

# A meta-analysis of leucine-rich repeat kinase 2 (LRRK2) polymorphisms in Alzheimer's disease

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## Abstract

Pathogenesis and the development of Alzheimer's disease (AD) are subject to several environmental and genetic factors. This study was aimed to estimate the frequency of mutations in leucine-rich repeat kinase 2 (*LRRK2*) gene to examine the association between these mutations and risk of AD. For finding the articles, four databases including PubMed, Web of Science, Scopus, and Cochrane Library were checked up to August 2018. An analysis was done by RevMan 5.3 using crude odds ratio (OR) and 95% confidence intervals (CIs) to determine the association between *LRRK2* polymorphisms and the risk of AD. Of 359 articles identified in the databases, 13 studies were included and analysed in the meta-analysis. There was no significant risk of AD related to five *LRRK2* polymorphisms (*rs33949390*, *rs34778348*, *rs7308720*, *rs34637584*, and *rs35870237*). The results showed that *LRRK2* variants (*p.R1628P*, *p.G2385R*, *p.N551K*, *p.G2019S*, and *p.I2020T*) were not associated with the risk of AD and were not a common cause of AD in populations. Nevertheless, *p.R1628P* can be examined in patients with AD in other populations in the future studies.

**Key words:** Alzheimer's disease, *LRRK2*, variants, polymorphism, meta-analysis.

## Introduction

Alzheimer's disease (AD) is the leading neurodegenerative disease worldwide [12] and a common neurogenic disorder that mainly results in severe memory loss in the elderly (> 60 years) [14]. At present, there is no effective preventive treatment for AD [12]. AD is the most popular cause of dementia in the elderly and is considered a multifactorial disorder [19,21]. AD is largely sporadic although early-onset familial AD can represent up to 5% of the AD cases assessed in memory clinics [3]. The pathogenesis and development of AD include multiple envi-

ronmental and genetic factors [14]. Leucine-rich repeat kinase 2 (*LRRK2*), also recognized as dardarin, depends on the Roco family of the Ras/GTPase super family [22]. Mutations of *LRRK2* are the most popular genetic reason for Parkinson's disease (PD) [22] and it has been assumed they are also central factors in the AD pathogenesis [20]. Two polymorphic variants of dardarin, including G2385R and R1628P, have previously been reported to have a relative risk of 1.9 of PD development in Chinese patients [4]. The purpose of this study was to calculate the frequency of mutations in the *LRRK2* gene to investigate the association between the mutations and AD risk.

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## Material and methods

### Strategy of search

The Web of Science, PubMed, Scopus, and Cochrane Library databases were searched up to August 2018 using the search terms (“Alzheimer’s disease” or “Alzheimer disease”; “LRRK2” or “Leucine-rich repeat kinase 2”; and polymorphism or variant\* or gene or mutation\*) without language restriction.

### Eligibility criteria

One reviewer (M.S.) searched the articles and checked the titles, abstracts and then full texts of the studies to select the relevant studies based on the eligibility criteria. Another reviewer (R.F.) re-checked full texts. The inclusion criteria were the studies: 1) with case-control and cohort design; 2) including *LRRK2* polymorphisms (p.G2385R, p.R1628P, p.N551K, p.G2019S, or p.I2020T); 3) reporting the patients with AD; 4) reporting allele or genotype distributions; and 5) including AD diagnosis based on the protocols of NINCDS-ADRDA defined in the

Tamaoka’s study [16]. The exclusion criteria were: 1) animal studies; 2) reviews; and 3) case reports.

### Data extraction

Two reviewers (M.S. and R.F.) independently took out the data, including the surname of the first author, location of participants, publication year, source of controls, allele and genotype distribution of NSCL/P and controls, and genotyping method.

