Meta-analyses of seven *GIGYF2* polymorphisms with Parkinson's disease

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Abstract. Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects ~2% of the global population aged ≥65 years. Grb10-interacting GYF protein-2 (GIGYF2) can influence the development of PD through the regulation of insulin-like growth factor-1. The aim of the present meta-analysis study was to establish the contribution of *GIGYF2* polymorphisms to PD. The study was conducted based on nine eligible studies consisting of 7,246 PD patients and 7,544 healthy controls. The results indicated that the *GIGYF2* C.3630A>G polymorphism increased the risk of PD by 37% [P=0.008; odds ratio (OR), 1.37; 95% confidence interval (CI), 1.08-1.73] and that the *GIGYF2* C.167G>A polymorphism was significantly associated with PD (P=0.003; OR, 3.67; 95% CI, 1.56-8.68). The meta-analyses of the other five *GIGYF2* polymorphisms (C.1378C>A, C.1554G>A, C.2940A>G, C.1370C>A and C.3651G>A) did not reveal any significant associations. The present meta-analyses of the *GIGYF2* genetic polymorphisms may provide a comprehensive overview of this PD candidate gene for future studies.

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Introduction

Parkinson's disease (PD; OMIM: 168600) is the second most common neurodegenerative disorder, affecting ~2% of the global population aged ≥65 years (1,2). The clinical features of PD consist of resting tremor, muscular rigidity, bradykinesia and postural instability (3). PD can lead to pain (4), depression (5,6), visual hallucinations (6), dementia (7) and other non-motor symptoms (8-11). PD can cause damage and can even cause the human body to collapse.

The pathogenesis of PD is known to be associated with environmental and genetic factors. The environmental hypothesis of PD was popular in the 20th century (3). A number of environmental factors were found to be significantly associated with PD, including oxidative stress (12), smoking (13) and environmental toxins (14). In addition, genetic factors play an essential role in this complex disease. Twin (15) and family (16) studies have shown a higher PD susceptibility in twins and the first-degree relatives, respectively. Genome-wide linkage analysis provided evidence that the gene-by-gene interactions are important in PD susceptibility (17). A number of genetic markers have been identified for the risk of PD (18) and were shown to be potential therapeutic targets to PD (19,20).

Grb10-interacting GYF protein-2 (*GIGYF2*) is located within the PARK11 locus, an established locus of PD (21). The Grb10 adapter protein interacts with GIGYF2, which regulates the insulin-like growth factor-1 (IGF-1), stimulating the growth of the insulin signal (22,23). The IGFs affect the development of the nervous system by preventing the apoptosis of neuronal and brain-derived cells (24-26). A previous study found an association between serum IGF-1 and the progression of motor symptoms in the early stage of PD (27). In addition, IGF-1 was shown to correlate with the clinical variables and diagnosis of PD (27-29). Therefore, *GIGYF2* may be a candidate factor for the risk of PD through its interaction with IGF-1.

Previously, several studies have performed an association study between the *GIGYF2* polymorphisms and PD (30-43). Among them, four studies showed a positive association of the *GIGYF2* polymorphisms with PD (30-33), whereas the

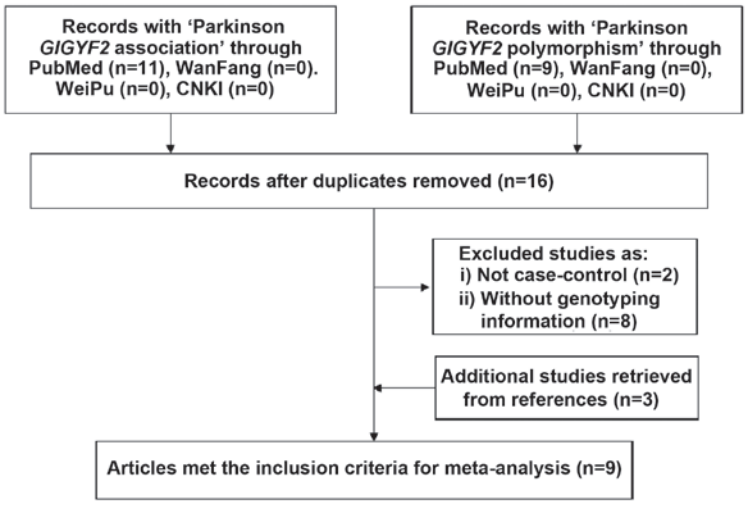

Figure 1. Flowchart of the meta-analyses selection process.

other 10 studies showed a negative association (34-43). These inconsistent results indicated that the exact role that *GIGYF2* played in the pathophysiology of PD remains to be elucidated. Meta-analysis is able to enhance the reliability of the conclusion from individual studies by combining the data from various studies. To determine the genetic effect of *GIGYF2* on PD, a comprehensive meta-analysis was performed among various case-control association studies with available genotypic and allelic frequencies.

