Research Article

Effect of GBA Mutations on Phenotype of Parkinson’s Disease: A Study on Chinese Population and a Meta-Analysis

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GBA has been identified as a genetic risk factor for PD. Whether the clinical manifestations of PD patients with or without GBA mutations are different has still not reached a consensus. We firstly detected the GBA mutation L444P in 1147 Chinese PD patients and simultaneously evaluated their corresponding clinical data. Then we compared the phenotypes between 646 PD patients with GBA mutations and 10344 PD patients without GBA mutations worldwide through meta-analysis. Through the method of meta-analysis, there was significant difference in age at onset (MD = −3.10 [95% CI: −4.88, −1.32]), bradykinesia as an initial symptom (OR = 1.49 [95% CI: 1.15, 1.94]), having family history (OR = 1.50 [95% CI: 1.18, 1.91]), and dementia (OR = 3.21 [95% CI: 1.97, 5.24]) during the comparison between PD patients with and without GBA mutations. While, in the aspect of tremor as an initial symptom (OR = 0.81 [95% CI: 0.64, 1.03]), the severity of motor symptoms such as H-Y (MD = 0.06 [95% CI: −0.06, 0.17]) and UPDRS-III (MD = 1.61 [95% CI: −0.65, 3.87]) and having dyskinesia (OR = 1.60 [95% CI: 0.90, 2.84]) during the comparison between the two groups revealed no statistical differences. Our results suggested that the phenotypes of PD patients with GBA mutations are different from GBA noncarriers.

1. Introduction

Parkinson’s disease (PD) is the second most common progressive neurodegenerative disorder. Though the etiology of PD remains unclear, there is an increasing evidence that genetic-factor contributes to the etiology of PD.

Mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (GBA) have been identified as a genetic risk factor for PD [1]. Aharon-Peretz and her colleagues [2] reported that the overall clinical manifestations and age at disease onset have no differences in PD patients with GBA mutations (GBA + PD) compared with those without mutations (GBA − PD) in 148 Ashkenazi PD patients. However, recent researches have shown that the clinical features of GBA + PD differ from GBA − PD to some extent. Winder-Rhodes et al. [3] showed that GBA carriers in PD were inclined to suffer an earlier age at onset (AAO) and more severe non-motor and motor symptoms. Hu and other researchers [4] reported that GBA mutations influenced the course of PD with respect to the appearance of dementia. Whether the clinical manifestations of PD patients with or without GBA mutations are different or not has still not reached a consensus.

In order to evaluate the effect of GBA on the phenotype of PD, we firstly explored the relationship between GBA mutations and their clinical characteristics in Chinese PD patients. Then the method of meta-analysis was used to assess the possible role of GBA in the phenotype of PD with larger sample size worldwide.
Study or subgroup | GBA carrier Events | Total | GBA uncarrier Events | Total | Weight | Odds ratio M-H, fixed, 95% CI | Odds ratio M-H, fixed, 95% CI
--- | --- | --- | --- | --- | --- | --- | ---
De Marco et al. 2008 | 1 | 11 | 42 | 384 | 2.0% | 0.81 [0.10, 6.52] |  
Gan-Or et al. 2010 | 27 | 109 | 85 | 402 | 25.9% | 1.23 [0.75, 2.02] |  
Lesage et al. 2011 | 69 | 100 | 717 | 1291 | 30.3% | 1.78 [1.15, 2.76] |  
ede Carvalho Guimarães et al. 2012 | 2 | 13 | 79 | 334 | 4.7% | 0.59 [0.13, 2.70] |  
Emelyanov et al. 2012 | 3 | 9 | 97 | 321 | 3.3% | 1.15 [0.28, 4.71] |  
Setó-Salvia et al. 2012 | 11 | 22 | 79 | 203 | 7.3% | 1.57 [0.65, 3.79] |  
Kumar et al. 2013 | 2 | 18 | 54 | 297 | 5.2% | 0.56 [0.13, 2.52] |  
Asselta et al. 2014 | 21 | 102 | 250 | 2153 | 17.0% | 1.97 [1.20, 3.25] |  
Pulkes et al. 2014 | 4 | 17 | 18 | 191 | 2.1% | 2.96 [0.87, 10.03] |  
Our data | 1 | 34 | 37 | 1113 | 2.0% | 0.88 [0.12, 6.62] |  
Total (95% CI) | 435 | 6689 | 100.0% | 1.50 [1.18, 1.91] |  
Total events | 141 | 1458 |  
Heterogeneity: $\chi^2 = 7.40, df = 9 (P = 0.60); I^2 = 0\%$  
Test for overall effect: $Z = 3.34 (P = 0.0008)$  

