detect joint effects. For our available sample size (893 case-control pairs), at a pre-specified alpha of 0.05 and beta of 0.20, we could detect pairwise interactions for REP1 score and CAGE score with odds ratios as small as 1.39. Nevertheless, the results of this study should be considered preliminary and await replication in larger samples. Our preliminary results and power calculations may also prove useful for the planning of future studies.

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Table 1

Demographic characteristics of Parkinson disease (PD) cases, sibling controls, and unrelated controls

	Cases-sibling control pairs		Cases-unrelated control pairs		All cases and controls	
	PD Cases	**Sibling Controls**	**PD Cases**	**Unrelated Controls**	**Cases**	**Controls**
Total sample, n	514	514	379	379	893	893
Men, n (%)	323 (62.8)	256 (49.8)	234 (61.7)	234 (61.7)	557 (62.4)	490 (54.9)
Women, n (%)	191 (37.2)	258 (50.2)	145 (38.3)	145 (38.3)	336 (37.6)	403 (45.1)
Age at onset of PD, median (range)	60.2 (29.4–86.9)	--	65.1 (23.3–88.0)	--	62.1 (23.3–88.0)	--
Age at study, median (range)[a]	66.1 (32.8–91.4)	64.8 (32.0–90.4)	70.4 (42.3–90.4)	71.3 (44.9–92.8)	67.9 (32.8–91.4)	67.2 (32.0–92.8)
Region of origin of parents, n (%)[b]						
Both parents of European origin	447 (87.0)	435 (84.6)	302 (79.7)	330 (97.1)	749 (83.9)	765 (85.7)
Only one parent of European origin[c]	40 (7.8)	47 (9.1)	54 (14.2)	33 (8.7)	94 (10.5)	80 (9.0)
One parent declared “American”[d]	17 (3.3)	16 (3.1)	20 (5.3)	15 (4.0)	37 (4.1)	31 (3.5)
Both parents declared “American”[d]	18 (3.5)	18 (3.5)	12 (3.2)	7 (1.8)	30 (3.4)	25 (2.8)
Both parents Asian	1 (0.2)	2 (0.4)	3 (0.8)	0 (0.0)	4 (0.4)	2 (0.2)
Both parents Mexican	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.1)	2 (0.2)
Both parents African	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	5 (1.0)	10 (1.9)	7 (1.8)	4 (1.1)	12 (1.3)	14 (1.6)

[a] Age at blood draw

[b] Self-reported by subjects

[c] Includes subjects for whom origin of one parent is unknown

[d] These subjects were all Caucasians and not Native Americans

Table 2

Results of case-control analyses for alcohol use (overall or by type), alcoholism, and risk of Parkinson disease

	Subjects, n[a]	Exposure frequency,%		Model[b]		Adjusted Model[c]	
		Cases	Controls	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Alcohol use							
Overall (ever vs. never)	887	68.7	72.9	0.74 (0.59–0.93)	0.01	0.88 (0.68–1.12)	0.29
Beer (ever vs. never)	889	51.4	53.1	0.79 (0.63–1)	0.05	0.96 (0.75–1.23)	0.73
Wine (ever vs. never)	882	29.5	28.3	1.09 (0.88–1.35)	0.43	1.19 (0.95–1.50)	0.14
Liquor (ever vs. never)	882	41.7	47.8	0.73 (0.60–0.90)	0.002	0.83 (0.67–1.02)	0.07
Alcoholism indicators							
CAGE score (2+ vs. <2)[d]	779	7.2	11	0.56 (0.38–0.81)	0.002	0.63 (0.43–0.93)	0.02
Medical history[e]	843	1.4	3.1	0.41 (0.20–0.84)	0.01	0.52 (0.25–1.08)	0.07

[a] Case-control pairs

[b] Adjusted for age at study and sex

[c] Also adjusted for education, smoking, and coffee (see text)

[d] Subjects were considered to have alcoholism if they scored 2 or more on the CAGE questionnaire

[e] Having at least one alcohol-related medical problem (treatment, liver problem, or hospitalization) was considered a medical indicator of alcoholism

Table3

Multivariate analyses for *SNCA* REP1 genotype score, alcoholism, and risk of Parkinson disease

Model[a]	**CAGE (2+)**[b] **OR (95% CI), *p*-value**	**Rep1 Scored**[c] **OR (95% CI), *p*-value**	**Interaction term OR (95% CI), *p*-value**
1. CAGE (2+)	0.63 (0.43–0.93), $p = 0.02$	--	--
2. Rep1 Scored	--	1.18 (1.01–1.38), $p = 0.04$	--
3. CAGE (2+) + Rep1 Scored	0.63 (0.43–0.92), $p = 0.02$	1.19 (1.01–1.39), $p = 0.03$	--
4. CAGE (2+) + Rep1 Scored + [CAGE (2+) * Rep1 Scored]	1.18 (0.47–3.00), $p = 0.72$	1.23 (1.04–1.45), $p = 0.01$	0.68 (0.41–1.14), $p = 0.15$

[a] Each model was adjusted for age at study, gender, education, smoking, and coffee; values in models 1 and 2 vary slightly from values of main effects reported in the results due to sub-setting in the table to subjects with complete data for both variables

[b] Subjects were considered to have alcoholism if they scored 2 or more on the CAGE questionnaire

[c] The REP1 score was considered as a continuous variable