Short communication

Association of Parkinson disease age of onset with *DRD2*, *DRD3* and *GRIN2B* polymorphisms

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ABSTRACT

Introduction: Dopamine and glutamate are crucial neurotransmitters in Parkinson disease (PD). While recent large meta-analyses reported that genetic variation of dopamine (DRD2, DRD3) and glutamine (NMDA, GRIN2B) neurotransmitter receptors was not associated with PD risk, they could conceivably influence PD phenotype. We studied the association of these receptor polymorphisms relating to PD age of onset.
Methods: There were 664 PD patients and 718 controls, all Caucasian, with stored DNA at Mayo Clinic, Jacksonville, Florida. Genotyping was performed for *DRD2* (*Taq 1A,* rs1800497), *DRD3* (rs6280), and NMDA (*GRIN2B,* rs7301328) polymorphisms with ABI Taqman assays. Single nucleotide polymorphism associations with age of onset were evaluated using dominant, recessive, and additive genotypic models.
Results: *DRD3* variant carriers had an approximate 4.4-year decrease in mean age of onset when both copies of the minor allele were present ($P = 0.0034$) and an approximate 1.5-year decrease in mean age at onset for every additional minor allele ($P = 0.023$) (recessive and additive models, respectively). There was no association with age of onset for *DRD2* or *GRIN2B* under any statistical model (all $P \geq 0.22$).
Conclusions: The *DRD3* (rs6280) polymorphism, but not *DRD2* (Taq1A) or *GRIN2B*, influences younger PD age of onset in the US Caucasian population. Validation of these findings in larger studies with other ethnic groups is indicated.

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1. Background

The cardinal motor signs of Parkinson disease (PD) emerge following the loss of a critical mass of dopaminergic neurons within the substantia nigra. The neurotransmitters dopamine and glutamate play a central role in basal ganglia circuitry, and dopamine also modulates glutamatergic influences on the basal ganglia [1,2]. Therefore, inherent genetic variation in dopaminergic or glutamatergic neurotransmission might conceivably influence either the risk of developing PD or its phenotype.

The association of PD risk with dopamine receptor (*DRD2*, *DRD3*) and glutamate-N-methyl-D-aspartate (NMDA) receptor polymorphisms has already been examined extensively over the past couple of decades. Several case-control studies have reported variable associations of *DRD2* polymorphisms with PD risk [3–8]. Certain *DRD3* polymorphisms have been associated with PD risk (e.g. rs2134655) [8], while others (e.g. rs6280) [4,5] and the NMDA *GRIN2B* receptor polymorphisms were not apparently associated with PD risk [6]. Recently, two very large meta-analysis studies found no association with genetic variation in *DRD2*, *DRD3*, or NMDA *GRIN2B* relating to PD risk [9,10].

However the genetic influence of these dopamine and NMDA receptor polymorphisms on PD phenotype is less well studied. It is

logical that phenotypic variability in PD is likely influenced by genetic variability. One such phenotype is the age of onset of PD.

The primary aim of this study was to investigate the association of dopamine (*DRD2*, *DRD3*) and glutamate NMDA (*GRIN2B*) receptor polymorphisms in relation to PD age of onset in a Caucasian population.

2. Methods

The subjects included 664 PD patients evaluated by Mayo Clinic neurologists and 718 normal controls with stored DNA in the Mayo Clinic PD bank in Jacksonville, FL. All subjects provided written consent and the study was approved by the IRB. All subjects were Caucasian. In PD patients, the mean age was 76 ± 11 SD years (Range: 38−101), the mean age at PD onset was 67 ± 12 SD years (Range: 32−94), and 421 patients (63%) were male. The mean age in the control group was 72 ± 13 SD years (Range: 23−96) and 298 subjects (42%) were male. Age at PD onset was defined as the age of the first PD diagnosis by a neurologist.

Genotype polymorphism analysis for *DRD2* (*Taq 1A*, rs1800497), *DRD3* (rs6280), and NMDA *GRIN2B* (rs7301328) was performed with ABI Taqman assays (Life Technologies, Grand Island, NY) on the Sequenom iPLEX® platform (Agena Bioscience, San Diego, CA). There was no evidence of a departure from Hardy−Weinberg equilibrium in controls (all chi-square $P > .05$), and pair-wise linkage disequilibrium between variants was very weak (all $r^2 \leq 0.0021$ in controls).

Single nucleotide polymorphism (SNP) associations with PD age of onset were examined using linear regression models adjusted for gender. Additive models (effect of each additional minor allele), dominant models (presence *vs.* absence of the minor allele), and recessive models (presence *vs.* absence of two copies of the minor allele) were utilized. Regression coefficients and 95% confidence intervals (CIs) were estimated and were interpreted as the increase in mean age at PD onset corresponding to each additional minor allele (additive models), presence of the minor allele (dominant models), or presence of two copies of the minor allele (recessive models).

