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ORIGINAL COMMUNICATION

Association between the missense alcohol dehydrogenase rs1229984T variant with the risk for Parkinson's disease in women

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Abstract

Background/objective Several meta-analyses including retrospective case–control studies have shown that the risk of developing Parkinson's disease (PD) correlates inversely with alcohol consumption and (PD), although the results of prospective longitudinal studies are far from being conclusive. The reasons for this inverse association are not well-known. Because alcohol dehydrogenase is one of the most important alcohol-detoxification enzymes, we tried to replicate a putative association of the risk of developing PD with two missense gene variations affecting the alcohol dehydrogenase 1B (*ADH1B*) gene (one of them related with aversive effects to alcohol).

Methods In a cohort composed of 629 PD patients and 865 age- and gender-matched healthy individuals, we analyzed genotypes and allele frequencies for two common missense *ADH1B* single nucleotide polymorphisms (SNPs), namely rs1229984 (His48Arg) and rs6413413 (Thr60Ser) using specifically designed TaqMan assays.

Results The frequency of individuals carrying rs1229984T alleles in homozygosity or in heterozygosity was higher in PD than in controls in the whole study cohort ($P<0.001$ and $P=0.005$, respectively), and in women ($P<0.001$ and $P<0.001$, respectively). The genotypes for rs6413413 were similar in PD patients and control subjects. Age at onset of PD patients was not statistically related to rs1229984 or rs6413413 genotypes.

Conclusions The missense variant rs1229984T is statistically associated with the risk of developing PD mainly in women, which could explain differences in alcohol consumption in this gender.

Keywords ADH1B gene · Genetics · Polymorphisms · Parkinson's disease · Risk factors

Introduction

Parkinson's disease (PD) is a disorder initially described more than two centuries ago. However, its etiology remains unknown, although it is thought that it may be related with the interplay of both environmental and genetic factors. The research on the role of environmental risk and protective factors has been mainly conducted during the last four decades. Alcohol consumption, as part of lifestyle exposure, has been found inversely associated with the risk of developing PD, according to several meta-analyses including retrospective case–control studies [1–4], whereas the findings of prospective longitudinal studies are not conclusive enough [4, 5].

Classical hypotheses suggesting an inverse association between alcohol-drinking habit and the risk of developing PD, including a selective mortality of alcohol drinkers prone to develop PD, a possible "protective" effect of alcohol in PD development, and the existence of a "premorbid

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personality" or "premorbid attitude" of PD patients against alcohol consumption (perhaps reflecting a low dopaminergic state leading to suppress drinking behaviors) [4, 6, 7] are far from being proven. Together with these hypotheses, genetic factors could contribute to a trend towards lower alcohol consumption in patients suffering from PD.

Alcohol dehydrogenase (ADH) enzymes are responsible for the first and main ethanol metabolic pathways [8, 9], and they are crucial in the metabolism of dopamine and retinoic acid [10, 11]. ADH, together with the cytochrome P450 2E1 (CYP2E1, belonging to the microsomal ethanol oxidizing system) plays a prominent role in the primary step of alcohol metabolism in human liver, that is, oxidation to acetaldehyde. This toxic compound is oxidized, mainly by the aldehyde dehydrogenase (ALDH) enzyme, to acetate [12]. The genes coding for ADH enzymes in humans (*ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6*, and *ADH7*) are located on chromosome 4q23. One of these genes, namely *ADH1B* (Gene ID 125;MIM 103720) [13], holds two missense single nucleotide polymorphisms (SNPs), rs1229984 (His48Arg) and rs6413413 (Thr60Ser) that cause a strong effect on enzyme activity. Because *ADH1B* rs1229984T allele (which encodes the most active form of the ADH1B enzyme) may lead to more rapid biotransformation of alcohol to acetaldehyde, it could be related with aversive effects to alcohol and to lower alcohol consumption [14].