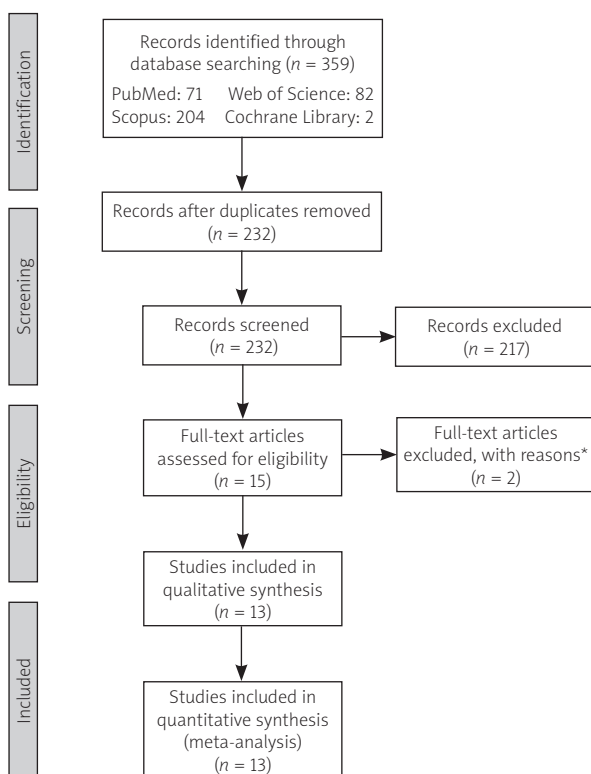
### Statistical analysis

An analysis was done by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) using crude odds ratio (OR) and 95% confidence intervals (CIs) to determine the strength of association between *LRRK2* polymorphisms and the risk of AD. The association was determined under the following five genetic models of the allelic, the homozygote, the heterozygote, the dominant, and the recessive. The significance of the pooled OR was evaluated when  $p < 0.05$ . Heterogeneity across studies was evaluated using both Cochrane Q test and  $I^2$  statistic. There was statistically significant heterogeneity if  $p < 0.1$  or  $I^2 > 50\%$ . If no significant heterogeneity was found, the fixed-effect model was used to calculate the values. In any other way, the random-effect model was applied.

## Results

A total of 359 articles were shown in the databases. After excluding the non-eligible articles, 13 studies were included and analysed in the meta-analysis (Fig. 1).

The information of the articles involved in the meta-analysis is shown in Table I. Four studies [8,10,17,21] reported the patients/controls from Singapore, two studies [1,9] from China, and also Taiwan [2], England [11], Brazil [15], Norway [19], Italy [18], Europe/South America [5], and the USA [20], one study each. Four studies [1,2,9,17] checked the distributions of rs34778348 polymorphism, three studies [1,9,21] rs33949390 polymorphism, and two studies [1,9] rs7308720 polymorphism in the patients with AD and the controls. Out of seven studies [1,5,8,15,18-20] reporting the distributions of rs34637584 polymorphism, just two studies [1,5] reported this polymorphism in the patients with AD and the controls. Out of two studies [1,8] reporting rs35870237 polymorphism, just one study [1] reported this polymorphism in both groups. A total number of genotypes of each poly-



\*1 study was a case report, 1 study was a review article

Fig. 1. Flow-chart of the study selection.

**Table I.** Characteristics of the studies included in the meta-analysis

The first author, year	Location of participants	Source of controls	Genotype method	SNP cDNA Gene	Genotype	Case	Control
Bi, 2014 [1]	China	HB	PCR-SBE	Rs34778348 7153G>A G2385R	GG/AG/AA	1353/72/0	1651/88/3
Li, 2013 [9]	China	PB	PCR-RFLP				
Chang, 2010 [2]	Taiwan	PB	PCR-MALDI-TOF MS				
Tan, 2009 [17]	Singapore	HB	PCR				
Bi, 2014 [1]	China	HB	PCR-SBE	Rs33949390 4883G>C R1628P	GG/CG/CC	1203/42/0	1966/61/20
Li, 2013 [9]	China	PB	PCR-RFLP				
Zhao, 2011 [21]	Singapore	HB	PCR				
Patel, 2017 [11]	England	PB	PCR	Rs7308720 1653C>G N551K	CC/CG/GG	667/132/4	673/126/3
Ng, 2017 [10]	Singapore	HB	PCR				
Toft, 2005 [19]	Norway	NCG	PCR-TaqMan	Rs34637584 6055G>A G2019S	GG/AG/AA	2771/1/0	3499/0/0
Santos-Rebouças, 2009 [15]	Brazil	NCG	–				
Zabetian, 2006 [20]	USA	NCG	PCR-TaqMan				
Bi, 2014 [1]	China	HB	PCR-SBE				
Tedde, 2007 [18]	Italy	NCG	PCR				
Lee, 2006 [8]	Singapore	NCG	PCR				
Hernandez, 2005 [5]	Europe/South America	PB	PCR-TaqMan				
Bi, 2014 [1]	China	HB	PCR-SBE	Rs35870237 6059T>C I2020T	TT/CT/CC	763/0/0	819/0/0
Lee, 2006 [8]	Singapore	NCG	PCR				

SNP – single nucleotide polymorphism, PB – population-based, HB – hospital-based, NCG – no control group, MALDI-TOF – matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, SBE – single-base extension, PCR – polymerase chain reaction

morphism based on the included studies is shown in Table I. For two other polymorphisms (rs34637584 and rs35870237), we could not use the genetics models.

