Original Article

HOMER1 Polymorphism and Parkinson's Disease–Psychosis: Is there an Association?

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Abstract

Objective: Homer1, a postsynaptic protein coded by the *HOMER1* gene, presumably has a role in homeostatic plasticity that dampens neuronal responsiveness when the input activity is too high. *HOMER1* polymorphism has been studied in major psychiatric disorders such as schizophrenia. The objective of this study is to investigate if polymorphisms of the *HOMER1* gene are associated with psychosis in Parkinson's disease (PD-P). **Methods:** One hundred patients with Parkinson's disease (PD) and 100 healthy controls were enrolled consecutively in a PD-P biomarker study at the National Institute of Mental Health and Neurosciences, Bangalore, India. Of the 100 PD patients, 50 had psychosis (PD-P) and 50 did not have psychosis (PD-NP). Two single-nucleotide polymorphisms of *HOMER1* (rs4704559 and rs4704560) were analyzed from the DNA isolated from peripheral blood. The allele and genotype frequencies in the PD-P and PD-NP groups were compared. **Results:** Analysis of *HOMER1* rs4704560 revealed a significant difference in both genotype and allele levels between PD-P and PD-NP groups. There was an overrepresentation of T-allele (42% vs. 16%; $P < 0.001$) and TT genotype (24% vs. 6%; $P < 0.001$) in the PD-P group compared to PD-NP group. There was no significant difference between PD-P and PD-NP groups when various genotypes and allele frequencies related to HOMER1 rs4704559 were compared. **Conclusion:** PD-P is probably associated with overrepresentation of T-allele of *HOMER1* rs4704560, and larger studies are warranted to confirm our results.

Keywords: Glutamate, hallucinations, HOMER, Parkinson's disease, psychosis

Introduction

Psychosis is a debilitating nonmotor symptom (NMS) of Parkinson's disease (PD), which affects a substantial majority of patients during the course of the disease.[1] Psychosis in PD (PD-P) usually manifests with complex visual hallucinations and/or minor hallucinations such as illusions and false sense of presence/passage.[2,3] PD-P has several negative repercussions, that is, increased caregiver distress, risk of dementia, nursing home placement, health-care expenditure, and mortality.[4,5] Therefore, it is crucial to identify the factors that are potentially associated with the emergence of PD-P. Several studies have reported old age, cognitive impairment, presence of rapid eye movement sleep behavior disorder, and depression as some of the factors associated with PD-P; however, the precise etiology and pathogenesis remain elusive.[6-9]

Several studies have explored the genetic correlates of PD-P, largely through polymorphism analyses.[10] Among the genes studied for polymorphism in PD-P are the genes for dopamine receptors (*DRD*), dopamine transporter *(DAT),* cholecystokinin *(CCK)*, apolipoprotein-E (*ApoE*), microtubule-associated protein tau (*MAPT*), 5-hydroxytryptamine receptor (*HTR*), angiotensin converting enzyme (A*CE)*, catechol-o-methyl transferase (C*OMT)*, ankyrin repeat and kinase domain containing 1 (*ANKK1*), and Homer (*HOMER*).[10,11] These studies are limited in number and have not yielded consistent results.

HOMER1, located in chromosome 5, codes for a postsynaptic density protein at the excitatory synapses. The major functions of this protein are synaptic plasticity and glutamate signal transduction.[12] It presumably has a role in homeostatic plasticity that dampens neuronal responsiveness when the input activity is too high. Two groups investigated *HOMER1* polymorphisms in two different populations (Brazilian and Italian) and reported significant association of the rs4704559 and rs4704560 single-nucleotide polymorphisms (SNPs) with PD-P.[13,14] *HOMER1* polymorphisms have also been investigated in major psychiatric disorders such as schizophrenia.[15] Considering population-related genetic variations and the impact of ethnicity on NMS of PD,[16] it is important to explore these polymorphisms in the context of PD-P among different ethnicities. We, therefore, aimed to

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investigate *HOMER1* polymorphisms in a cohort of Indian PD-P patients.