Figure 2: (a) Forest plot of family history in GBA + PD and GBA − PD. (b) Funnel plot of family history in GBA + PD and GBA − PD.
### Study or subgroup  |  GBA carrier  |  GBA uncarrier  |  Mean difference  
|---------------------|--------------|-----------------|-------------------|-------------------|-------------------|
|                     | Mean | SD | Total | Mean | SD | Total | Weight | Mean difference | IV, random, 95% CI | Mean difference | IV, random, 95% CI |
| Socal et al. 2009    | 37.5 | 2.7 | 6     | 41.4 | 10.5 | 53    | 8.4%    | −3.90          | [−7.35, −0.45]  | −3.90            | [−7.35, −0.45]  |
| Mao et al. 2010      | 54.9 | 11.97 | 20    | 54.63 | 13.7 | 596   | 8.6%    | −2.30          | [−5.56, 0.96]   | −2.30            | [−5.56, 0.96]   |
| Lesage et al. 2011   | 51   | 12.7 | 96    | 50   | 13.7 | 1220  | 9.6%    | −0.64          | [−7.07, 5.79]   | −0.64            | [−7.07, 5.79]   |
| Seto-Salvia et al. 2012 | 54.2 | 6.6 | 22    | 56.5 | 12.7 | 203   | 8.6%    | −2.30          | [−5.56, 0.96]   | −2.30            | [−5.56, 0.96]   |
| Wang et al. 2012     | 56.14 | 8.34 | 7     | 56.78 | 13.08 | 208   | 4.7%    | −0.64          | [−7.07, 5.79]   | −0.64            | [−7.07, 5.79]   |
| Lesage et al. 2011   | 51   | 12.7 | 96    | 50   | 13.7 | 1220  | 9.6%    | −0.64          | [−7.07, 5.79]   | −0.64            | [−7.07, 5.79]   |
| Seto-Salvia et al. 2012 | 54.2 | 6.6 | 22    | 56.5 | 12.7 | 203   | 8.6%    | −2.30          | [−5.56, 0.96]   | −2.30            | [−5.56, 0.96]   |
| Krejci et al. 2013   | 53   | 8.2 | 18    | 53.3 | 10   | 32    | 6.1%    | −0.30          | [−5.43, 4.83]   | −0.30            | [−5.43, 4.83]   |
| Kumar et al. 2013    | 49.68 | 9.68 | 19    | 52.4 | 11.1 | 302   | 6.8%    | −2.72          | [−7.25, 1.81]   | −2.72            | [−7.25, 1.81]   |
| Asselta et al. 2014  | 51.54 | 10.63 | 102   | 56.69 | 10.51 | 2182  | 10.4%   | −5.15          | [−7.26, −3.04]  | −5.15           | [−7.26, −3.04]  |
| Y. Li et al. 2014    | 49.1 | 11.7 | 34    | 51.3 | 14.5 | 113   | 6.5%    | −2.20          | [−6.96, 2.56]   | −2.20            | [−6.96, 2.56]   |
| Malec-Litwinowicz et al. 2014 | 57.2 | 2.8 | 5     | 57.6 | 10.9 | 117   | 8.8%    | −0.40          | [−3.55, 2.75]   | −0.40            | [−3.55, 2.75]   |
| Pulkes et al. 2014   | 43.1 | 10.2 | 17    | 54.4 | 13.9 | 191   | 5.9%    | −11.30         | [−16.53, −6.07] | −11.30          | [−16.53, −6.07] |
| Wang et al. 2014     | 51.45 | 9.14 | 49    | 58.41 | 11.03 | 1366  | 9.6%    | −6.96          | [−9.59, −4.33]  | −6.96            | [−9.59, −4.33]  |
| Our data             | 50.18 | 9.44 | 34    | 54.74 | 11.52 | 1113  | 8.7%    | −4.56          | [−7.80, −1.32]  | −4.56            | [−7.80, −1.32]  |

**Total (95% CI):** 429, 7696, 100.0%  
Heterogeneity: $\chi^2 = 6.77$, df = 12 ($P = 0.0002$); $I^2 = 68\%$

Test for overall effect: $Z = 3.41$ ($P = 0.0006$)

#### Figure 3: (a) Forest plot of age at onset in GBA + PD and GBA−PD. (b) Funnel plot of age at onset in GBA + PD and GBA−PD.