A recent Chinese case–control study involving 115 PD patients and 214 healthy individuals showed the lack of association of *ADH1B* rs1229984 variants with the risk of developing PD [15], although it should be stated that rs1229984 genotype frequencies are completely different in Asian populations in comparison with those in Caucasian individuals. To our knowledge, the association between *ADH1B* gene polymorphisms and the risk for PD has never been investigated in the European populations. In this study, we analyzed the two missense SNPs (rs1229984 and rs6413413) SNPs in a large cohort of Spanish PD patients and healthy controls with a Caucasian descent.

Methods

Study participants

Demographic information from the 629 patients (all of them above age 18 years) who fulfilled the standardized diagnostic criteria for PD (UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria), is summarized in Table 1. These criteria include the presence of bradykinesia plus one of the following at least: rigidity, postural instability, pharmacological response to dopaminergic drugs, resting tremor, and, in all cases, the absence of other causes of parkinsonism or atypical features [16]. All patients were examined by consultant neurologists who specialized in movement disorders. Table 1 also summarizes information from the 865 healthy controls who were matched for age ($P=0.836$) and gender ($P=0.924$) with patients (Table 1). All control individuals underwent a medical examination, had no systemic or neurological diseases, and had no family history of PD. They were Caucasian Spanish individuals who were recruited from the Infanta Cristina University Hospital, Badajoz, Spain (404 subjects, who were staff or students from the University of Extremadura), and 461 subjects were recruited from the Clinica Universitaria de Navarra, Pamplona, Spain (healthy spouses of patients visiting this Hospital). The recruitment of participants was done between January 2003 and march 2018.

Ethical aspects

The recruitment was done in accordance with the principles of the Helsinki declaration. After full explanation of the purpose of the study and the study procedure, all the participants gave their written informed consent. The study was approved by the corresponding ethics committees of the hospitals involved, specifically, the Ethic Committees of Clinical Investigation of the Clínica Universitaria de Navarra (Pamplona, Spain), the Hospital Universitari Mutua de Terrassa (Terrassa, Barcelona, Spain), and the Infanta Cristina University Hospital (Badajoz, Spain).

Table 1 Demographic data

Group	PD ($n=629$)	Controls ($n=865$)	*P*
Age, y, mean (SD)	66.98 (12.75)	63.18 (26.63)	0.836
Age range, y	22–95	19–92	–
AAO, y, mean (SD)	57.68 (14.03)	NA	–
AAO range, y	14–85	NA	–
Men, *n* (%)/women, *n* (%)	295 (46.9)/334 (53.1)	392 (45.3)/473(54.7)	0.924

PD Parkinson's disease, *y* years, *AAO* age at onset, *SD* standard deviation, *NA* not available

Genetic analyses

Two nonsynonymous *ADH1B* SNPs (both occurring in the Spanish population, [12]), that were selected on the basis of their allele frequencies in the population studied (minor allele frequency 6.4% for rs1229984 and 1.6% for rs6413413) [12] and their functional effect, were analyzed by real-time PCR with the following TaqMan probes: rs1229984 (C___2688467_20), and rs6413413 (C__29127160_10, Life Technologies, Alcobendas, Madrid, Spain). For this purpose, an Applied Biosystems 7500 qPCR thermocycler was used. Details for the amplification procedure are reported elsewhere [12].

Statistical analysis

The Hardy–Weinberg equilibrium was analyzed using the online application (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The allele and the genotype frequency analyses were performed using the statistical package PLINK [17], and the rest of statistical analyses were carried out using the SPSS 20.0 package (SPSS Inc., Chicago, IL, USA). Intergroup comparisons were carried out using the Chi square test or, when appropriate, Fisher test. Correction for multiple testing was assessed by means of the false discovery rate procedure [18]. For each intergroup comparison, we obtained both crude and corrected values (*P* and Pc, respectively) including all genotypes or all alleles.