Methods

One hundred patients with PD and 100 healthy controls were enrolled consecutively in a PD-P biomarker study at the National Institute of Mental Health and Neurosciences, Bangalore, India. This prospective study was approved by the local Institutional Ethics Committee and informed consent was taken. Of the 100 PD patients, 50 had psychosis (PD-P) and 50 did not have psychosis (PD-NP). The diagnosis of PD was done as per the United Kingdom PD Society Brain Bank Diagnostic Criteria.[17] PD-P was diagnosed as per the criteria proposed by the National Institute of Neurological Disorders and Stroke and the National Institutes of Mental Health.[18] Severity of the motor symptoms was assessed by part III of the unified Parkinson's disease rating scale, and stage of PD was assessed by Hoehn and Yahr scale. Anxiety and depression were screened by Hamilton rating scale for anxiety (HAM-A) and Hamilton rating scale for depression, respectively.[19,20]

Polymorphism analysis

Genomic DNA was isolated from 3 to 5 ml of blood using the phenol–chloroform method described previously.[21] The *HOMER1* polymorphisms (rs4704559 and rs4704560) were determined by the TaqMan allelic discrimination assay using predesigned probes (assay IDs: C_27886733_10 and C_432432_20, respectively). The Applied Biosystems® 7500 fast real-time polymerase chain reaction machine was used for amplification with the following polymerase chain reaction conditions: 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min.

Results

Demographic and clinical characteristics

The mean age at the onset of motor symptoms was comparable between the two PD groups (PD-NP: 50.9 ± 9.8 years, PD-P: 51.5 ± 7.5 years). As shown in Table 1, the two PD groups were compared for several clinical characteristics. Significant difference was observed in the following: (1) anxiety measured by HAM-A (PD-NP: 6.3 ± 4.1 vs. PD-P: 8.7 ± 5.4; $P = 0.01$) and (2) total levodopa equivalent dose per day (PD-NP: 565.4 ± 203.6 vs. PD-P: 689.9 ± 319.7; $P < 0.02$).

Details regarding the types of hallucinations and delusions experienced by the PD-P group patients are presented in Table 2.

HOMER1 polymorphism

Genotypes and alleles of two SNPs belonging to *HOMER1* (rs4704559, rs4704560) were analyzed. Both these alleles followed the Hardy–Weinberg equilibrium principle.[22] There was no significant difference in any of the genotypes of rs4704559 between controls and the overall patient group. Similar to the results obtained on comparing controls and the overall PD group, there was no significant difference between PD-P and PD-NP either at the genotype level or at the allele level [A in Table 3].

There was no significant difference in distribution of any of the genotypes of rs4704560 (CC, CT, TT) or alleles (C or T) between controls and the overall PD cohort. However, a significant difference in the genotype level as well as in the allele level was found when PD-P and PD-NP were compared. There was overrepresentation of T-allele in the PD-P group (odds ratio: 2.62) [B in Table 3].

Discussion

Two principal results were obtained in this study: (1) there was no significant difference in the distribution of genotypes and alleles related to rs4704559 and (2) there was a significant difference in the proportion of CC/CT/TT genotype and C/T alleles of rs4704560 in PD-P patients compared to PD-NP patients.

HOMER1 (on chromosome 5) codes for a postsynaptic neuronal protein known as Homer1. This protein is widely distributed in the central nervous system and other peripheral tissues. It constitutes a major part of the postsynaptic densities and has binding sites in glutamate receptors. Homer is considered to be

Table 1: Summary of key demographic and clinical characteristics

Parameters	HC (n=100)	PD-NP (n=50)	PD-P (n=50)	Significance
Gender (F:M)	23:77	8:42	10:40	NS
Mean age (in years)	57.0±5.4	57.8±6.9	58.3±8.1	NS
AAO (in years)	-	50.9±9.8	51.5±7.5	NS
Duration of PD (in years)	-	5.8±2.4	5.8±2.4	NS
UPDRS-III (off)	-	34.6±8.2	36.0±8.4	NS
H&Y stage	-	2.3±0.3	2.4±0.2	NS
HAM-A score	-	6.3±4.1	8.7±5.4	$P = 0.01$
HAM-D score	-	6.9±4.8	8.6±5.4	NS
LEDD	-	565.4±203.6	689.9±319.7	$P = 0.02$