### 2. Methods

#### 2.1. Subjects and Clinical Characteristics

1147 PD patients were collected continuously from 2005 to 2014 from the outpatient neurology clinics of Xiangya Hospital of China. PD was diagnosed by two or more experienced neurologists according to the United Kingdom Parkinson Disease Society Brain Bank criteria (UKBB) [5] with the exception that a positive family history was not a part of the exclusion criteria. None had a history of neurologic or psychiatric conditions other than PD. We collected age at onset and initial motor symptom from all participants. Other assessments were blindly performed during the "on" motor state. Hoehn-Yahr rating scale (H-Y) and part III of unified Parkinson disease rating scale (UPDRS-III) were used to evaluate the severity of 424 PD patients' motor symptoms, who were continuously collected from 2011 to 2014. The presentation of dyskinesia was evaluated through UPDRS-IV in 424 PD patients, continuously collected from 2011 to 2014. Dementia status of 268 PD patients who were continuously collected from 2013 to 2014 was evaluated according to the Movement Disorder Society task force (MDS-TF) consensus criteria. All clinical information was shown in Table 1.

#### 2.2. Genetic Analysis

All 1147 PD patients were detected for GBA gene L444P mutation, the most common PD-associated GBA mutation in Chinese population [24]. The screening procedures and details have been reported recently [25].

#### 2.3. Meta-Analysis

Including our own data of Chinese population, a meta-analysis related to the above topic was conducted. Eligible studies had to meet the following criteria: (1) being a case-control study except for reviews, case reports, editorials, or functional researches; (2) all PD patients being diagnosed according to UKBB criteria with the exception that a positive family history was not a part of the exclusion criteria; (3) only including publications related to GBA mutation analysis; (4) clearly reporting results of GBA mutations and corresponding clinical data. Then we searched electronic databases including Embase, PubMed, Cochrane Library, and Web of Knowledge and Wanfang database and CNKI up to May 1, 2015, using combination of following keywords:
| First author        | Country     | Group         | Number | Family history | AAO (n)a | Tremor (n)a | Bradykinesia (n)a | H-Y (n)a | UPDRS-III (n)a | Dementia (n)a | Dyskinesia (n)a |
|---------------------|-------------|---------------|--------|----------------|----------|--------------|-------------------|----------|----------------|---------------|-----------------|
| Our own data        | China       | GBA + PD      | 34     | 1              | 50.18 ± 9.44 | 21         | 23                | 2.82 ± 0.97 (14) | 33.43 ± 23.02 (14) | 5 (6)         | 6 (14)          |
| Wang 2014 [6]       | China       | GBA + PD      | 49     | —              | 51.45 ± 9.14 | 26 (49)    | 18 (45)            | 2.02 ± 0.68       | 25.80 ± 13.49     | —              | 5 (37)          |
| Pulkes 2014 [7]     | China       | GBA + PD      | 17     | 4              | 43.1 ± 10.2  | —           | —                 | —         | —              | —              | 7               |
| Malec-Litwinowicz   | Poland      | GBA + PD      | 5      | —              | 57.2 ± 2.8   | —           | —                 | 2.9 ± 1.0          | 36.4 ± 18.5       | 3              | —               |
| Li 2014 [9]         | Japan       | GBA + PD      | 34     | 34             | 49.1 ± 11.7  | —           | —                 | —         | —              | 12             | 10              |
| Asselta 2014 [10]   | Italy       | GBA + PD      | 102    | 21             | 51.54 ± 10.63| —           | —                 | —         | —              | 18             | 37              |
| Kumar 2013 [11]     | Serbia      | GBA + PD      | 21     | 2 (18)         | 49.68 ± 9.68 (19)| 6 (15)    | 4 (14)            | 2.74 ± 0.77 (19)  | —              | 0 (19)         |
| Kresojević 2013 [12]| Serbia      | GBA + PD      | 18     | —              | 53.0 ± 8.2   | —           | —                 | 2.7 ± 1.1          | 38.6 ± 21.4       | —              | —               |
| Wang 2012 [13]      | China       | GBA + PD      | 7      | —              | 53.3 ± 10.0  | —           | —                 | 2.4 ± 0.8          | 35.9 ± 15.5       | —              | —               |
| Setó-Salvà 2012 [14]| Europe      | GBA + PD      | 22     | 11             | 54.2 ± 6.6   | —           | —                 | 2.5 ± 0.82         | —              | 11             |
| Emelyanov 2012 [15] | Russia      | GBA + PD      | 9      | 3              | 56.14 ± 8.34 | —           | —                 | —         | —              | —              | —               |
| de Carvalho Guimarães 2012 [16]| Brazil | GBA + PD | 13 | 2 | — | — | — | 2.67 ± 0.98 | — | 48 |
| Alcalay 2012 [17]   | Multisites  | GBA + PD      | 33     | —              | —           | —           | —                 | —         | —              | —              | —               |
| Lesage 2011 [18]    | Europe      | GBA + PD      | 100    | 69             | 51.0 ± 12.7 (96)| 45 (88)  | 64 (88)           | 1.9 ± 0.8 (52)    | 19 ± 11 (56)      | —              | 21 (75)         |
| Huang 2011 [19]     | China       | GBA + PD      | 36     | —              | —           | —           | —                 | —         | —              | —              | —               |
| Mao 2010 [20]       | China       | GBA + PD      | 20     | —              | 54.90 ± 11.97| 6 (20)     | 12 (20)           | 2.55 ± 1.04       | —              | —              | —               |
| Gan-Or 2010 [21]    | Israel      | GBA + PD      | 109    | 27             | 37.5 ± 2.7   | —           | —                 | —         | —              | —              | —               |
| Socall 2009 [22]    | Brazil      | GBA + PD      | 6      | —              | 41.4 ± 10    | —           | —                 | —         | —              | —              | —               |
| De Marco 2008 [23]  | Italy       | GBA + PD      | 11     | —              | —           | —           | —                 | —         | —              | 5              | —               |