The sample size was calculated on the basis of the minor allele frequencies in control individuals, by analyzing the frequency for carriers of the risk gene, using an RR value equal to 2 ($P=0.05$) [19, 20]. The statistical power in this study, which is based on the allele frequencies observed in patients and in healthy controls was, for one-tailed and two-tailed associations, respectively, which is as follows: rs1229984 100% and 99.9%, and rs6413413 46.4% and 34.5%. We calculated the negative predictive values as described elsewhere [21]. The comparison of the age at onset across genotype categories for both SNPs was performed using the ANOVA test for independent samples.

Results

The rs1229984 and rs6413413 genotypes were in Hardy–Weinberg's equilibrium both for PD patients and control groups. The genotype and allelic frequencies of the rs6413413 SNP did not significantly differ when comparing PD patients and healthy controls (Table 2), However, the frequencies for the rs1229984CT genotype and the rs1229984T allele were significantly higher in PD patients as compared to controls. These differences remained as significant after multiple comparisons, both in the whole series (Table 2) and

Table 2 *ADH1B* genotypes and allelic variants of patients with PD and healthy volunteers

Genotype	PD Patients ($N=629$, 1258 alleles)	Controls ($N=865$, 1730 alleles)	OR (95% CI), *P*; Pc; NPV (95% CI)
ADH1B rs1229984 C/C	496 (78.9; 75.7–82.0)	730 (84.4; 82.0–86.8)	0.69 (0.48–0.99); 0.006; 0.024; 0.50 (0.43–0.58)
ADH1B rs1229984 C/T	125 (19.9; 16.8–23.0)	129 (14.9; 12.5–17.3)	1.42 (0.98–2.04); 0.012; 0.024; 0.60 (0.58–0.61)
ADH1B rs1229984 T/T	8 (1.3; 0.4–2.1)	6 (0.7; 0.1–1.2)	1.84 (0.44–8.01); 0.252; 0.366; 0.58 (0.58–0.58)
ADH1B rs6413413 T/T	623 (99.0; 98.3–99.8)	856 (99.0; 98.3–99.6)	1.09 (0.87–1.38); 0.868; 0.868; 0.60 (0.54–0.66)
ADH1B rs6413413 T/A	6 (1.0; 0.2–1.7)	9 (1.0; 0.4–1.7)	0.916 (0.22–3.73); 0.868; 0.868; 0.58 (0.58–0.58)
ADH1B rs6413413 A/A	0 (0.0; 0.0–0.0)	0 (0.0; 0.0–0.0)	–
Alleles			
ADH1B rs1229984 C	1117 (88.8; 87.0–90.5)	1589 (91.8; 90.6–93.1)	0.70 (0.51–0.98); 0.005; 0.010; 0.50 (0.43–0.57)
ADH1B rs1229984 T	141 (11.2; 9.5–13.0)	141 (8.2; 6.9–9.4)	1.42 (1.02–1.98); 0.005; 0.010, 0.59 (0.58–0.60)
ADH1B rs6413413 T	1252 (99.5; 99.1–99.9)	1721 (99.5; 99.1–99.8)	1.09 (0.27–4.58); 0.869; 0.869; 0.60 (0.27–0.86)
ADH1B rs6413413 A	6 (0.5; 0.1–0.9)	9 (0.5; 0.2–0.9)	0.92 (0.22–3.71); 0.869; 0.869; 0.58 (0.58–0.58)

The values in each cell represent number (percentage; 95% confidence intervals)

Test for trend for ADH1B rs1229984: OR 1.35; Chi square = 1.77; $P=0.1829$

P crude probability, *Pc* probability after multiple comparisons, *NPV* negative predictive value

in women (Table 3), although in the whole series, statistical significance was low (Pc = 0.024 for rs1229984CT genotype and Pc = 0.01 for rs1229984T allele). When age and gender were included in the comparisons as confounding factors, the associations that were significant in Table 2 remained significant, as follows: *ADH1B* rs1229984 C/C, $P = 0.028$; *ADH1B* rs1229984 C/T, $P = 0.022$; *ADH1B* rs1229984 C, $P = 0.011$; *ADH1B* rs1229984 T, $P = 0.011$.

