Association between NMD3 and symptoms of Parkinson's disease in Chinese

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Research article

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Abstract

Background: Parkinson's disease (PD) is a progressive neurodegenerative movement disorder which is characterized by motor symptoms such as tremor, rigidity, slowness of movement and problems with gait. Large-scale meta-analyses of genome-wide association studies (GWAS) have identified few susceptibility loci in sporadic PD. The aim of this study was to investigate the association between NMD3 single nucleotide polymorphism (SNP) and symptoms of PD patients in southern Chinese.

Methods: A total of 217 PD patients were recruited in this study and were genotyped by using SNaPshot technique and the polymer chain reaction. All subjects were evaluated by Mini-Mental State Examination (MMSE), Beijing version Montreal Cognitive Assessment (MoCA), Sniffin' Sticks 16 (SS-16), Hamilton anxiety rating scale, Hamilton depression rating scale, 39-item Parkinson's disease Questionnaire (PDQ-39) and MDS Unified PD Rating Scale (MDS-UPDRS).

Results: NMD3 rs34016896 (T) carriers have worse cognitive function (MMSE: p 0.042, NMD3 wildtype: 27.44 ± 2.89, NMD3 carriers: 26.31 ± 3.79; MoCA: p 0.005, NMD3 wildtype: 23.15 ± 4.20, NMD3 carriers: 20.75 ± 6.68).

Conclusions: The recessive and overdominant model of NMD3 rs34016896 was associated with cognitive impairment in PD patients.

Background

Parkinson's disease (PD) is one of the most common neurodegenerative diseases which affects approximately 1.7% of people over the age of 65, and the annual incidence ranged from 1.5 to 8.7/100,000 in the People's Republic of China[1]. The pathological features of PD are the abnormal aggregation of α-synuclein and the loss of dopaminergic neurons in substantia nigra[2]. Both acquired and inherited risk factors have been implicated in death of dopaminergic neurons[3]. Genetic factors play a crucial role in the pathogenesis of sporadic PD. Genome-wide association studies (GWAS) have identified several susceptibility loci for PD[4–6]. Genes like LRRK2, SNC A etc. were associated with the pathogenesis of PD[7,8]. Marie Y. Davis reported that GBA variants predicted a more rapid progression of cognitive dysfunction and motor symptoms in patients with PD[9].

Recently, variants at NMD3 were found related to substantia nigra neuronal loss and PD susceptibility[10,11]. The minor allele frequency of NMD3 rs34016896 was 0.41 in Chinese PD population, and 0.45 in Chinese healthy population[11]. NMD3 encodes ribosome-binding protein. Nmd3 is a structural mimic of eIF5A, and activates the cpGTPase Lsg1 during 60S ribosome biogenesis[12]. The association of NMD3 rs34016896 with clinical pathological phenotypes has been discovered. JM Shulman and colleagues found that NMD3 rs34016896 was related to the severity of nigral neuronal loss and not with Lewy bodies[13]. However, the function of NMD3 to PD is unknown. Besides, it is obliged to investigate the association between NMD3 and clinical symptoms of PD, which could indicate the pathogenesis of PD.
In this study, we try to discover the clinical hallmarks of \textit{NMD3} rs34016896 (C>T) in southern Chinese PD patients.

**Methods**

- **Study Population**

PD was collected from outpatients clinic of Ren Ji Hospital (South Campus) and diagnosed by movement disorder specialists based on diagnostic criteria brought up by movement disorders society (MDS)\cite{14}. As for PD patients, Hoehn-Yahr staging and their disease duration were recorded. Family history of PD was also recorded. Parkinsonism with secondary causes, such as inflammatory, drug-induced, vascular and toxin-induced parkinsonism, were excluded. Parkinsonism with other neurodegenerative diseases, such as Wilson's disease, progressive supranuclear palsy, cerebral-basal degeneration and multiple system atrophy was also excluded. This study was approved by the ethic committee of Ren Ji Hospital. All participants signed consent forms.