Associations of each SNP with PD risk were evaluated using logistic regression models adjusted for age and gender. Additive, dominant, and recessive models were again utilized. Odds ratios (ORs) and 95% CIs were estimated. We adjusted for multiple testing using a single-step minP permutation correction separately for each outcome (9 tests for both PD risk and age of onset analysis), after which *P* values ≤ 0.0073 (age of onset analysis) and ≤0.0077 (PD risk analysis) were considered to be statistically significant. All statistical analyses were performed using R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Single-SNP associations with age at onset and PD risk are displayed in the Table 1. Age of onset of PD was significantly associated with the *DRD3* (rs6280) variant under a recessive model, with an approximate 4.4 year decrease in mean age of onset when both copies of the minor allele were present ($P = 0.0034$, Fig. 1). After correcting for multiple testing, the association between the *DRD3* (rs6280) variant under an additive model and age at PD onset was not significant ($P = 0.023$) and there was no notable association under a dominant model ($P = 0.22$). There was no evidence of an association with PD age of onset for *DRD2 (Taq1A)* and NMDA *GRIN2B* under any statistical model (all $P \geq 0.22$).

Additionally, we assessed the variants for association with PD risk (Table 1). We observed a significant association between the *DRD2* variant and risk of PD under an additive model (OR: 1.31, $P = 0.0065$). No other significant associations with PD risk were observed after multiple testing correction, though nominally significant associations were noted for the *DRD2* variant under an additive model ($P = 0.0096$) and the NDMA *GRIN2B* variant under a dominant model ($P = 0.048$) (Table 1). Allele and genotype frequencies for PD patients and controls are displayed for each variant in the Supplemental Table.

4. Discussion

We investigated dopamine and glutamate candidate gene variants for association with age of onset of PD. In this Caucasian population sample, the *DRD3* (rs6280) variant was associated with earlier PD age of onset (recessive model), and the *DRD2* and NMDA *GRIN2B* polymorphisms were not. Risk of PD was associated with the *DRD2* variant alone.

Table 1
Single-SNP associations with age at PD onset and risk of PD DRD2 (Taq 1A rs1800497), DRD3 (rs6280) and NMDA GRIN2B (rs7301328).

Association with age at PD onset									
SNP	MA	MAF	Additive model		Dominant model		Recessive model		
			Regression coefficient (95% CI)	P-value	Regression coefficient (95% CI)	P-value	Regression coefficient (95% CI)	P-value	
rs1800497	A	22.1%	0.25 (−1.27, 1.78)	0.75	0.07 (−1.78, 1.92)	0.94	1.47 (−2.61, 5.56)	0.48	
rs6280	C	32.7%	−1.59 (−2.96, −0.22)	0.023	−1.13 (−2.96, 0.70)	0.22	−4.42 (−7.38, −1.47)	0.0034	
rs7301328	C	40.1%	0.02 (−1.34, 1.38)	0.98	0.94 (−0.98, 2.86)	0.34	−1.63 (−4.22, 0.95)	0.22	
Association with risk of PD									
			Additive model		Dominant model		Recessive model		
			OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	
rs1800497	A	20.1%	1.31 (1.08, 1.59)	0.0065	1.36 (1.08, 1.71)	0.0096	1.54 (0.89, 2.67)	0.12	
rs6280	C	33.3%	0.97 (0.82, 1.15)	0.73	0.97 (0.77, 1.21)	0.76	0.96 (0.68, 1.37)	0.82	
rs7301328	C	39.1%	1.11 (0.95, 1.31)	0.20	1.26 (1.00, 1.59)	0.048	0.97 (0.71, 1.33)	0.86	

SNP = single nucleotide polymorphism. MA = minor allele. MAF = minor allele frequency. OR = odds ratio. PD = Parkinson Disease. CI = confidence interval. MAFs in PD patients are given for associations with age at PD onset, while MAFs in the overall sample are given for associations with risk of PD. Single-SNP associations with age at PD onset were evaluated using linear regression models adjusted for gender. Regression coefficients and 95% CIs are interpreted as the increase in mean age at PD onset corresponding to each additional minor allele (additive models), presence of the minor allele (dominant models), or presence of two copies of the minor allele (recessive models). Single-SNP associations with risk of PD were evaluated using logistic regression models adjusted for age and gender. ORs correspond to each additional minor allele (additive models), presence of the minor allele (dominant models), or presence of two copies of the minor allele (recessive models). After applying a single-step minP permutation adjustment for multiple testing, P values ≤ 0.0073 (associations with age at PD onset) and ≤0.0077 (associations with risk of PD) were considered as statistically significant.