(n)a: number of patients whose clinical information was available.
### Table 1: Forest Plot of GBA Carriers and Uncarriers With Parkinson’s Disease

| Study or subgroup | GBA carrier | GBA uncarrier | Odds ratio | Odds ratio |
|------------------|-------------|---------------|------------|------------|
|                  | Events      | Total         | Events     | Total       | M-H, fixed, 95% CI | M-H, fixed, 95% CI |
|                   |             |               |            |             |                     |                     |
| Gan-Or et al. 2010 | 27          | 109           | 61         | 402         | 21.3%              | 1.84 [1.10, 3.08]   |
| Mao et al. 2010   | 12          | 20            | 293        | 596         | 8.3%               | 1.55 [0.63, 3.85]   |
| Lesage et al. 2011| 64          | 88            | 641        | 1069        | 28.9%              | 1.78 [1.10, 2.89]   |
| Kumar et al. 2013 | 4           | 14            | 78         | 280         | 5.8%               | 1.04 [0.32, 3.40]   |
| Wang et al. 2014  | 18          | 45            | 475        | 1362        | 19.8%              | 1.24 [0.68, 2.28]   |
| Our data          | 23          | 34            | 768        | 1113        | 16.0%              | 0.94 [0.45, 1.95]   |
| **Total (95% CI)**| **310**     | **4822**      | **100.0%** | **1.49**    | **[1.15, 1.94]**   |                     |

**Total events**: 148 / 2316

**Heterogeneity**: $\chi^2 = 3.41$, df = 5 ($P = 0.64$); $I^2 = 0$

**Test for overall effect**: $Z = 2.99$ ($P = 0.003$)

### GBA, glucocerebrosidase, and Parkinson’s Disease

GBA, glucocerebrosidase, and Parkinson’s Disease both in English and in Chinese. Reference lists and personal communications of authors were also referred to as sources to include articles cited elsewhere.

To select studies for further assessment, two authors independently scanned the abstracts, titles, or both sections of each retrieved record. All potentially relevant articles were investigated in full text. For studies satisfying the aforesaid criteria, two authors independently abstracted the following data: year of publication, first author’s surname, country of participants, numbers of PD patients with and without GBA mutations, and corresponding clinical information.
| Study or subgroup | GBA carrier | GBA uncarrier | Weight | Mean difference | Mean difference |
|------------------|------------|--------------|--------|----------------|----------------|
| Mao et al. 2010  | 2.55 1.04  | 2.29 0.98    | 20     | 6.3%           | 0.26 [-0.20, 0.72] |
| Lesage et al. 2011| 1.9 0.8    | 2.1 0.9      | 743    | 26.4%          | -0.20 [-0.43, 0.03] |
| Seto-Salvia et al 2012 | 2.5 0.82 | 2.67 0.98    | 203    | 10.0%          | -0.17 [-0.54, 0.20] |
| Kresojevic et al. 2013 | 2.7 1.1    | 2.4 0.8      | 32     | 4.1%           | 0.30 [-0.28, 0.88] |
| Kumar et al. 2013   | 2.74 0.77  | 2.4 0.79     | 303    | 10.6%          | 0.34 [-0.02, 0.70] |
| Malec-Litwinowicz et al. 2014 | 2.9 1     | 2.2 0.8      | 117    | 1.7%           | 0.70 [-0.19, 1.59] |
| Wang et al. 2014    | 2.02 0.68  | 1.94 0.78    | 1366   | 35.8%          | 0.08 [-0.11, 0.27] |
| Our data            | 2.82 0.97  | 2.41 0.95    | 410    | 5.1%           | 0.41 [-0.11, 0.93] |
| **Total (95% CI)**  |            | ****         | 3770   | **100.0%**     | **0.06 [-0.06, 0.17]** |