- **Evaluation**

Each PD patient included in this study received evaluation including the following rating scales: Unified PD Rating Scale provided by movement disorders society (MDS-UPDRS) was used to assess the status of PD\cite{15}. Mini-Mental State Examination (MMSE) and Beijing version Montreal Cognitive Assessment (MoCA) were adopted to assess cognitive function. SS−16 was used to assess olfactory function\cite{16}. Hamilton anxiety rating scale and Hamilton depression rating scale were used to assess anxiety and depression. Non-motor symptoms scale (NMSS) was used to assess non-motor symptoms. Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) was used to assess autonomic symptoms. The 39-item Parkinson's disease Questionnaire (PDQ−39) was taken as to assess life quality of PD. Researchers were received strict training of these scales before assessing PD patients. We also documented the presence (yes/no) of the following symptoms which assessed by two individual neurologists: hallucination, apathy, excessive daytime sleepiness, pain, frequent urination, constipation, postural hypotension, sialorrhea, restless legs syndrome (RLS), delusion, double vision, decreased attention, decreased recent memory, nycturia, sexual dysfunction, hypogeusia, change of weight, daytime sweatiness, nocturnal sweatiness, urgent urination or urinary incontinence, sensitive to light, sensitive to cold, sensitive to hot, anxiety, depression, probable rapid eye movement sleep behavior disorder (RBD). Probable RBD was diagnosed via RBD screening questionnaire\cite{17}. The method of detecting \textit{NMD3} rs34016896 was followed Li and colleagues\cite{18}.

- **Statistics**

R (version 3.5.1), stats package (version 3.5.1) and CATT (version 2.0) was used to perform statistical analysis. Student t test was performed to calculate the difference of numeric variables between \textit{NMD3}
carriers and wildtypes. As for comparing categorical variables, Chi square test was performed. Cochran-Armitage test was used to assess ordinary variables between NMD3 carriers and wildtypes, and additive model of NMD3. Logistic regression was used to assess the association between additive model/dominant model/recessive model/overdominant model of NMD3 and clinical phenotypes. Odds ratio (OR) and its 95% confidence intervals (CI) were also used. We also adjusted age, gender and Hoehn-Yahr staging results.

Results

There were 217 PD patients included in this study. SNPs of two PD patients failed to be detected. In all, there were 39 NMD3 wildtypes and 178 NMD3 carriers in our study. The minor allele frequency in our group was 0.41 which is similar to previous genetic association study in southern eastern China\cite{11}. There was no difference of age, gender, disease duration, family history, and Hoehn-Yahr staging in two groups. In NMD3 wildtype group, the age was 55.69 ± 10.24 years (mean ± SD) and there were 17 (43.59%) female were included in this study. In NMD3 carrier group, the average of age was 57.03 ± 10.16 years (mean ± SD) and there were 73 (41.01%) female were included. There was no difference of total scores of NMSS, SCOPA-AUT, PDQ–39 between two groups. Cognitive function assessed by MMSE and MoCA of NMD3 wildtypes was better than NMD3 carriers (MMSE: p 0.042, NMD3 wildtype: 27.44 ± 2.89, NMD3 carriers: 26.31 ± 3.79; MoCA: p 0.005, NMD3 wildtype: 23.15 ± 4.20, NMD3 carriers: 20.75 ± 6.68). (Table 1)

The presence of hallucination, postural hypotension, delusion were associated with the additive model (hallucination: p 0.025; postural hypotension: p 0.007, delusion: p 0.038). Besides, trends of the presence of apathy, decreased recent memory and change of weight were found under the additive model (apathy: p 0.092; decreased recent memory: p 0.064; change of weight: p 0.073). (Table 2)

Under the dominant model, the presence of postural hypotension were found (p 0.052, OR: 2.38, 1.05–6.16, before adjustment; p 0.050, OR: 2.43, 1.05–6.38, after adjustment). (Table 2)

Under the recessive model, the presence of hallucination, apathy, postural hypotension and delusion were found (Hallucination: p 0.012, OR: 2.96, 1.29–7.10, before adjustment; p 0.014, OR: 2.95, 1.26–7.21, after adjustment. Apathy: p 0.011, OR: 2.06, 1.18–3.61, before adjustment; p 0.012, OR: 2.07, 2.28–3.67, after adjustment. Postural hypotension: p 0.017, OR: 2.04, 1.14–3.68, before adjustment; p 0.016, OR: 2.08, 1.15–3.82, after adjustment. Delusion: p 0.014, OR: 3.94, 1.38–12.92, before adjustment; p 0.012, OR: 4.41, 1.46–15.47, after adjustment.). Trends of decreased attention, decreased recent memory, hypogeusia and change of weight were associated with the recessive model (decreased attention: p 0.068, OR: 1.76, 0.58–3.02, before adjustment; p 0.075, OR: 1.78, 0.94–3.38, after adjustment. Decreased recent memory: p 0.075, OR: 1.68, 0.96–3.00, before adjustment; p 0.069, OR: 1.71, 0.96–3.09, after adjustment. Hypogeusia: p 0.086, OR: 1.63, 0.93–2.85, before adjustment; p 0.080, OR: 1.65, 0.94–2.89,
after adjustment. Change of weight: $p = 0.097$, OR: 0.17, 0.01—0.94, before adjustment; $p = 0.089$, OR: 0.16, 0.01—0.90, after adjustment.\textsuperscript{(Table 3)}

