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Dopamine β-*hydroxylase* -1021C>T association and Parkinson's disease

Owen A. Ross[1,*], **Michael G. Heckman**[1], **Alexandra I. Soto**[1], **Nancy N. Diehl**[1], **Kristoffer Haugarvoll**[1,2,3], **Carles Vilariño-Güell**[1], **Jan O. Aasly**[2,3], **Sigrid Sando**[3], **J. Mark Gibson**[4], **Timothy Lynch**[5], **Anna Krygowska-Wajs**[6], **Grzegorz Opala**[7], **Maria Barcikowska**[8], **Krzysztof Czyzewski**[9], **Uitti J Ryan**[10], **Zbigniew K. Wszolek**[10], and **Matthew J. Farrer**[1]

[1] *Department of Neuroscience, Mayo Clinic College of Medicine, Jacksonville, Florida, USA* [2] *Department of Neurology, St. Olav's Hospital, Trondheim, Norway* [3] *Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway* [4] *Department of Neurology, Royal Victoria Hospital, Belfast, Ireland* [5] *Department of Neurology, Mater Misericordiae Hospital, Dublin, and University College Dublin Conway Neuroscience Investigator, Ireland* [6] *Department of Neurology, Jagiellonian University, Krakow, Poland* [7] *Department of Neurology, Ageing Degenerative and Cerebrovascular Diseases, Medical University of Silesia, Katowice, Poland* [8] *Department of Neurodegenerative Disorders, Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland* [9] *Department of Neurology, MSWiA Hospital, Warsaw, Poland* [10] *Department of Neurology, Mayo Clinic College of Medicine, Jacksonville, Florida, USA*

Abstract

A single nucleotide polymorphism in the promoter region of the *dopamine* β-*hydroxylase* gene (*DBH* -1021C>T; rs1611115) is reported to regulate plasma enzyme activity levels. This variant has also been the focus of two large association studies in Parkinson's disease yielding conflicting results. We examined this association in four Caucasian patient-control series (n=2696). A modest protective association was observed in the Norwegian series (OR=0.81, p=0.03; n=1676), however the effect was in the opposite direction in the Polish series (OR=2.01, p=0.01; n=224). No association was observed for *DBH* -1021C>T with disease susceptibility in the US and Irish series, or combining all four series (OR=0.91, p=0.16, n=2696). We observed a modest association between *DBH* -1021C>T and AAO in the combined series (p=0.01). Taken together, these findings indicate that *DBH* -1021C>T does not play a major role in the pathogenesis of Parkinson's disease.

Keywords

Genetics; PD; DBH; promoter SNP

Introduction

The identification of genetic variants that influence susceptibility to Parkinson's disease (PD) determines functional studies, the generation of model systems and directs therapeutic

*Corresponding author: Owen A. Ross PhD, Molecular Genetics Laboratory and Core, Morris K. Udall Parkinson's Disease Research Center of Excellence, Mayo Clinic, Department of Neuroscience, 4500 San Pablo Road, Jacksonville, FL 32224, Tel: (904)-953-0963, Fax: (904)-953-7370, Email: ross.owen@mayo.edu.

strategies. To date, classical candidate gene association studies and genome-wide approaches have failed to find reproducible genetic risk factors in sporadic PD. However the identification of Lrrk2 G2385R and R1628P demonstrates that common variants which can increase risk by as much as two-fold do exist [1,2]. Although these two variants appear to be specific for individuals of Asian descent, consistent association between genetic variability within the *SNCA* locus and susceptibility to PD is observed (OR~1.5) in diverse ethnicities however the functional pathogenic variant has yet to be determined [3–5]. These findings support the hypothesis that complex disorders like sporadic PD may be the result of multiple factors with relatively small individual effect sizes.

A single nucleotide polymorphism (SNP) in the promoter region of *dopamine β-hydroxylase* (*DBH*) gene has been reported to substantially affect plasma activity of the dopamine β-hydroxylase enzyme [6,7]. Two large association studies have examined the role of this functional SNP (*DBH* -1021C>T; rs1611115) with PD susceptibility [8,9]. Healy et al. (2004) reported a significant increase of the TT genotype in controls, thus protective against PD in a UK Caucasian population [9]. Chun et al. (2007) attempted to replicate these findings in a US Caucasian series of 1244 PD patients and 1186 control subjects. In contrast with previous data, this study showed no evidence of association for *DBH* -1021C>T with either PD susceptibility or age-at-onset (AAO) in patients [8].