AAO = Age at onset, F = Female, HAM-A = Hamilton rating scale for anxiety, HAM-D = Hamilton rating scale for depression, H&Y = Hoehn and Yahr stage, HC = Healthy controls, LEDD = Levodopa equivalent dose/day, M = Male, NS = Not significant, PD=Parkinson's disease, PD-NP = PD patients with no psychosis, PD-P = PD patients with psychosis, UPDRS-III = Part III of the unified Parkinson disease rating scale. Continuous variables are represented as mean ± SD

Table 2: Summary of the pattern of psychotic symptoms documented in Parkinson's disease patients with psychosis

Type of psychotic symptom	Number of patients ($n=50$)
Minor hallucinations	26
Formed visual hallucinations	10
Minor hallucinations + Visual hallucinations	4
Visual hallucinations + delusion of persecution	2
Visual hallucinations + auditory hallucinations	1
Auditory hallucinations + delusion of persecution	2
Auditory hallucinations + delusion of infidelity	1
Auditory hallucinations + minor hallucinations	1
Isolated auditory hallucinations	1
Minor hallucinations + tactile hallucinations + Olfactory hallucinations	1
Isolated delusion	1

Table 3: Comparison of genotype and allele distribution HOMER1 single nucleotide polymorphisms (rs4704559 and rs4704560) between Parkinson's disease patients with and without psychosis

A: Comparison of HOMER1 rs4704559

Genotype distribution

	AA	AG	GG	Significance
PD-P (n = 50)	40 (80%)	10 (20%)	0 (0%)	P = 0.33
PD-NP (n = 50)	38 (76%)	11 (22%)	1 (2%)	

Allele distribution

	A-allele	G-allele	Significance
PD-P (n = 50)	90 (90%)	10 (10%)	P = 0.65
PD-NP (n = 50)	87 (87%)	13 (13%)	

B. Comparison of HOMER1 rs4704560

Genotype distribution

	CC	CT	TT	Significance
PD-P (n = 50)	20 (40%)	18 (36%)	12 (24%)	P < 0.001
PD-NP (n = 50)	37 (74%)	10 (20%)	3 (6%)	

Allele distribution

	C-allele	T-allele	Significance
PD-P (n = 50)	58 (58%)	42 (42%)	P < 0.001
PD-NP (n = 50)	84 (84%)	16 (16%)	

PD = Parkinson's disease, PD-NP = PD patients with no psychosis, PD-P = PD patients with psychosis

a part of a mechanism of homeostatic plasticity that dampens neuronal responsiveness when the input activity is too high. As mentioned above, two polymorphisms of *HOMER1* have been studied (rs4704559 and rs4704560) in PD-P patients and PD patients with other NMS.[10] In a study involving Italian patients with PD, De Luca *et al*.[13] reported that the A-allele of the rs4704559 marker increases the susceptibility to psychotic symptoms in PD. However, in the current study, there was no difference between PD-P and PD-NP, either at the genotype level or at the allele level. The overall PD cohort also did not differ from the controls. Interestingly, another study on a cohort of Brazilian patients with PD has reported that the G-allele of rs4704559 has a protective role for the drug-related side effects such as psychosis.[14] The inconsistencies across studies may be attributed to the different ethnicities of the study group subjects. Hence, further studies are required to confirm the role of rs4704559 polymorphism in the pathogenesis of PD-P.