Under the overdominant model, the presence of apathy and delusion were found (Apathy: $p = 0.011$, OR: 2.05, 1.19—3.57, before adjustment; $p = 0.012$, OR: 2.06, 1.18—3.64, after adjustment.\textsuperscript{)} Trend of association between hallucination and the overdominant model was found ($p = 0.071$, OR: 2.32, 0.97—6.17, before adjustment; $p = 0.086$, OR: 2.26, 0.93—6.13, after adjustment).\textsuperscript{(Table 4)}

We performed Bonferroni correction for correction for adjusting p values. However, there was no statistically significant results remained.

**Discussion**

Our study found that *NMD3* carriers had worse cognitive function. The additive model of *NMD3* was associated with hallucination, postural hypotension and delusion. The dominant model of *NMD3* was associated with postural hypotension. The recessive model of *NMD3* was associated with hallucination, apathy, postural hypotension and delusion. The overdominant model of *NMD3* was associated with apathy and delusion. Trends of association between the additive model of *NMD3* and apathy, decreased recent memory and change of weight were found. Trends of association between the recessive model of *NMD3* and decreased attention, decreased recent memory, hypogeusia and change of weight were found. Trends of association between the overdominant model of *NMD3* and hallucination was found. To our knowledge, this is the first study to investigate the association between *NMD3* and its clinical symptoms in Chinese PD patients.

*NMD3* encodes a cytoplasmic protein for stable 60S ribosomal subunits\textsuperscript{[19,20]}. The function of ribosome in the pathogenesis of PD were still unknown. A study revealed that Parkin—PARIS (Parkin interacting substrate) played a deleterious role in rRNA transcription in PD, which indicated that ribosome might be involved in the pathogenesis of PD\textsuperscript{[21]}. A possible hypothesis of the function of *NMD3* is that the dysfunction or dysregulation of ribosome to produce relevant proteins of PD. More relationships between eukaryotic ribosome and PD should be discovered.

JM Shulman and colleagues found that *NMD3* rs34016896 was associated to nigral neuronal loss and not with Lewy bodies\textsuperscript{[13]}. This research indicated that *NMD3* rs34016896 was associated with nigral neurodegeneration rather than the formation of Lewy bodies. Neuronal loss, especially dopaminergic neuronal loss, is associated with the pathogenesis of PD. However, we have no clue on the detailed type of neurons for the neuronal loss. So far, there was no studies on clinical phenotype to detailed pathological phenotypes. It is hard to elucidate the impact to clinical phenotypes of neuronal loss. Further researches on NMD3-related neuronal loss could unveil the presence of those relevant symptoms.
The strengths of our study are that PD were assessed by structured scale which is widely accepted. The diagnosis was based on MDS criteria. We also covered a wide range assessment from the point of motor function, non-motor symptoms and life quality of PD.

This study has some weakness and limitations. First, we did not perform objective clinical methods such as electrophysiology to assess symptoms. Second, we did not perform stratifications due to small sample. Third, the sample of our study is small and our study was a single center study. More multicenter and larger studies are warranted. In conclusion, \( NMD3 \) carriers had worse cognitive function. The additive model of \( NMD3 \) was associated with hallucination, postural hypotension and delusion. The dominant model of \( NMD3 \) was associated with postural hypotension. The recessive model of \( NMD3 \) was associated with hallucination, apathy, postural hypotension and delusion. The overdominant model of \( NMD3 \) was associated with apathy and delusion. More larger and multicentral studies are warranted.