Dopamine β-hydroxylase converts dopamine to noradrenaline and subjects with low *DBH* expression may subsequently have protection against PD symptoms [9]. *DBH* is therefore a plausible biological candidate for PD susceptibility and highlights dopamine β-hydroxylase levels as a preclinical biomarker and a potential therapeutic target. Therefore, to elucidate the role of the *DBH* -1021C>T in PD, we have investigated its association in four PD patient-control series.

Subjects and Methods

Four independent Caucasian PD patient-controls series from the US, Ireland, Norway and Poland were examined. The combined series provides a total sample size similar to the two previous studies, with 1037 PD patients and 1659 control subjects. The demographics for each individual series are displayed in Table 1. All patients were examined and observed longitudinally by a movement disorders neurologist and diagnosed with PD according to published criteria [10]. For the Irish and US series each patient was individually selected and matched based on age (+/− 4 years), gender, and ethnicity to an unrelated control without evidence of neurological disease. Patients were consecutively selected in the Norwegian and Polish series and controls were not individually matched for age and gender. All subjects are negative for Lrrk2 G2019S. The ethical review boards at each institution approved the study, and all participants provided informed consent.

Genotyping of *DBH* -1021C>T was performed on a Sequenom MassArray iPLEX platform (San Diego, CA); all primer sequences are available on request. For the US and Irish matched series, associations between PD and *DBH* -1021C>T were measured by odds ratios (OR) and corresponding 95% confidence intervals (CI) obtained from single variable conditional logistic regression models. For the Norwegian, Polish, and combined series, associations between PD and *DBH* -1021C>T were measured by OR and 95% CI obtained from logistic regression models adjusted for age, sex, and series (combined series only). In PD cases, linear regression models adjusted for sex and series (combined series only) were used to examine associations between AAO and *DBH* -1021C>T. The effect of *DBH* -1021C>T on plasma dopamine β-hydroxylase activity is reported to be additive [6], therefore we used this model for all association tests. Statistical significance was determined at the 5% level.

Results

Genotype and allele frequencies are displayed in Table 2. There was an association between *DBH* -1021C>T and PD in the Norwegian series (OR=0.81, 95% CI: 0.67 – 0.98, p=0.03), with a similar trend in the Irish series albeit not statistically significant (OR: 0.84, 95% CI: 0.59 – 1.19, p=0.33). An effect in the opposite direction was observed in the smaller Polish series (OR=2.01, 95% CI: 1.24 – 3.25, p=0.01). There was no association observed in the US series (OR=0.94, 95% CI: 0.69 – 1.28, p=0.70), or when all four series were combined (OR=0.91, 95% CI: 0.79 – 1.04, p=0.16). In the combined series with 1037 cases and 1659 controls, we had greater than 95% power to detect the odds ratio of 0.46 described in Healy et al. in comparing T/T versus C/C patients, assuming at 20% minor allele frequency at the 5% significance level.Meta-analysis of our results with the previous published data [8,9] showed no association between *DBH* -1021C>T and susceptibility to PD (Table 3).

The assessment of *DBH* -1021C>T influence on AAO revealed a trend towards association between the minor allele (T) and later AAO in the Irish series (p=0.01). Similar trends, although substantially weaker and not statistically significant, were observed in the US and Norwegian series. In the combined patient series (n=1037) this protective effect remained statistically significant (p=0.01) with AAO increasing by 1.6 years (95% CI: 0.4 – 2.8) for every additional "T" allele.

Discussion

Sporadic PD is a complex multigenic trait, which may be a result of a combination of genetic variants with small effect sizes. Future therapeutic intervention strategies may be determined by the individual patient's genomic background. This genetic differentiation may also predict symptomatic motor and non-motor phenotype (e.g. AAO, presence of depression, autonomic dysfunction, dementia and response to treatment).

Previous studies have reported conflicting association results between the functional variant *DBH* -1021C>T and PD [8,9]. Our findings would suggest that *DBH* -1021C>T does not dramatically decrease the risk of disease although it may marginally affect symptomatic AAO. However, whether AAO is relevant to the majority of patients is still debatable. The vast majority of patients have an AAO that falls within the 55–75 years of age category, therefore to truly assess AAO as a disease trait requires a large series of patients aged <40 years and >80 years. Evidence from studies of familial and apparent monogenic forms of PD have also shown that AAO can greatly vary between affected family members with the same mutation.

