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MUTATIONS OF *GLUCOCEREBROSIDASE* GENE AND SUSCEPTIBILITY TO PARKINSON'S DISEASE: AN UPDATED META-ANALYSIS IN A EUROPEAN POPULATION

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Abstract—This meta-analysis aims to investigate the association between mutations of *glucocerebrosidase* (*GBA*) gene and susceptibility to Parkinson's disease (PD) in a European population. Several electronic databases were extensively searched. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the association. In total, fourteen published papers screening *L444P*, *N370S* and other *GBA* variants were identified. The *GBA* mutations were significantly associated with PD in the European population. Subgroup analysis stratified by the age of onset (AAO) revealed that the association between *GBA* mutations and PD existed in the patients with age at onset ⩽50 years but did not exist in the patients with age at onset >50 years. Furthermore, the associations between *N370S*, and *L444P* with PD were also analyzed to explore the roles of the two most frequent *GBA* mutations in the development of PD. The results showed that significant associations between *N370S*, and *L444P* with PD were observed, respectively. Overall, the study supported that *GBA* mutations were a risk factor for PD in the European population. Patients with early-onset were more likely to carry *GBA* mutations than those with late-onset. Moreover, both *L444P* and *N370S* were associated with increased PD risk.

Key words: meta-analysis, mutation, *glucocerebrosidase* (*GBA*), Parkinson's disease (PD), European, age at onset (AAO).

INTRODUCTION

Parkinson's disease (PD) is a common and complex progressive bradykinetic disorder that can be accurately diagnosed (Lees et al., 2009). Although the pathogenesis and exact cause of PD remains unclear, genetic and environmental influences have been proposed as critical factors for the onset and development of PD (Dumitriu et al., 2012). A number of susceptibility genes including mutations in *a-Synuclein* (*SNCA*), *leucine-rich repeat kinase 2* (*LRRK2*), *microtubule-associated protein tau* (*MAPT*) genes and other genomic loci were identified (Trinh and Farrer, 2013).

Glucocerebrosidase gene (*GBA*), located on chromosome1q21, encodes the enzyme glucocerebrosidase activity (Barneveld et al., 1983). The glucocerebrosidase enzyme hydrolyzes glucocerebroside to glucose and ceramide. Mutations in the *GBA* gene can cause deficiency of glucocerebrosidase enzyme, leading to an intracellular accumulation of glucocerebroside within the lysosomes (Grabowski, 1993). Up to now, there are approximately 335 mutations that have been reported in the *GBA* gene, with most of them considered to cause the loss of enzyme function (Human Gene Mutation Database, HGMD http://www.hgmd.cf. ac.uk/ac/index/.php). Among the reported variants, the two most common and clinically important mutations are *N370S* and *L444P* (Eblan et al., 2006; Nishioka et al., 2010; Lesage et al., 2011b; Choi et al., 2012; Emelyanov et al., 2012; Kumar et al., 2013). It remains unknown how *GBA* mutations increase the risk of PD. Aharon-Peretz suggested that the underlying causes of *CBA* mutations leading to Parkinson's disease were likely to be related to the faulty processing of toxic, unwanted proteins, exacerbation of the relative decrease in glucocerebrosidase activity and accumulation of glucocerebroside (Aharon-Peretz et al., 2004).

To date, numerous case–control studies were conducted to investigate the possible role of *GBA* mutations in the pathogenesis of PD among various ethnic populations (Lwin et al., 2004; Clark et al., 2005; Gan-Or et al., 2008; Spitz et al., 2008; Bras et al., 2009; Mitsui et al., 2009; Moraitou et al., 2011; Wang et al., 2012). However, the results were inconsistent. Although meta-analysis and multi-center studies have arrived at a positive conclusion that *GBA* mutations were associated with PD (Sidransky et al., 2009; Mao et al., 2013; Chen et al., 2014; Liu and Zhang, 2014), there were limitations

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Abbreviations: AAO, age at onset; CIs, confidence intervals; *GBA*, *glucocerebrosidase*; *LRRK2*, *leucine-rich repeat kinase 2*; *MAPT*, *microtubule-associated protein tau*; NOS, Newcastle–Ottawa Scale; ORs, odds ratios; PD, Parkinson's disease; *SNCA*, *a-Synuclein*.

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present and new issues emerged. For instance, *N370S* and *L444P* may exert a large effect on the susceptibility of PD, but the association between the two mutations and PD risk varied in different ethnic groups (Aharon-Peretz et al., 2004; Eblan et al., 2006; Toft et al., 2006; De Marco et al., 2008, Noreau et al., 2011; Lesage et al., 2011a; Gonzalez-Del Rincon Mde et al., 2013). Furthermore, the relationship between age at onset (AAO) and *GBA* mutations has not been clearly established (De Marco et al., 2008; Kalinderi et al., 2009; Emelyanov et al., 2012; Duran et al., 2013). Several studies concerning the above issues have been performed in the European population, but have not been comprehensively expounded. Therefore, the meta-analysis was conducted to draw a more comprehensive association between *GBA* mutations and PD risk coupled with the relationship between *GBA* mutations and the age at onset of PD in the European population.

