Published in final edited form as:
Neurosci Lett. 2009 September 18; 461(2): 74–75. doi:10.1016/j.neulet.2009.05.084.

DRD3 Ser9Gly and *HS1BP3* Ala265Gly are not associated with Parkinson Disease

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Abstract

Variants in the *dopamine receptor D3* (*DRD3*) and *HCLS1 binding protein 3* (*HS1BP3*) have been nominated as risk factors for Essential Tremor (ET). Although ET and Parkinson disease (PD) are considered different entities, they have many overlapping clinical and pathological features. We aim to evaluate the role of the Ser9Gly variant in *DRD3* and Ala265Gly in *HS1BP3* in PD development. To this end, we genotyped these two variants in a PD matched case-control series from the United States. Statistical analysis failed to identify significant differences in the frequency of these variants between the case and control groups, therefore our results do not support a role for these *DRD3* and *HS1BP3* variants in PD.

Keywords

Essential tremor; Parkinson disease; DRD3; HS1BP3

Introduction

Essential tremor (ET) is a progressive neurological disorder characterized by postural tremor exacerbated by movement [5,11,12]. ET is the most common tremor disorder with a prevalence of approximately 4% among individuals aged 40 years or older [1]. While there is currently no cohesive hypothesis regarding the pathogenesis of ET [11,12], there is an emerging school of thought that ET might represent a family of complex diseases characterized by a common kinetic tremor rather than a single condition [1,12]. A serine to glycine substitution in dopamine receptor D3 (*DRD3* - rs6280) and an alanine to glycine substitution in HCLS1 binding protein 3 (*HS1BP3* - rs11680700) have been nominated as potential factors conferring increased risk of developing ET [8,9]. However several subsequent studies have failed to replicate the results implicating these variants in *DRD3* and *HS1BP3* in ET pathogenesis [3,6,16,18]. These two genes have been functionally implicated in Parkinson disease (PD); studies of DRD3 agonists in PD rat models have shown a reduction in disease progression [20], and the specific serine to glycine mutation found associated with ET has been shown to affect the therapeutic efficacy

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of pramipexole in PD patients [10]. HS1BP3 proteins are highly expressed in motor neurons and Purkinje cells and appear to be involved in the protein kinase activation of tyrosine hydroxylase, which catalyzes the rate limiting step in dopamine synthesis [8].

Although ET and PD are considered distinct entities, they present overlapping clinical and pathological features [15]. The strongest evidence for a common genetic component in both diseases is provided by the four-fold increased risk of both incident and drug induced PD in patients with ET, increased prevalence of ET in relatives of PD patients and the presence of action tremor preceding the onset of PD symptoms indicating ET as an early manifestation of PD [2,15]. Given the potential functional role of DRD3 and HS1BP3 in PD, and the complex relationship between ET and PD, we set out to evaluate the role of the two risk variants DRD3 Ser9Gly and HS1BP3 Gly265Ala in a case-control series of PD patients from the United States.

Methods

We included 448 PD patients (mean age 72.2 ± 10.9 years; age at onset 61.8 ± 12.5 years; range 5-85 years) and 428 unrelated controls without evidence of ET or PD, matched for gender, age, and ethnicity. The PD series had a 1:1.2 female to male ratio and was comprised of both familial, of which 11.8% also had family history of ET, and sporadic cases. Control subjects were collected at the Mayo Clinic Florida outpatient clinic and consist of spouses and unrelated individuals. All patients were longitudinally assessed by a movement disorders neurologist and diagnosed with PD in accordance with published criteria [19]. The involved ethical review board approved the study and all participants supplied informed consent. Genomic DNA was purified from whole blood and genotyped on an ABI7900 using TaqMan probes and analyzed using SDS 2.2 software. Genotypic associations between PD and each SNP were examined by chi-square test.

Results

The genotype frequencies and statistical analysis for the ET susceptibility variants located in *DRD3* and *HS1BP3* are given in Table 1. Both SNPs are in Hardy-Weinberg equilibrium ($p > 0.05$) and the minor allele frequencies (MAF) in the control group are similar to those reported previously [3,8-10,18]. Statistical analysis did not identify a difference in the frequency of *DRD3* rs6280 ($p=0.229$) or *HS1BP3* rs11680700 ($p=0.301$) between PD cases and the controls.

Discussion

We assessed the role in PD of two missense variants (rs6280 and rs11680700) located in *DRD3* and *HS1BP3* in a case-control series from the US. The analysis did not reveal statistical differences in the frequency of these polymorphisms between PD cases and controls ($p > 0.05$). *HS1BP3* Ala265Gly variant had been previously reported in small studies consisting of PD patients and controls from North America [6,7]. The data herein reported for *HS1BP3* is consistent with this previous report, and refute a role for the Ala265Gly variant in PD. This is the first association study reporting the frequency of *DRD3* Ser9Gly variant in PD cases and controls. In summary, our results suggest that the Ser9Gly variant in *DRD3* and the Ala265Gly in *HS1BP3* are unlikely to contribute to PD susceptibility in the US population.

Despite the similarities observed between PD and ET patients, a genetic link still remains to be found. Few studies have failed to identify the presence of PD pathogenic mutations in the *LRRK2* gene in ET patients [4,17,21]. Similarly, a small study did not find a significant association between *SNCA* haplotypes in an Italian ET case-control series [14]. Further studies are necessary to evaluate the role of PD genes in ET, with particular interest in *SNCA* found to be associated in most PD case-control series [13].

Acknowledgements

The authors wish to thank the patients and families who participated in the study. This work was supported by the Morris K. Udall Center, National Institute of Neurological Disorders and Stroke P50 NS40256 and The Mayo Clinic Florida Research Committee, Essential Tremor: Clinical and Molecular Genetic Studies (CR program). ZKW is also partially funded by P01 AG017216, R01 NS057567, R01 AG015866, CIHR 121849, and PARF C06-01.

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Table 1

Genotype frequencies and statistical analysis for *DRD3* rs6280 and *HS1BP3* rs11680700 patient and control.

Gene	SNP ID	Genotype	Controls		PD		MAF	Chi-square	P-value
			No.	%	No.	%			
DRD3	rs6280	CC	196	48.0	178	43.8	0.34	1.45	0.229
		CT	164	40.2	177	43.6			
		TT	48	11.8	51	12.6			
HS1BP3	rs11680700	CC	342	86.8	376	89.1	0.06	1.07	0.301
		CG	48	12.2	43	10.2			
		GG	4	1.0	3	0.7			

MAF, minor allele frequency.

Neurosci Lett. Author manuscript; available in PMC 2010 September 18.