**List Of Abbreviations**

- \( CI \), confidence interval
- \( MDS \), movement disorders society
- \( MMSE \), Mini-Mental State Examination \( MoCA \), Montreal Cognitive Assessment \( NMSS \), non-motor symptoms scale
- \( OR \), odds ratio
- \( PARIS \), Parkin interacting substrate
- \( PD \), Parkinson's disease
- \( PDQ-39 \), 39-item Parkinson's disease Questionnaire \( RBD \), rapid eye movement sleep behavior disorder
- \( RLS \), restless legs syndrome
- \( SCOPA-AUT \), scales for Outcomes in Parkinson's disease - autonomic questionnaire
- \( SS-16 \), Sniffin’ Sticks 16
- \( UPDRS \), unified Parkinson's disease rating scale

**Declarations**

- Ethics approval and consent to participate

This study was approved by the Research Ethics Committee, Renji Hospital, Shanghai, China.
• Consent for publication

The authors declare that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed meet the qualifications for authorship and have reviewed and approved the final manuscript that is enclosed.

• Availability of data and materials

Not applicable

• Competing interests

The authors declare that there is no competing interests.

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• Authors’ contributions

Hui Wu and Hui Li collected the PD and control data, performed the statistical analysis and drafted the manuscript. Zhiqiang Shi, Jiajia Tang, Shuya Mei and Tianyi Ai collected the PD data.

Zhenzhou He designed the study, supervised the study, doublechecked the statistical analysis and revised the manuscript.

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Tables

Table 1. Demographic data and symptoms in PD patients involved in this study.
|                                         | NMD3 carriers (n = 178) | NMD3 wildtypes (n = 39) | p value |
|-----------------------------------------|-------------------------|-------------------------|---------|
| Age, mean (SD)                          | 57.03 (10.16)           | 55.69 (10.24)           | 0.461   |
| Gender, female, N(%)                    | 73 (41.01)              | 17 (43.59)              | 0.907   |
| Disease duration, mean (SD)             | 4.79 (4.28)             | 5.56 (3.89)             | 0.275   |
| Family history, N(%)                    | 17 (9.55)               | 5 (12.82)               | 0.550   |
| Hoehn – Yahr staging, N(%)              |                         |                         | 0.869   |
| 1.0                                     | 41 (23.03)              | 10 (25.64)              |         |
| 1.5                                     | 29 (16.29)              | 4 (10.26)               |         |
| 2.0                                     | 60 (33.71)              | 14 (35.90)              |         |
| 2.5                                     | 32 (17.98)              | 7 (17.95)               |         |
| 3.0                                     | 12 (6.74)               | 4 (10.26)               |         |
| 4.0                                     | 4 (2.24)                | 0 (0.00)                |         |
| 5.0                                     | 0 (0.00)                | 0 (0.00)                |         |
| MDS-UPDRS, mean (SD)                    | 48.34 (27.10)           | 43.05 (20.51)           | 0.175   |
| Part I                                  | 8.66 (6.16)             | 7.51 (5.43)             | 0.249   |
| Part II                                 | 11.60 (7.71)            | 10.08 (5.81)            | 0.168   |
| Part III                                | 28.08 (17.45)           | 25.46 (14.10)           | 0.318   |
| NMSS, mean (SD)                         | 36.23 (35.57)           | 31.03 (27.42)           | 0.315   |
| SCOPA-AUT, mean (SD)                    | 10.92 (9.06)            | 9.08 (8.56)             | 0.233   |
| PDQ-39, mean (SD)                       | 19.31 (17.84)           | 16.23 (13.93)           | 0.241   |
| MMSE, mean (SD)                         | 26.31 (3.79)            | 27.44 (2.89)            | 0.042   |
| MoCA, mean (SD)                         | 20.75 (6.68)            | 23.15 (4.20)            | 0.005   |