EXPERIMENTAL PROCEDURES

Data source and search strategy

Published studies were extensively searched through Pubmed, The Google Scholar, Springer Link and Elsevier. The following search terms were used: "*glucocerebrosidase*", "*GBA*" and "Parkinson's disease", "PD", "Parkinson disease" in combination with "variant", "mutation", "polymorphism". The last search was updated on 6 March 2015.

Inclusion and exclusion criteria

Each potentially eligible study was checked to guarantee that they all met the following inclusion criteria. The inclusion criteria included: (1) involving the associations between *GBA* mutations and PD in the European population; (2) providing complete data on genotype number or frequency of cases and controls for calculating odd ratios (ORs) and 95% confidence intervals (CIs); (3) case–control studies. The exclusion criteria were as follows: (1) a case report or a comment or a review; (2) not reporting the complete genotype frequencies. If studies contained overlapping data, only the most recent study was included in this meta-analysis.

Data extraction

The following information was extracted from eligible studies included in the final meta-analysis: name of the first author, year of publication, country of study population, screened mutations, mutation carriers of cases and controls and the frequency of *N370S* and *L444P* mutations.

Statistical analyses

The qualities of case–control studies in the present meta-analysis were assessed by the Newcastle–Ottawa Scale (NOS) (Wells et al., 2015). Odds ratio (OR) and 95% confidence interval (95% CI) were applied to measure the association between *GBA* mutations and PD risk with a random effect model. The chi-squared (x^2) test and I^2 statistics were calculated to quantify the heterogeneity. $I^2 > 50\%$ indicated an obvious between-study heterogeneity. To better understand the effect of *GBA* mutations on the age at onset of PD, the subgroup was categorized as early-onset PD and late-onset PD (early-onset $\leqslant$50 years; late-onset $>$50 years). The associations between *N370S*, *L444P* and PD were also investigated to explore the impact of the two most frequent *GBA* variants on the development of PD. In addition, sensitivity analyses were undertaken to assess the stability of the meta-analysis results. Finally, the potential publication bias was identified using Begg's and Egger's test (Egger et al., 1997). The statistical analyses were conducted with Stata 11.0 (StataCrop, College Station, TX, USA). All the *p* values were two sided, and less than 0.05 were considered statistically significant.

RESULT

Characteristics and qualities of eligible studies

A comprehensive process for searching qualified studies is shown in Fig. 1. At least 314 studies were collected through extensive research. After careful selection, 14 eligible studies encompassing 7555 cases and 7057 controls, which examined *L444P*, *N370S* and other *GBA* mutations such as *D409H*, *E326K*, *H255Q*, *RecNcil* were included in this meta-analysis (Toft et al., 2006; De Marco et al., 2008; Mata et al., 2008; Bras et al., 2009; Kalinderi et al., 2009; Neumann et al., 2009; Dos Santos et al., 2010; Moraitou et al., 2011; Lesage et al., 2011a; Seto-Salvia et al., 2012; Duran et al., 2013; Kumar et al., 2013; Nalls et al., 2013; Asselta et al., 2014). The quality of the studies showed a mean score of 6 (range 3–7), indicating the high overall quality of the studies. Among cases and controls, a total of 414 *GBA* mutations (lumped together any mutation in cases)

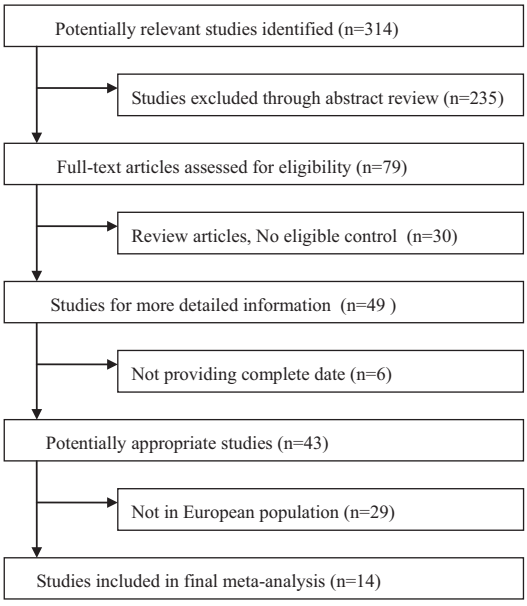

Fig. 1. Flow chart showing the explicit process for identifying qualified studies.