**Heterogeneity:** $\chi^2 = 14.08$, df = 7 ($P = 0.05$); $I^2 = 50$

Test for overall effect: $Z = 0.95$ ($P = 0.34$)

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| Study or subgroup | GBA carrier | GBA uncarrier | Weight | Mean difference | Mean difference |
|------------------|------------|--------------|--------|----------------|----------------|
| Lesage et al. 2011| 19 11      | 19 13        | 792    | 56.1%          | 0.00 [-3.02, 3.02] |
| Kresojevic et al. 2013 | 38.6 21.4  | 35.9 15.5    | 32     | 4.0%           | 2.70 [-8.55, 13.95] |
| Malec-Litwinowicz et al. 2014 | 36.4 18.5  | 23.9 12.3    | 117    | 1.9%           | 12.50 [-3.87, 28.87] |
| Wang et al. 2014    | 25.8 13.49 | 23.35 13.95  | 1366   | 34.5%          | 2.45 [-1.40, 6.30] |
| Our data            | 33.43 23.02| 21.52 13.84  | 410    | 3.5%           | 11.91 [-0.22, 24.04] |
| **Total (95% CI)**  |            | ****         | 2717   | **100.0%**     | **1.61 [-0.65, 3.87]** |

**Heterogeneity:** $\chi^2 = 5.78$, df = 4 ($P = 0.22$); $I^2 = 31$

Test for overall effect: $Z = 1.39$ ($P = 0.16$)

The flowchart of studies selection and reasons for exclusion are presented in Figure 1. The qualities of the included studies were evaluated by the Newcastle-Ottawa Scale (NOS) [26].

In order to assess the strength of association between GBA mutations and clinical manifestation, dichotomous outcome was expressed as odds ratio (OR) while continuous outcome was expressed as mean difference (MD) with 95% confidence intervals (CI). Heterogeneity across individual studies was identified by a standard Q test with a significance level of $\alpha = 0.1$ and $I^2$. If heterogeneity did not exist ($Q > 0.10$) or the severity of heterogeneity was accepted ($I^2 \leq 50\%$), the fixed effect model was adopted to calculate the pooled OR and MD value. Otherwise, the random effect model was used. Funnel-plot analysis was used to assess the reporting bias. All analyses were carried out by using the Review Manager software package v.5.3 (The Cochrane Collaboration, Oxford, England).
### 3. Results

34 GBA + PD and 1113 GBA − PD were available in our own data from Chinese. A total of 18 eligible studies were included during the process of meta-analysis. The main characteristics of all included studies are summarized in Table 1.

#### 3.1. Onset Characteristics

**3.1.1. Family History.** PD patients with family history are defined as having at least one first- or second-degree relative with the diagnosis of PD. There are 38 PD patients (1 GBA + PD, 37 GBA − PD) with family history in our own data. We included another 9 publications to assess the relationship between GBA status and family history of PD patients. The pooled OR of family history in GBA + PD and GBA − PD was 1.50 [95% CI: 1.18, 1.91] (Figure 2(a)). That means GBA + PD was more likely to be exposed to family history than GBA − PD, even though the relationship was negative in our own data. The funnel plot was symmetric (Figure 2(b)).

**3.1.2. Age at Onset (AAO).** A total of 429 GBA carriers and 7696 GBA uncarrriers were included in the analysis of relationship between AAO of PD patients and GBA status. The pooled MD of AAO between GBA + PD and GBA − PD was −3.10 [95% CI: −4.88, −1.32] (Figure 3(a)). It means that the AAO is nearly 3 years earlier in GBA + PD than GBA − PD. The funnel plot was asymmetric and the bias leaned to no difference in the two groups (Figure 3(b)). The AAO of GBA + PD and GBA − PD are 50.18 ± 9.44 and 54.74 ± 11.52 individually in our own data from Chinese population, which was consistent with the results of meta-analysis.