When considering a dominant model, the sum of the frequencies for the rs1229984T genotypes in heterozygosity or homozygosity, compared with the frequencies of rs1229984CC genotypes, was significantly higher in women suffering from PD than that observed in the healthy female group (OR 2.28; 95% CI 1.38–3.75; $P = < 0.001$).

When the recessive model was tested, the comparison between rs1229984 and rs6413413 genotypes was not statistically significant ($P = 0.206$ and $P = 1.000$, respectively) in the overall study group. When the recessive model was considered in different genders (Table 3), the results were the following: rs1229984 ($P = 0.153$ for women and $P = 0.753$ for men), rs6413413 ($P = 1.000$ for both genders). These results could be expected because of the relatively low minor allele frequencies for both SNPs.

The age at onset of PD did not significantly change when comparing different genotypes for both SNPs, both in the whole series (Table 4) and considering women only (Table 5).

Table 3 *ADH1B* genotypes and allelic variants of patients with PD and healthy volunteers distributed by gender

Genotype	PD women (*N* = 334, 668 alleles)	Control women (*N* = 473, 946 alleles)	Intergroup comparison, OR (95%CI), *P*; Pc; NPV (95%CI)	PD men (*N* = 295, 590 alleles)	Control men (*N* = 392, 784 alleles)	Intergroup comparison, OR (95%CI) *P*; Pc; NPV (95%CI)
ADH1B rs1229984 C/C	251 (75.1; 70.5–79.8)	413 (87.3; 84.3–90.3)	0.44 (0.27–0.72); <0.001; 0.002; 0.42 (0.32–0.52)	245 (83.1; 78.8–87.3)	317 (80.9; 77.0–84.8)	1.16 (0.68–1.98); 0.463; 0.926; 0.60 (0.49–0.70)
ADH1B rs1229984 C/T	78 (23.4; 18.8–27.9)	57 (12.1; 9.1–15.0)	2.22 (1.34–3.70); <0.001; 0.002; 0.62 (0.60–0.64)	47 (15.9; 11.8–20.1)	72 (18.4; 14.5–22.2)	0.84 (0.49–1.46); 0.404; 0.926; 0.56 (0.54–0.59)
ADH1B rs1229984 T/T	5 (1.5; 0.2–2.8)	3 (0.6; 0.1–1.3)	2.38 (0.35–18.05); 0.223; 0.297; 0.59 (0.58–0.59)	3 (1.0; 0.1–2.2)	3 (0.8; 0.1–1.6)	1.33 (0.15–12.07); 0.726; 0.927; 0.57 (0.57–0.58)
ADH1B rs6413413 T/T	332 (99.4; 98.6–100.2)	469 (99.2; 98.3–100.0)	1.42 (0.15–16.63); 0.668; 0.668; 0.67 (0.18–0.96)	291 (98.6; 97.3–100.0)	387 (98.7; 97.6–99.8)	0.94 (0.16–5.87); 0.927; 0.927; 0.56 (0.18–0.89)
ADH1B rs6413413 T/A	2 (0.6; 0.2–1.4)	4 (0.8; 0.0–1.7)	0.71 (0.06–6.53); 0.668; 0.668; 0.59 (0.58–0.59)	4 (1.4; 0.0–2.7)	5 (1.3; 0.2–2.4)	1.06 (0.17–6.40); 0.927; 0.927; 0.57 (0.57–0.58)
ADH1B rs6413413 A/A	0 (0.0; 0.0–0.0)	0 (0.0; 0.0–0.0)	–	0 (0.0; 0.0–0.0)	0 (0.0; 0.0–0.0)	–
Alleles						
ADH1B rs1229984 C	580 (86.8; 84.3–89.4)	883 (93.3; 91.8–94.9)	0.47 (0.30–0.74); <0.001; 0.002; 0.42 (0.32–0.52)	537 (91.0; 88.7–93.3)	706 (90.1; 88.0–92.1)	1.12 (0.68–1.84); 0.546; 0.927; 0.60 (0.49–0.70)
ADH1B rs1229984 T	88 (13.2; 10.6–15.7)	63 (6.7; 5.1–8.2)	2.13 (1.34–3.37); <0.001; 0.002; 0.60 (0.59–0.61)	53 (9.0; 6.7–11.3)	78 (9.9; 7.9–12.0)	0.89 (0.54–1.47); 0.546; 0.927; 0.57 (0.56–0.58)
ADH1B rs6413413 T	666 (99.7; 99.3–100.1)	942 (99.6; 99.2–100.0)	1.41 (0.15–16.55); 0.688; 0.688; 0.67 (0.18–0.96)	586 (99.3; 98.7–100.0)	779 (99.4; 98.8–99.9)	0.94 (0.16–5.83); 0.927; 0.927; 0.56 (0.18–0.89)
ADH1B rs6413413 A	2 (0.3; 0.1–0.7)	4 (0.4; 0.0–0.8)	0.71 (0.06–6.50); 0.688; 0.688; 0.59 (0.59–0.59)	4 (0.7; 0.0–1.3)	5 (0.6; 0.1–1.2)	1.06 (0.17–6.35); 0.927; 0.927; 0.57 (0.57–0.57)