However, comparison of the genotype distribution and allele frequency of the marker rs4704560 revealed a significant difference in the T-allele frequency between the groups. The PD-P group had a higher frequency of T-allele compared to the PD-NP group ($P < 0.001$, odds ratio: 2.62). Although previous studies did not find any association of this polymorphism with PD-P, positive result obtained in our study certainly raises the possibility that the T-allele is a risk factor for psychosis in Indian PD patients. This result reinforces the fact that alterations in glutamate transmission may have a certain role in the pathogenesis of PD-P. It has been speculated that Homer is a part of a mechanism of homeostatic plasticity that dampens neuronal responsiveness when the input activity is too high.[23,24] Homer1 Konckout (KO) mice show impaired prepulse inhibition, that is, a deficit in filtering irrelevant sensory information, which could contribute to the genesis of hallucinations.[25] In other words, in the context of genesis of hallucinations, Homer1 perhaps plays a critical role in reducing the noise-to-signal ratio. In addition, animal models of PD have documented overexpression of *Homer1* after administration of dopaminergic medications.[26-28] As long-term dopaminergic medications have been regarded as a risk factor for the emergence of psychotic symptoms in PD, it is possible that the rs4704560 polymorphism is perhaps associated with altered expression of Homer1, which results in decreased dampening of neuronal responsiveness. Considering the fact that there is emerging evidence in favor of the glutamate hypothesis of pathogenesis of schizophrenia,[29] it is possible that faulty glutamate signaling, along similar lines, also contributes toward genesis of psychotic symptoms in PD. In schizophrenia, rs4704560 polymorphism has been reported to have associations with several positive and negative symptoms, as well as with the therapeutic response to antipsychotics.[15] It has been hypothesized that Homer1 protein interacts with other postsynaptic density proteins and glutamatergic receptor genes to modulate dopamine–glutamate signaling, thus contributing to the pathogenesis of psychotic symptoms.[30] The exact mechanism by which T-allele of the marker rs4704560 increases the susceptibility to psychotic symptoms in PD remains unclear. Future gene expression studies may provide better insights into the genetic correlates of PD-P. The reason why we did not see a significant difference in the allele or genotype distribution of rs4704560 between controls and overall PD patients is unclear. We speculate that although we see an association between T-allele and psychosis, it may not be the only factor in the pathogenesis, and other genes might be interacting in the process. Therefore, even though there is no difference between controls and overall PD patients in terms of T-allele distribution, the latter are more prone to have psychosis. Future

studies should consider comparing *HOMER1* rs4704560 in PD-P patients and patients with primary psychiatric diseases, especially schizophrenia.

While the current study provides valuable insights regarding the potential role of *HOMER1* polymorphism in PD-P, there are several limitations that need to be considered. A multitude of studies have suggested that pathogenesis of PD-P is multifactorial as it involves structural and functional abnormalities in a variety of brain networks. Hence, *HOMER1* polymorphism, alone, may not be responsible for the hallucinogenesis; rather, a combination of several factors may be playing a role. Future investigations utilizing model-based analyses that consider a range of risk factors for psychosis in conjunction with genetic polymorphisms are poised to offer valuable insights. As an exploratory study, the sample size of the study was low, which may limit generalizability of the results and importantly, as most of the study subjects were South Indians, our population is not representative of the entire Indian population.

Conclusion

HOMER1 polymorphism (rs4704560) has an association with PD-P. Precisely, the presence of T-allele of rs4704560 increases the odds of psychosis in our cohort of PD patients. Additional studies with larger sample size and involvement of different ethnic groups are warranted to obtain detailed insight into the role of *HOMER1* polymorphism by using T-allele as a biomarker.

Author contributions

1) Research project: A. conception, B. organization, C. execution.
2) Statistical analysis: A. design, B. execution, C. review and critique.
3) Manuscript: A. writing of the first draft, B. review and critique.

AL: 1A, 1B, 1C, 2A, 2B, 3A.

PS: 1C, 2A, 2B, 3A.

RC: 1A, 1B, 2A, 2C, 3B.

SSA: 1A, 1B, 2C, 3B.

SH: 1A, 1B, 2C, 3B.

RY: 1A, 1B, 2C, 3B.

PKP: 1A, 1B, 2C, 3B.

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Conflicts of interest

There are no conflicts of interest.

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