**3.1.3. Initial Motor Symptom.** We analyzed two common initial motor symptoms: bradykinesia and tremor. The pooled OR of bradykinesia as an initial symptom between GBA + PD and GBA − PD was 1.49 [95% CI: 1.15, 1.94] (Figure 4(a)). The pooled OR of tremor as an initial symptom between GBA + PD and GBA − PD was 0.81 [95% CI: 0.64, 1.03] (Figure 4(b)). The two funnel plots were symmetric (Figures 4(c) and 4(d)). Unfortunately, there was no significant difference in our own data from Chinese population, which was consistent with publications that referred to Chinese population [6, 20].

#### 3.2. Progression Features

**3.2.1. Severity of PD Motor Symptoms.** We continuously evaluated the H-Y and UPDRS-III in 14 GBA + PD and 410 GBA − PD in Chinese mainland population from 2011 to 2014. Together with the included publications’ data, the pooled MD
| Study or subgroup | GBA carrier | GBA uncarrier | Weight | Odds ratio | Odds ratio |
|------------------|-------------|---------------|--------|------------|------------|
|                   | Events      | Total         | Events | Total      | M-H, random, 95% CI | M-H, random, 95% CI |
| Lesage et al. 2011 | 21          | 75            | 263    | 894        | 0.93 [0.55, 1.58]    |
| Kumar et al. 2013 | 0           | 19            | 2      | 287        | 2.93 [0.14, 63.13]   |
| Y. Li et al. 2014 | 10          | 34            | 37     | 113        | 0.86 [0.37, 1.97]    |
| Pulkes et al. 2014 | 7           | 17            | 24     | 191        | 4.87 [1.69, 14.01]   |
| Wang et al. 2014  | 5           | 37            | 76     | 922        | 1.74 [0.66, 4.59]    |
| Our data          | 6           | 14            | 99     | 410        | 2.36 [0.80, 6.95]    |
| **Total**         | **196**     | **2817**      | **100.0%** | **1.60** [**0.90, 2.84**] |

of H-Y between GBA + PD and GBA – PD was 0.06 [95% CI: −0.06, 0.17] (Figure 5(a)). The pooled MD of UPDRS-III among the two groups was 1.61 [95% CI: −0.65, 3.87] (Figure 5(b)). The two funnel plots were asymmetric which tended to positive results (Figures 5(c) and 5(d)). The MDs of H-Y and UPDRS-III showed no significant differences between GBA carriers and uncarriers in mainland Chinese population and other centers.

3.2.3. Dyskinesia. We evaluated the presentation of dyskinesia among 424 PD patients (14 GBA + PD and 410 GBA – PD) through UPDRS-IV, who were continuously collected from 2011 to 2014. 105 PD patients (6 GBA + PD and 99 GBA – PD) presented with dyskinesia. Besides, 5 publications were included to illustrate the connection between dyskinesia and GBA status in PD. The pooled OR of dyskinesia between GBA + PD and GBA – PD was 1.64 [95% CI: 0.91, 2.94] (Figure 7(a)). The funnel plot was symmetric (Figure 7(b)).

4. Discussion

We firstly presented an extensive and detailed phenotype description of GBA + PD in Chinese together with meta-analysis worldwide, focusing on not only the disease onset features but also disease progression characteristics. The phenotype of GBA + PD, sharing a spectrum of Parkinsonian phenotype, differs from GBA – PD in the following aspects: AAO, initial motor symptom, presentation with family history, and dementia.

Totally, 646 GBA + PD and 10344 GBA – PD were included. The NOS scores of all included publications were rated from 6 stars to 9 stars, which showed that none of the included publications were of low quality.
Additionally, there was no obvious publication reporting bias from the symmetric funnel plots related to the analysis in family history, bradykinesia or tremor as an initial symptom, dementia, and dyskinesia. Even though there was no different in the funnel plot of AAO, we still figured out the earlier onset age of GBA + PD than that of GBA − PD. Thus, we can conclude that the GBA + PD patients are more likely to onset with earlier age than GBA − PD, which are easily ignored by clinical doctors because PD is more likely to develop in the old. In the same way, the MDs of H-Y and UPDRS – III showed no significant differences with so many positive reports. That is to say, GBA mutations in PD patients are not related to the severity in PD.