Materials and methods

Data collection. Studies were selected from PubMed using the following key words: 'Parkinson *GIGYF2* association' and 'Parkinson *GIGYF2* polymorphism'. Eligible studies for the meta-analysis were required to meet the following criteria: i) An original case-control study with the assessment of the association between *GIGYF2* and PD; ii) the study provides enough data for obtaining or calculating the odds ratios (ORs) and 95% confidence intervals (CIs) with the data of the study; iii) contains genotype distribution of each polymorphism that meet the Hardy-Weinberg equilibrium (HWE); and iv) the study is involved with polymorphisms reported by >3 independent studies. As shown in the previous studies (44-47), the following information was extracted or calculated from each study: Genetic locus, first author's name, year of publication, country, numbers of cases and controls, ethnicity, reported association results, power of each case-control study and the minor allele frequency (MAF) of controls.

Statistical analysis. HWE was tested by the Arlequin program (48). The power of each study was calculated by the Power and Sample Size Calculation program. Statistical heterogeneity across the studies included in the meta-analysis was assessed by Cochran's Q statistic and I^2 test (49) to determine the type of analysis. In the meta-analysis, the fixed-effect model was used for the studies with minimal to moderate heterogeneity (I^2<50%) and the random-effect model was used for the studies with significant heterogeneity (I^2≥50%). Funnel plots were also generated to observe the potential publication bias. The statistical analyses of meta-analyses were performed in Review Manager 5 (50).

Results

Associations between PD and GIGYF2 polymorphisms. As shown in Fig. 1, 20 studies regarding the association of *GIGYF2* with PD were obtained from PubMed. There were no relevant studies found in the Chinese database WanFang, WeiPu and China National Knowledge Infrastructure. In total, four duplicates, two non-case-control and eight without genotyping information studies were removed and three studies were added that were obtained from the references. Therefore, there were nine studies selected regarding seven *GIGYF2* polymorphisms, which were C.1378C>A, C.167G>A, C.1554G>A, C.2940A>G, C.1370C>A, C.3630A>G and C.3651G>A (Table I). In particular, there were six studies with 2,281 cases and 1,815 controls for C.1378C>A, five with 5,519 cases and 6,316 controls for C.167G>A, four with 1,611 cases and 1,460 controls for C.1554G>A, four with 1,611 cases and 1,460 controls for C.2940A>G, three with 3,876 cases and 4,688 controls for C.1370C>A, three with 1,311 cases and 1,260 controls for C.3630A>G and three studies with 1,311 cases and 1,260 controls for the C.3651G>A.

A significant association was found between the C.3630A>G (P=0.008; OR, 1.37; 95% CI, 1.08-1.73; Table II; Fig. 2) and C.167G>A (P=0.003; OR, 3.67; 95% CI, 1.56-8.68; Table II; Fig. 2) polymorphisms and PD. There were no other positive results in the remaining allelic analysis (P>0.05; Table II; Fig. 2). Low heterogeneity was found for C.1378C>A (I^2=0%), C.167G>A (I^2=41%), C.3651G>A (I^2=0%), C.1370C>A (I^2=0%), C.3630A>G (I^2=28%) and C.2940A>G (I^2=40%). By contrast, a significant statistical heterogeneity was observed in the meta-analysis of C.1554G>A (I^2=82%). There was no publication bias for all the meta-analyses (Fig. 3).

As shown in Tables I and II, the present meta-analyses showed a much stronger power than for each of the individual studies. There was sufficient power (Power>0.8) for the meta-analyses of C.2940A>G (Power=0.885) and C.3651G>A (Power=0.824). By contrast, relatively lower

Table I. Characteristics of the case-control studies in the current meta-analyses.