The values in each cell represent number (percentage; 95% confidence intervals)

Test for trend for ADH1B rs1229984 T in women: OR 2.03; Chi square = 19.33; $P = 0.00001$

P crude probability, *Pc* probability after multiple comparisons, *NPV* negative predictive value

Table 4 Age at onset of PD according to the *ADH1B* genotypes

	Age at onset (years)	Two-tailed *T* test compared to C/C	Two-tailed *T* test compared to C/T
ADH1B rs1229984 C/C	57.74 ± 12.53		
ADH1B rs1229984 C/T	56.99 ± 12.29	$P = 0.602$	
ADH1B rs1229984 T/T	61.71 ± 8.83	$P = 0.404$	$P = 0.322$
		Two-tailed *T* test compared to T/T	Two-tailed *T* test compared to T/A
ADH1B rs6413413 T/T	57.24 ± 12.42		
ADH1B rs6413413 T/A	58.33 ± 11.72	$P = 0.831$	
ADH1B rs6413413 A/A	–	–	–

Table 5 Age at onset of PD according to the ADH1B genotypes in women only

	Age at onset (years)	Two-tailed *T* test compared to C/C	Two-tailed *T* test compared to C/T
ADH1B rs1229984 C/C	59.38 ± 12.30		
ADH1B rs1229984 C/T	59.57 ± 10.56	$P = 0.926$	
ADH1B rs1229984 T/T	61.80 ± 10.76	$P = 0.664$	$P = 0.657$
		Two-tailed *T* test compared to T/T	Two-tailed *T* test compared to T/A
ADH1B rs6413413 T/T	59.27 ± 12.12		
ADH1B rs6413413 T/A	60.23 ± 23.18	$P = 0.735$	
ADH1B rs6413413 A/A	–	–	–

Discussion

Many retrospective studies, including four meta-analyses, have shown an inverse association between the risk of developing PD and alcohol consumption [1–4], although the reasons for this association are not well-understood. The effects of alcohol on the dopaminergic system include [22]: (A) functional changes of dopaminergic receptors in several brain areas; (B) increased discharges of dopaminergic neurons in the ventral tegmental area and in the substantia nigra; (C) increased dopamine release in the amygdala and in the nucleus accumbens.