The risk of AD related to LRRK2 rs34778348, rs33949390, and rs7308720 polymorphisms based on five genetic models is shown in supplementary Figures 2-4, respectively. The pooled results have been summarized in Table II. There was no significant risk of AD related to three LRRK2 polymorphisms (rs34778348, rs33949390, and rs7308720). Also, based on Table I, there was no significant risk of AD related to two other LRRK2 polymorphisms (rs34637584 and rs35870237).

## Discussion

It is interesting to consider that the mutations of *LRRK2* have been linked with AD-like pathology [22] and also with the activation of programmed cell death signalling including the FADD/caspase-8 metabolic pathways [6].

This meta-analysis evaluated the correlation of LRRK2 mutations with the AD risk. The results showed that rs34778348, rs33949390, rs7308720, rs34637584, and rs35870237 polymorphisms had no association with the risk of AD. Among the studies involved in the meta-analysis, two studies [1,21]

**Table II.** The analysis of risk of Alzheimer’s disease (AD) related to leucine-rich repeat kinase 2 (LRRK2) mutations

SNP ID	A vs. G			AA vs. GG			AG vs. GG			AA + AG vs. GG			AA vs. AG + GG		
	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>
Rs34778348	0.94 (0.69, 1.28)	0	0.52	0.18 (0.01, 3.50)	–	–	1.00 (0.73, 1.38)	0	0.70	0.97 (0.71, 1.33)	0	0.60	0.18 (0.01, 3.53)	–	–
	C vs. G			CC vs. GG			CG vs. GG			CC + CG vs. GG			CC vs. CG + GG		
	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>
Rs33949390	1.07 (0.41, 2.77)	79	0.009	–	–	–	1.07 (0.41, 2.83)	79	0.008	1.07 (0.41, 2.83)	79	0.008	–	–	–
	G vs. C			GG vs. CC			CG vs. CC			GG + CG vs. CC			GG vs. CG + CC		
	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>	OR (95%CI)	I <sup>2</sup> (%)	P <sub>h</sub>
Rs7308720	1.06 (0.77, 1.47)	9	0.3	1.11 (0.27, 4.66)	0	0.92	1.04 (0.79, 1.36)	0	0.38	1.04 (0.80, 1.36)	0	0.33	1.10 (0.26, 4.61)	0	0.94

reported that p.R1628P (rs33949390) mutation was significantly linked with the risk of AD in Chinese and Singaporean individuals; whereas, another study [9] reported a significant protective role of this polymorphism in the Han Chinese population. With regard to other polymorphisms, no study showed a significant relationship between them and the risk of AD.

The p.G2019S mutation occurs at a frequency of around 1.3% in PD patients (0.7% in sporadic and 3% in familial PD) and 0.06% in controls [7]. The frequency of this mutation in patients with PD changes from 0 in Chinese to 41% in North African Arabs populations across the world [13]. The variant of p.G2385R is an idea to be “East Asian”-specific, specifically in Han Chinese and Japanese populations [2]. Zhao *et al.* [21] showed that the p.R1628P increments the risk of AD around two-fold in the Singaporean population. Lee *et al.* [8] reported that p.I2020T mutation was found to be a cause of autosomal dominant PD family in Japan, but the prevalence of p.G2019S might be different among ethnic races. The p.N551K is in connection disequilibrium with p.R1398H. It is possible that its protective action is controlled mainly by p.R1398H [10]. Four studies [1,2,9,17] reporting p.G2385R (Rs34778348) mutation among 1425 patients with AD and 1742 controls showed that the mutation occurred in 72 patients (4.2%) and 91 controls (5.2%). The p.R1628P (rs33949390) mutation in 1245 patients with AD and 2050 controls included 42

patients (3.4%) and 81 controls (3.9%) based on two studies included in the meta-analysis [1,9,21]. Two studies [10,11] reported that the p.N551K (rs7308720) mutation occurred in 16.9% of patients with AD and 16.1% of controls. Seven studies [1,5,8,15,18-20] included 2772 patients and 3499 controls and found that p.G2019S (rs34637584) mutation occurred in 0.36% of patients and none of controls. In addition, p.I2020T (rs35870237) mutation was reported in none of the patients and controls. The studies were reported in few populations, which can be one of the most important limitations of this study.

### Conclusions

This meta-analysis concluded that the LRRK2 polymorphisms (p.G2385R, p.R1628P, p.N551K, p.G2019S, and p.I2020T) could not be associated with the risk of AD and were not a common cause of AD in populations. Nevertheless, p.R1628P can be examined in patients with AD in other populations in future studies.

### Note

The Figures 2-4 are included as a data supplement available with the online version of this article.

### Disclosure

The authors report no conflict of interest.

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