First author	Year	Country	Cases/controls	Ethnicity	Results[a]	Power	MAF	(Refs.)
GIGYF2 C.1378C>A								
Lautier	2008	Italy	249/227	European	NS	0.068	0.0198	(40)
Guo	2009	USA	310/120	European	NS	0.053	0.0167	(33)
Cao	2010	China	510/481	Asian	NS	0.313	0.1455	(35)
Guella	2011	Italy	552/552	European	NS	0.114	0.0281	(54)
Wang	2011	China	300/200	Asian	NS	0.207	0.1975	(30)
Meeus	2011	Belgium	305/360	European	NS	0.112	0.0680	(43)
GIGYF2 C.167G>A								
Lautier	2008	Italy	249/227	European	NS	NA	0.0000	(40)
Zimprich	2009	Austria	699/1051	European	NS	0.056	0.0005	(38)
Bonetti	2009	Italy	2928/3410	European	NS	0.053	0.0001	(41)
Vilarino-Guell	2009	Norway & USA	1338/1268	European	S	NA	0.0000	(42)
Meeus	2011	Belgium	305/360	European	NS	0.059	0.0056	(43)
GIGYF2 C.1554G>A								
Lautier	2008	Italy	249/227	European	NS	0.083	0.0352	(40)
Cao	2010	China	510/481	Asians	S	0.254	0.1071	(35)
Wang	2011	China	300/200	Asian	NS	0.197	0.1825	(30)
Guella	2011	Italy	552/552	European	NS	0.147	0.0426	(54)
GIGYF2 C.2940A>G								
Lautier	2008	Italy	249/227	European	NS	0.264	0.3194	(40)
Cao	2010	China	510/481	Asian	NS	0.298	0.1351	(35)
Wang	2011	China	300/200	Asian	S	0.275	0.3550	(30)
Guella	2011	Italy	552/552	European	NS	0.505	0.2870	(54)
GIGYF2 C.1370C>A								
Lautier	2008	Italy	249/227	Europeans	NS	NA	0.0000	(40)
Zimprich	2009	Austria	699/1051	European	NS	0.059	0.0014	(38)
Bonetti	2009	Italy	2928/3410	European	NS	0.053	0.0006	(41)
GIGYF2 C.3630A>G								
Lautier	2008	Italy	249/227	European	NS	0.070	0.0220	(40)
Cao	2010	China	510/481	Asian	S	0.297	0.1341	(35)
Guella	2011	Italy	552/552	European	NS	0.056	0.0027	(54)
GIGYF2 C.3651G>A								
Lautier	2008	Italy	249/227	European	NS	0.223	0.2247	(40)
Cao	2010	China	510/481	Asian	NS	0.335	0.1611	(35)
Guella	2011	Italy	552/552	European	NS	0.463	0.2391	(54)

[a]Association of *GIGYF2* with Parkinson's disease. MAF, minor allele frequency; *GIGYF2*, Grb10-interacting GYF protein-2; NS, no significant; NA, not applicable; S, significant.

power values were found for the meta-analyses of C.1378C>A (Power=0.634), C.1554G>A (Power=0.547), C.3630A>G (Power=0.357), C.167G>A (Power=0.063) and C.1370C>A (Power=0.065).

Discussion

GIGYF2 is potentially involved in the pathogenesis of PD due to the effect of IGF-1 in the insulin signaling in the central nervous system (51-53). In the present study, a meta-analyses was performed among 7,246 cases and 7,544 controls to evaluate the association between seven polymorphisms of *GIGYF2* and PD.

An increased risk of PD by 37% was observed for C.3630A>G. *GIGYF2* C.3630A>G is a key polymorphism in the previous PD studies (35,40,54). Since the power of C.3630A>G was moderate, further studies should be conducted to confirm this positive finding. The C.3630G allele frequency was 13.4% in the Asian population, which was much higher compared to the European population (Table I), although a low heterogeneity was found for this polymorphism. In addition, meta-analysis of C.167C>A from five studies (38,40-43) was also shown to be significantly associated with the risk of PD. No significant association was found for the other five *GIGYF2* polymorphisms, which