The rs1229984 SNP functional consequences affect liver function (ADH1B protein product plays an important role in hepatic alcohol oxidation) [23], alcohol biotransformation and drinking behaviors (protective effects against alcohol dependence and maximum number of alcoholic drinks have been shown by GWAS) [23, 24]. In addition, this SNP is related to the risk of developing several types of cancer including head and neck [23–27], colorectal [28], and esophagus [25], cardiovascular disease [29], and hypertension [30]. Regarding its influence on neurological diseases, a lack of association of the rs1229984 SNP with the risk for essential tremor in the Caucasian Spanish population [31] and with PD in Chinese [15] has been shown. By turn, the rs1229984TT genotype seems to be associated with increased risk of developing Alzheimer's disease (OR 2.54, 95% CI 1.19–5.41) [32], and the minor allele (rs1229984T) frequency seems to be decreased in migraine patients as compared to healthy controls but increased in migraine patients reporting that alcohol consumption triggered migraine attacks [33]. On the other hand, carriers of rs1229984T allele have shown a significantly increased risk of developing restless legs syndrome (OR 1.88, 95% CI 1.26–2.79), with slight influence on age at onset of this disease, as reported in a recent case–control study [34].

Among the multiple studies reported on genomic and pharmacogenomic biomarkers of PD (revised in references [35,36]), the increased risk of developing PD has been described in individuals carrying allelic variants of the *ADHA1* gene in a single study [10], but not in another one [37], as well as an association of PD risk with a missense mutation in the *ADH1C* causing the change G78Stop [11].

In this study, we identified an association between the risk of developing PD in women, and the frequency of the minor allele (T) of the rs1229984 SNP. This could explain in part the tendency to lower alcohol consumption (as compared to the general population) in PD patients, at least for

women. By turn, the rs6413413 SNP was not associated with the risk for PD. The reason why rs1229984T allele was statistically associated with the risk of developing PD only in women is uncertain, although it could be related both with a relatively higher frequency of this allele in male controls (9.1% in control men vs 6.7% in control women) and in PD women (13.2% in PD women vs 9.0% in PD men, Table 2). These data contrast with those of a recent meta-analysis of retrospective case–control studies regarding alcohol consumption and risk for PD stratified by gender, in which the frequency of never drinkers was higher in PD than in controls for both genders (although statistical significance was only reached in men), and the frequency of heavy + moderate alcohol consumption was significantly lower in PD than in controls only in men [4]. In addition, women and men have shown significant differences in alcohol pharmacokinetic parameters: when compared with men, women have shown higher average of time to peak concentration, peak concentration, and area under the concentration–time curve, and the rate of alcohol metabolism is higher in women than in men [12].

The limitations of this study include the chances of a selection bias, that could be due to patient recruitment in a hospital setting, the lack of previous similar studies in Caucasian populations and the limited sample size. The two latter limitations suggest that replication studies are needed. In addition, the fact that the possibility that some healthy subjects who participated as part of the control group might develop PD, cannot be ruled out. However, according to the incidence rates of PD in subjects older than 65 in Spain [186.8 (95% CI 110.4–263.2) per 100.000 person-years] [38], given the low proportion of healthy controls carrying the risk genotype that might eventually develop PD, their influence on the results of this study is likely to be very low.

In sum, this study suggests a weak, although statistically significant, association between the risk of developing PD in Caucasian Spanish women (OR 2.13, 95% CI 1.34–3.37 for rs1229984T allele), and the occurrence of the rs1229984 SNP.

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Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflicts of interests.

Ethical standards The study was approved by the corresponding ethics committees of the hospitals involved. Specifically, the Ethic Committees of Clinical Investigation of the Clínica Universitaria de Navarra (Pamplona, Spain), the Hospital Universitari Mutua de Terrassa (Terrassa, Barcelona, Spain), and the Infanta Cristina University Hospital (Badajoz, Spain). Written informed consent was obtained from all the participants before study enrollment.

Data accessibility statement All data related to the current study, intended for reasonable use, is available from J.A.G. Agúndez (University Institute of Molecular Pathology Biomarkers, University of Extremadura -UNEx ARADyAL Instituto de Salud Carlos III, Av/ de la Universidad S/N, E10071 Cáceres. Spain) and F.J. Jiménez-Jiménez (Section of Neurology, Hospital del Sureste, Arganda del Rey, Madrid, Spain).

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