What is more, both genetic and clinical heterogeneities exist during the analysis process. All heterogeneities may originate from the following parts: firstly, the frequency of the different GBA mutations varies according to ethnicity [27]. For instance, in Ashkenazi Jewish (AJ), N370S is the most frequent mutation, whereas the L444P is more common in Asian population than others. Still, other variations, like R120W and D409H, were also reported in several studies but rarely showed positive outcomes. We could not extract single GBA mutation and corresponding clinical information from included publications. Thus, mixed GBA carriers and their clinical data together may affect the final results, especially for the ethnicity related data. Even in the same ethnicity, the heterogeneity also could not be avoided due to different genetic screening methods, other susceptible genes apart from GBA, and different degree of effects by the different GBA mutations [28]. Secondly, studies which did not adjust for age, sex, disease duration, environmental exposures, and other cofactors may influence clinical phenotype of PD.

The foundation underlying the relation of GBA genotype to clinical characteristics of PD remains elusive. Mutant alleles of GBA can result in widespread deficiency of the enzymatic activity that might be involved in abnormal synuclein aggregation [1]. Besides, both histopathologic and positron emission tomography studies have suggested that GBA carriers were significantly more likely than noncarriers to have diffused Lewy bodies which might be associated with a higher prevalence and severity of cognitive impairment and neuropsychiatric characteristics [29, 30].

5. Conclusion

In conclusion, our results suggest that PD phenotype of GBA mutation carriers is more likely to appear with family history, earlier AAO, bradykinesia as an initial symptom, and presentation with dementia compared with those uncarrriers. Further studies, especially cofactors, matched single mutation of GBA, and its correspondent clinical data are needed to further illustrate the relationship.

Conflict of Interests

The authors declare that they have no financial disclosures.

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References

[1] M. Siebert, E. Sidransky, and W. Westbroek, “Glucocerebrosidase is shaking up the synucleinopathies,” Brain, vol. 137, no. 5, pp. 1304–1322, 2014.
[2] J. Aharon-Peretz, S. Badarny, H. Rosenbaum, and R. Gershoni-Baruch, “Mutations in the glucocerebrosidase gene and Parkinson disease: phenotype-genotype correlation,” Neurology, vol. 65, no. 9, pp. 1460–1461, 2005.
[3] S. E. Winder-Rhodes, J. R. Evans, M. Ban et al., “Glucocerebrosidase mutations influence the natural history of Parkinson’s disease in a community-based incident cohort,” Brain, vol. 136, no. 2, pp. 392–399, 2013.
[4] F.-Y. Hu, J. Xi, J. Guo et al., “Association of the glucocerebrosidase N370S allele with Parkinson’s disease in two separate Chinese Han populations of mainland China,” European Journal of Neurology, vol. 17, no. 12, pp. 1476–1478, 2010.
[5] A. J. Hughes, S. E. Daniel, L. Kilford, and A. J. Lees, “Accuracy of clinical diagnosis of idiopathic Parkinson’s disease: a clinicopathological study of 100 cases,” Journal of Neurology Neurosurgery and Psychiatry, vol. 55, no. 3, pp. 181–184, 1992.
[6] C. Wang, Y. Cai, Z. Gu et al., “Clinical profiles of Parkinson’s disease associated with common leucine-rich repeat kinase 2 and glucocerebrosidase genetic variants in Chinese individuals,” Neurobiology of Aging, vol. 35, no. 3, pp. 725.e1–725.e6, 2014.
[7] T. Pulkes, L. Choubtum, S. Chitphuk et al., “Glucocerebrosidase mutations in Thai patients with Parkinson’s disease,” Parkinsonism & Related Disorders, vol. 20, no. 9, pp. 986–991, 2014.
[8] M. Malec-Litwinowicz, M. Rudzińska, M. Szubiga, M. Michalski, T. Tomaszewski, and A. Szczudlik, “Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients,” Neurologia i Neurochirurgia Polska, vol. 48, no. 4, pp. 258–261, 2014.
[9] Y. Li, T. Sekine, M. Funayama et al., “Clinicogenetic study of GBA mutations in patients with familial Parkinson’s disease,” Neurobiology of Aging, vol. 35, no. 4, pp. 935.e3–935.e8, 2014.
[10] R. Asselta, V. Rimoldi, C. Siri et al., “Glucocerebrosidase mutations in primary parkinsonism,” Parkinsonism and Related Disorders, vol. 20, no. 11, pp. 1215–1220, 2014.
[11] K. R. Kumar, A. Ramirez, A. Göbel et al., “Glucocerebrosidase mutations in a Serbian Parkinson’s disease population,” European Journal of Neurology, vol. 20, no. 2, pp. 402–405, 2013.
[12] N. Kresojević, M. Mijajlović, S. Perić et al., “Transcranial sonography in patients with Parkinson’s disease with glucocerebrosidase mutations,” Parkinsonism and Related Disorders, vol. 19, no. 4, pp. 431–435, 2013.
[13] Y. Wang, L. Liu, J. Xiong et al., “Glucocerebrosidase L444P mutation confers genetic risk for Parkinson’s disease in central China,” Behavioral and Brain Functions, vol. 8, article 57, 2012.
[14] N. Setó-Salvia, J. Pagonabarraga, H. Houlden et al., “Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson’s Disease 9.
Parkinson's disease course,” *Movement Disorders*, vol. 27, no. 3, pp. 393–399, 2012.