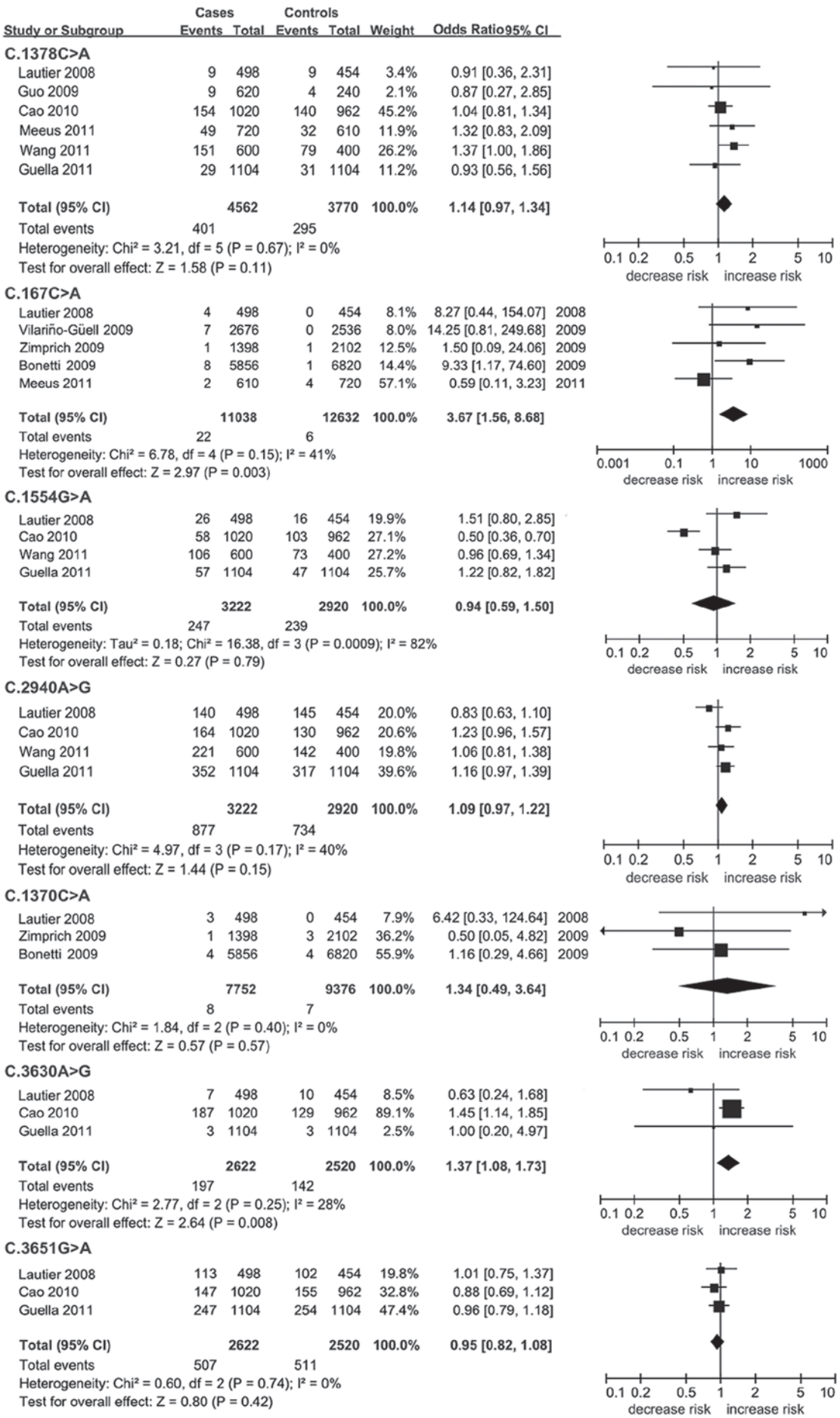

Figure 2. Forest plots of the *GIGYF2* polymorphisms with Parkinson's disease. *GIGYF2*, Grb10-interacting GYF protein-2; CI, confidence interval.

Table II. Meta-analyses of the *GIGYF2* polymorphisms with Parkinson's disease.

Genetic locus	Cases/controls	Genetic model	S	OR (95% CI)	P-value	I^2, %	Power
GIGYF2 C.1378C>A	2281/1815	Overall (C vs. A)	6	1.14 (0.97-1.34)	0.110	0	0.634
GIGYF2 C.167C>A	5519/6316	Overall (G vs. A)	5	3.67 (1.56-8.68)	0.003[a]	41	0.063
GIGYF2 C.1554G>A	1611/1460	Overall (G vs. A)	4	0.94 (0.59-1.50)	0.790	82	0.526
GIGYF2 C.2940A>G	1611/1460	Overall (A vs. G)	4	1.09 (0.97-1.22)	0.150	40	0.885
GIGYF2 C.1370C>A	3876/4688	Overall (C vs. A)	3	1.34 (0.49-3.64)	0.570	0	0.065
GIGYF2 C.3630A>G	1311/1260	Overall (A vs. G)	3	1.37 (1.08-1.73)	0.008[a]	28	0.347
GIGYF2 C.3651G>A	1311/1260	Overall (G vs. A)	3	0.95 (0.82-1.08)	0.420	0	0.769

[a]P≤0.05. *GIGYF2*, Grb10-interacting GYF protein-2; S, amount of studies; OR, odds ratio; CI, confidence interval.