The *DBH* gene is located on chromosome 9q34.2, a region which has not been previously implicated in PD, neither by linkage nor association, see www.PDgene.org [11]. A combined analysis (n=6984) of our results with the data of Healy et al. and Chun et al. do not support a role for *DBH* -1021C>T in susceptibility to PD. These studies however have only examined this one SNP in the *DBH* gene and therefore we can not rule out the possibility of other variants at this locus affecting susceptibility to PD. To date, identification and consistent association of risk factors in PD have been revealed through linkage studies of familial forms of autosomal dominantly inherited parkinsonism (*SNCA* and *LRRK2*). Therefore further pedigree-based linkage studies may be the best approach to identifying variants which affect susceptibility to sporadic PD and related neurodegenerative disorders.

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Table 1

PD patient-control series demographics

Series	PD patients	Controls
US	*n=224*	*n=224*
Age	73 ± 10 (38 – 90)	73 ± 10 (38 – 90)
Age at onset	62 ± 12 (26 – 82)	N/A
Familial PD (%)	155 (37)	N/A
Gender (Male)	115 (51%)	115 (51%)
Ireland	*n=174*	*n=174*
Age	61 ± 12 (33 – 90)	61 ± 12 (33 – 90)
Age at onset	49 ± 11 (18 – 77)	N/A
Familial PD (%)	28 (16)	N/A
Gender (Male)	68 (39%)	68 (39%)
Norway	*n=538*	*n=1138*
Age	72 ± 11 (30 – 99)	73 ± 11 (43 – 106)
Age at onset	59 ± 11 (25 – 88)	N/A
Familial PD (%)	120 (23)	N/A
Gender (Male)	325 (60%)	538 (47%)
Poland	*n=101*	*n=123*
Age	75 ± 7 (56 – 86)	70 ± 11 (34 – 89)
Age at onset	64 ± 7 (38 – 76)	N/A
Familial PD (%)	13 (13)	N/A
Gender (Male)	40 (40%)	48 (39%)

- The sample mean ± standard deviation (minimum, maximum) is given for *age* and *age at onset*. Total sample sizes given for each series do not account for genotyping failure, which occurred in <2% of samples.

Table 2

Allele and genotype frequencies of *DBH* -1021C>T (rs1611115)

Series	Affection status	Samples No.	Genotype CC No. (%)	Genotype CT No. (%)	Genotype TT No. (%)	C allele No. (%)	T allele No. (%)	Odds ratio (95% CI)	p-value
US	Patient	224	128 (60)	71 (33)	15 (7)	327 (76)	101 (24)	0.94 (0.69–1.28)	0.70
	Control	224	125 (57)	85 (38)	11 (5)	335 (76)	107 (24)		
Ireland	Patient	74	116 (67)	49 (28)	8 (5)	281 (81)	65 (19)	0.84 (0.59–1.19)	0.33
	Control	174	107 (62)	55 (32)	10 (6)	269 (78)	75 (22)		
Norway	Patient	538	368 (69)	150 (28)	13 (2)	886 (83)	176 (17)	0.81 (0.67–0.98)	0.03
	Control	1138	731 (65)	344 (31)	48 (4)	1806 (80)	440 (20)		
Poland	Patient	101	56 (55)	37 (37)	8 (8)	149 (74)	53 (26)	2.01 (1.24–3.25)	0.01
	Control	123	85 (69)	35 (28)	3 (2)	205 (83)	41 (17)		
Combined	Patient	1037	668 (66)	307 (30)	44 (4)	1643 (81)	395 (19)	0.91 (0.79–1.04)	0.16
	Control	1659	1048 (64)	519 (32)	72 (4)	2615 (80)	663 (20)		

- For the matched US and Irish series, estimated odds ratios and p-values result from single variable conditional logistic regression models. For the Norwegian, Polish, and combined series, estimated odds ratios and p-values result from logistic regression models adjusted for age, sex, and series (combined series only). Under an additive model odds ratios correspond an increase of one “T” allele. Total sample sizes given for each series do not account for genotyping failure, which occurred in <2% of samples.

Table 3

Combined meta-analysis of the present study and the studies of Healy[9] and Chun et al[8]

Genotype	Patients, No. (%)	Controls, No. (%)	Estimated OR	95% CI	p-value
C/C	1,946 (63%)	2,464 (63%)	Reference		
C/T	996 (32%)	1,264 (32%)	0.97	0.88 – 1.08	0.60
T/T	130 (4%)	184 (5%)	0.86	0.68 – 1.09	0.22

- P-values result from a logistic regression model adjusted for series (Chun, Healy, Irish, US, Norwegian, Polish). In an additive model, for every additional “T” allele the estimated odds of PD increase multiplicatively by 0.95 (95% CI: 0.88 – 1.04, p=0.26)