MDS, movement disorders society; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NMSS, non-motor symptoms scale; SCOPA-AUT, scales for Outcomes in Parkinson's disease - autonomic questionnaire; SD, standard deviation; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's disease Questionnaire; UPDRS, unified Parkinson's disease rating scale
Table 2. The association between symptoms and genetic models (additive and dominant models) of *NMD3* rs34016896.
| Condition                          | Additive model | Dominant model | Dominant model | Dominant model |
|-----------------------------------|----------------|----------------|----------------|---------------|
|                                   |                | p value | OR | 95% CI     | p value | OR | 95% CI     |
| Hallucination                     | 0.025          | 0.368   | 1.78 | (0.58, 7.79) | 0.341   | 1.86 | (0.59, 8.26) |
| Apathy                            | 0.092          | 0.941   | 0.97 | (0.49, 1.97) | 0.955   | 0.98 | (0.48, 2.01) |
| Excessive daytime sleepiness      | 0.444          | 0.908   | 0.95 | (0.38, 2.15) | 0.896   | 0.94 | (0.38, 2.15) |
| Pain                              | 0.696          | 0.474   | 0.77 | (0.37, 1.56) | 0.513   | 0.78 | (0.37, 1.60) |
| Frequent urination                | 0.639          | 0.491   | 1.28 | (0.64, 2.58) | 0.526   | 1.27 | (0.60, 2.72) |
| Constipation                      | 0.930          | 0.656   | 0.85 | (0.42, 1.71) | 0.528   | 0.78 | (0.36, 1.66) |
| Postural hypotension              | 0.007          | 0.052   | 2.38 | (1.05, 6.16) | 0.050   | 2.43 | (1.05, 6.38) |
| Sialorrhea                        | 0.487          | 0.600   | 1.20 | (0.60, 2.42) | 0.617   | 1.22 | (0.56, 2.62) |
| RLS                               | 0.905          | 0.266   | 0.66 | (0.32, 1.40) | 0.259   | 0.65 | (0.31, 1.40) |
| Delusion                          | 0.038          | 0.557   | 1.58 | (0.42, 10.33) | 0.605   | 1.51 | (0.38, 10.10) |
| Double vision                     | 0.197          | 0.144   | 3.02 | (0.85, 19.31) | 0.133   | 3.22 | (0.86, 21.14) |
| Decreased attention               | 0.124          | 0.570   | 1.27 | (0.58, 3.00) | 0.554   | 1.29 | (0.57, 3.14) |
| Decreased recent memory           | 0.064          | 0.227   | 1.54 | (0.76, 3.09) | 0.232   | 1.54 | (0.76, 3.13) |
| Nocturia                          | 0.870          | 0.845   | 1.08 | (0.47, 2.34) | 0.932   | 1.04 | (0.43, 2.36) |
| Sexual dysfunction                | 0.188          | 0.272   | 1.64 | (0.71, 4.27) | 0.254   | 1.69 | (0.72, 4.48) |
| Hypoguesia                        | 0.202          | 0.827   | 1.08 | (0.54, 2.22) | 0.859   | 1.07 | (0.53, 2.19) |
| Change of weight                  | 0.073          | 0.323   | 0.49 | (0.13, 2.38) | 0.298   | 0.47 | (0.12, 2.29) |
| Daytime sweatiness                | 0.449          | 0.964   | 1.02 | (0.49, 2.17) | 0.918   | 1.04 | (0.49, 2.29) |
| Nocturnal sweatiness              | 0.405          | 0.847   | 0.93 | (0.46, 1.96) | 0.874   | 0.94 | (0.45, 2.04) |
| Urgent urination or urinary incontinence | 0.724  | 0.891   | 1.05 | (0.52, 2.10) | 0.946   | 1.03 | (0.48, 2.18) |
| Sensitive to light                | 0.142          | 0.387   | 2.50 | (0.47, 46.44) | 0.381   | 2.55 | (0.46, 47.88) |
| Sensitive to cold                 | 0.484          | 0.589   | 1.30 | (0.53, 3.66) | 0.588   | 1.30 | (0.53, 3.68) |
| Sensitive to hot                  | 0.481          | 0.311   | 0.63 | (0.27, 1.62) | 0.283   | 0.60 | (0.25, 1.59) |
| Anxiety                           | 0.155          | 0.404   | 1.49 | (0.62, 4.19) | 0.335   | 1.64 | (0.63, 4.86) |
| Depression                        | 0.935          | 0.644   | 1.35 | (0.43, 6.64) | 0.664   | 1.34 | (0.41, 6.64) |
RBD & 0.957 & 0.542 & 0.80 & (0.39, 1.67) & 0.498 & 0.77 & (0.37, 1.65) \\
Olfactory dysfunction & 0.784 & 0.845 & 1.08 & (0.47, 2.34) & 0.934 & 1.03 & (0.44, 2.26) \\

CI, confidence interval; OR, odds ratio; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome

*adjusted by age, gender and Hoehn-Yahr staging

Table 3. The association between symptoms and genetic models (recessive models) of *NMD3* rs34016896.
| Condition                        | Recessive model | Recessive model (adjusted)* |
|---------------------------------|-----------------|----------------------------|
|                                 | p value         | OR  | 95% CI               | p value         | OR  | 95% CI               |
| Hallucination                   | 0.012           | 2.96 | (1.29, 7.10)        | 0.014           | 2.95 | (1.26, 7.21)        |
| Apathy                          | 0.011           | 2.06 | (1.18, 3.61)        | 0.012           | 2.07 | (2.28, 3.67)        |
| Excessive daytime sleepiness    | 0.221           | 1.55 | (0.78, 3.19)        | 0.213           | 1.56 | (0.79, 3.23)        |
| Pain                            | 0.252           | 1.39 | (0.79, 2.46)        | 0.286           | 1.36 | (0.77, 2.42)        |
| Frequent urination              | 0.879           | 1.04 | (0.60, 1.81)        | 0.916           | 1.03 | (0.57, 1.86)        |
| Constipation                    | 0.629           | 1.15 | (0.66, 2.00)        | 0.649           | 1.15 | (0.64, 2.07)        |
| Postural hypotension            | 0.017           | 2.04 | (1.14, 3.68)        | 0.016           | 2.08 | (1.15, 3.82)        |
| Sialorrhea                      | 0.536           | 1.19 | (0.68, 2.09)        | 0.552           | 1.20 | (0.65, 2.23)        |
| RLS                             | 0.480           | 1.24 | (0.68, 2.26)        | 0.520           | 1.22 | (0.66, 2.26)        |
| Delusion                        | 0.014           | 3.94 | (1.38, 12.92)       | 0.012           | 4.41 | (1.46, 15.47)       |
| Double vision                   | 0.480           | 1.34 | (0.58, 3.02)        | 0.420           | 1.43 | (0.59, 3.40)        |
| Decreased attention             | 0.068           | 1.76 | (0.96, 3.26)        | 0.075           | 1.78 | (0.94, 3.38)        |
| Decreased recent memory         | 0.075           | 1.68 | (0.96, 3.00)        | 0.069           | 1.71 | (0.96, 3.09)        |
| Nocturia                        | 0.930           | 1.03 | (0.55, 1.97)        | 0.940           | 1.02 | (0.52, 2.03)        |
| Sexual dysfunction              | 0.281           | 1.41 | (0.75, 2.63)        | 0.317           | 1.39 | (0.73, 2.63)        |
| Hypoguesia                      | 0.086           | 1.63 | (0.93, 2.85)        | 0.080           | 1.65 | (0.94, 2.89)        |
| Change of weight                | 0.097           | 0.17 | (0.01, 0.94)        | 0.089           | 0.16 | (0.01, 0.90)        |
| Daytime sweatiness              | 0.247           | 0.71 | (0.39, 1.27)        | 0.176           | 0.65 | (0.35, 1.20)        |
| Nocturnal sweatiness            | 0.280           | 0.72 | (0.40, 1.29)        | 0.199           | 0.67 | (0.36, 1.23)        |
| Urgent urination or urinary incontinence | 0.677   | 1.12 | (0.65, 1.96)        | 0.718           | 1.12 | (0.62, 2.03)        |
| Sensitive to light              | 0.151           | 2.38 | (0.73, 8.28)        | 0.163           | 2.37 | (0.71, 8.50)        |
| Sensitive to cold               | 0.541           | 1.24 | (0.61, 2.49)        | 0.561           | 1.23 | (0.60, 2.47)        |
| Sensitive to hot                | 0.809           | 0.91 | (0.41, 1.94)        | 0.768           | 0.88 | (0.39, 1.96)        |
| Anxiety                         | 0.149           | 1.63 | (0.83, 3.20)        | 0.143           | 1.72 | (0.83, 3.58)        |
| Depression                      | 0.626           | 0.79 | (0.29, 1.99)        | 0.581           | 0.76 | (0.27, 1.99)        |
| RBD                             | 0.573           | 1.18 | (0.66, 2.10)        | 0.591           | 1.18 | (0.65, 2.14)        |
| Olfactory dysfunction           | 0.574           | 0.83 | (0.45, 1.58)        | 0.593           | 0.84 | (0.44, 1.61)        |

CI, confidence interval; OR, odds ratio; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome

*adjusted by age, gender and Hoehn-Yahr staging
Table 4. The association between symptoms and genetic models (overdominant models) of NMD3 rs34016896.
| Condition                        | Overdominant model | Overdominant model (adjusted)* |
|--------------------------------|--------------------|--------------------------------|
|                                | p value | OR     | 95% CI            | p value | OR     | 95% CI            |
| Hallucination                   | 0.071   | 2.32   | (0.97, 6.17)      | 0.086   | 2.26   | (0.93, 6.13)      |
| Apathy                          | 0.011   | 2.05   | (1.19, 3.57)      | 0.012   | 2.06   | (1.18, 3.64)      |
| Excessive daytime sleepiness    | 0.198   | 1.54   | (0.80, 2.97)      | 0.186   | 1.56   | (0.81, 3.03)      |
| Pain                            | 0.094   | 1.60   | (0.92, 2.76)      | 0.121   | 1.55   | (0.89, 2.70)      |
| Frequent urination              | 0.700   | 0.90   | (0.53, 1.54)      | 0.698   | 0.89   | (0.50, 1.59)      |
| Constipation                    | 0.413   | 1.25   | (0.73, 2.15)      | 0.349   | 1.32   | (0.74, 2.36)      |
| Postural hypotension            | 0.414   | 1.27   | (0.71, 2.30)      | 0.407   | 1.29   | (0.71, 2.36)      |
| Sialorrhea                      | 0.841   | 1.06   | (0.61, 1.82)      | 0.845   | 1.06   | (0.55, 1.93)      |
| RLS                             | 0.121   | 1.62   | (0.89, 3.01)      | 0.131   | 1.62   | (0.87, 3.06)      |
| Delusion                        | 0.048   | 3.66   | (1.14, 16.31)     | 0.035   | 4.35   | (1.25, 20.99)     |
| Double vision                   | 0.625   | 0.82   | (0.36, 1.85)      | 0.669   | 0.83   | (0.35, 1.98)      |
| Decreased attention             | 0.176   | 1.53   | (0.83, 2.88)      | 0.195   | 1.53   | (0.81, 2.97)      |
| Decreased recent memory         | 0.416   | 1.25   | (0.73, 2.17)      | 0.391   | 1.28   | (0.73, 2.23)      |
| Nocturia                        | 0.949   | 0.98   | (0.52, 1.83)      | 0.998   | 1.00   | (0.51, 1.94)      |
| Sexual dysfunction              | 0.839   | 1.07   | (0.57, 2.00)      | 0.928   | 1.03   | (0.54, 1.97)      |
| Hypogeusia                      | 0.131   | 1.53   | (0.88, 2.66)      | 0.114   | 1.56   | (0.90, 2.73)      |
| Change of weight                | 0.304   | 0.51   | (0.13, 1.83)      | 0.295   | 0.50   | (0.12, 1.82)      |
| Daytime sweatiness              | 0.243   | 0.71   | (0.40, 1.26)      | 0.157   | 0.65   | (0.36, 1.18)      |
| Nocturnal sweatiness            | 0.363   | 0.77   | (0.44, 1.35)      | 0.254   | 0.71   | (0.39, 1.28)      |
| Urgent urination or urinary incontinence | 0.763   | 1.09   | (0.63, 1.86)      | 0.762   | 1.09   | (0.61, 1.97)      |
| Sensitive to light              | 0.456   | 1.60   | (0.49, 6.14)      | 0.481   | 1.58   | (0.46, 6.28)      |
| Sensitive to cold               | 0.857   | 1.07   | (0.53, 2.16)      | 0.880   | 1.06   | (0.53, 2.15)      |
| Sensitive to hot                | 0.582   | 1.24   | (0.59, 2.69)      | 0.579   | 1.25   | (0.57, 2.84)      |
| Anxiety                         | 0.442   | 1.30   | (0.67, 2.60)      | 0.489   | 1.30   | (0.63, 2.75)      |
| Depression                      | 0.405   | 0.68   | (0.27, 1.69)      | 0.376   | 0.65   | (0.25, 1.69)      |
| RBD                             | 0.306   | 1.35   | (0.76, 2.40)      | 0.292   | 1.38   | (0.76, 2.51)      |
| Olfactory dysfunction           | 0.483   | 0.80   | (0.42, 1.49)      | 0.555   | 0.82   | (0.43, 1.56)      |

CI, confidence interval; OR, odds ratio; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome

*adjusted by age, gender and Hoehn-Yahr staging