[15] A. Emelyanov, T. Boukina, A. Yakimovskii et al., “Glucocerebrosidase gene mutations are associated with Parkinson's disease in Russia,” *Movement Disorders*, vol. 27, no. 1, pp. 158–159, 2012.

[16] B. de Carvalho Guimarães, A. C. Valente Pereira, F. da Costa Rodrigues et al., “Glucocerebrosidase N370S and L444P mutations as risk factors for Parkinson's disease in Brazilian patients,” *Parkinsonism and Related Disorders*, vol. 18, no. 5, pp. 688–689, 2012.

[17] R. N. Alcalay, E. Caccappolo, H. Mejia-Santana et al., “Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study,” *Neurology*, vol. 78, no. 18, pp. 1434–1440, 2012.

[18] S. Lesage, M. Anheim, C. Condroyer et al., “Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease,” *Human Molecular Genetics*, vol. 20, no. 1, pp. 202–210, 2011.

[19] C. L. Huang, Y.-H. Wu-Chou, S.-C. Lai et al., “Contribution of glucocerebrosidase mutation in a large cohort of sporadic Parkinson's disease in Taiwan,” *European Journal of Neurology*, vol. 18, no. 10, pp. 1227–1232, 2011.

[20] X.-Y. Mao, J.-M. Burgunder, Z.-J. Zhang et al., “Association between GBA L444P mutation and sporadic Parkinson's disease from Mainland China,” *Neuroscience Letters*, vol. 469, no. 2, pp. 256–259, 2010.

[21] Z. Gan-Or, A. Bar-Shira, A. Mirelman et al., “LRRK2 and GBA mutations differentially affect the initial presentation of Parkinson disease,” *Neurogenetics*, vol. 11, no. 1, pp. 121–125, 2010.

[22] M. P. Soclo, H. Bock, K. Michelin-Tirelli et al., “Parkinson's disease and the heterozygous state for glucocerebrosidase mutations among Brazilians,” *Parkinsonism & Related Disorders*, vol. 15, no. 1, pp. 76–78, 2009.

[23] E. V. De Marco, G. Annesi, P. Tarantino et al., “Glucocerebrosidase gene mutations are associated with Parkinson's disease in southern Italy,” *Movement Disorders*, vol. 23, no. 3, pp. 460–463, 2008.

[24] J. Chen, W. Li, T. Zhang et al., “Glucocerebrosidase gene mutations associated with Parkinson's disease: a meta-analysis in a Chinese population,” *PLoS ONE*, vol. 9, no. 12, Article ID e115747, 2014.

[25] J. F. Guo, K. Li, R. L. Yu et al., “Polygenic determinants of Parkinson's disease in a Chinese population,” *Neurobiology of Aging*, vol. 36, no. 4, pp. 1765.e1–1765.e6, 2015.

[26] A. Stang, “Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses,” *European Journal of Epidemiology*, vol. 25, no. 9, pp. 603–605, 2010.

[27] E. Sidransky, M. A. Nalls, J. O. Aasly et al., “Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease,” *The New England Journal of Medicine*, vol. 361, no. 17, pp. 1651–1661, 2009.

[28] Z. Gan-Or, N. Giladi, and A. Orr-Urtreger, “Differential phenotype in Parkinson's disease patients with severe versus mild GBA mutations,” *Brain*, vol. 132, no. 10, article e125, 2009.

[29] O. Goker-Alpan, J. C. Masdeu, P. D. Kohn et al., “The neurobiology of glucocerebrosidase-associated parkinsonism: a positron emission tomography study of dopamine synthesis and regional cerebral blood flow,” *Brain*, vol. 135, no. 8, pp. 2440–2448, 2012.

[30] J. Neumann, J. Bras, E. Deas et al., “Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease,” *Brain*, vol. 132, no. 7, pp. 1783–1794, 2009.