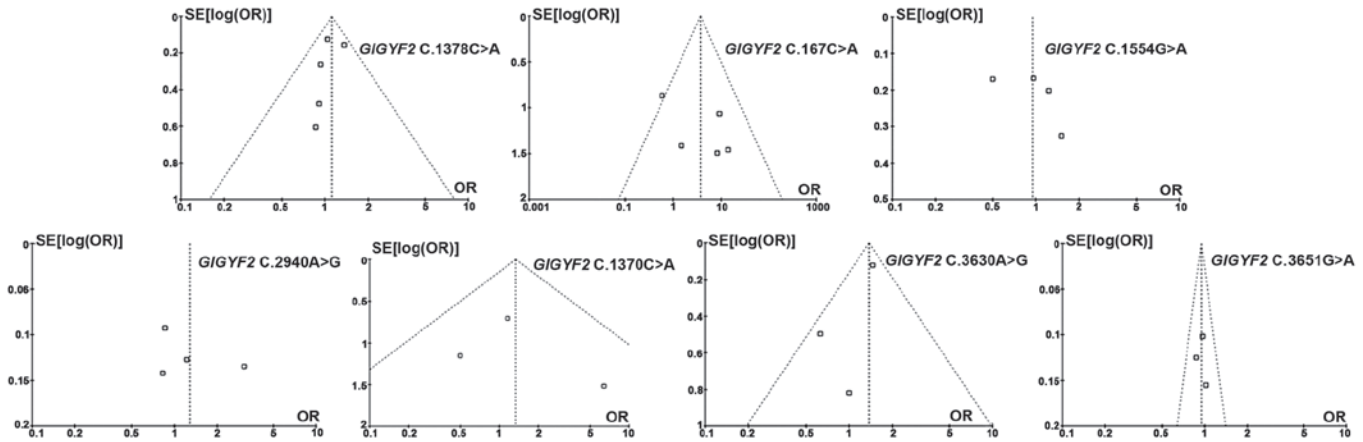

Figure 3. Funnel plots of the *GIGYF2* polymorphisms with Parkinson's disease. *GIGYF2*, Grb10-interacting GYF protein-2; SE, standard error; OR, odds ratio.

were C.1378C>A, C.1554G>A, C.2940A>G, C.1370C>A and C.3651G>A. The power was strong in the association studies of C.2940A>G and C.3651G>A polymorphisms, but was relatively weak for the remaining three polymorphisms, which were C.1378C>A, C.1554G>A and C.1370C>A. A significant difference was found between ethnicities for the C.1378C>A polymorphism (Fst=0.192), although there was minimal heterogeneity according to the meta-analysis of this polymorphism.

Several limitations of the present meta-analysis should be taken with caution. Firstly, only nine studies were included in the meta-analysis. The power values of the meta-analyses were low due to the MAF of certain polymorphisms. Secondly, PD is a complex and growing disease with a different physiological status existing in the PD cases. As the pathogenesis of familial and sporadic PD are not identical (55), family history as an independent risk factor for PD (56) should be emphasized in PD association studies. There were at least 1,818 sporadic and 861 familial PD patients involved in the present meta-analysis. Notably, two studies did not provide the information (41,42). A previous study strongly supported that *GIGYF2* was a causal factor of PD in the familial study (40). However, other studies showed a lack of association in sporadic PD studies (33,35,54). Subgroup analysis by the PD family history is required to establish the role of genetic factors in the pathogenesis of PD. Thirdly, only seven polymorphisms of *GIGYF2* were investigated, which may not fully reflect the function of *GIGYF2* in PD. There are 9571 variants in the *GIGYF2* according to the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/snp/?term=GIGYF2). Certain other variants, including C.684T>A, C.1219A>G and C.3583C>T, have been reported to be significantly associated with PD (37). In the present meta-analysis, those variants were not included due to a lack of relative information.

In conclusion, the present study found that the *GIGYF2* C.3630A>G and C.167G>A polymorphisms were associated with PD. Future investigations of other ethnic populations are required to establish the contribution of *GIGYF2* to the risk of PD.

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