



**Systematic review of genetic variants associated with cognitive impairment and depressive symptoms in Parkinson's disease**

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3 in regards to the genetic associations of depression in the context of PD. Serotonin and  
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5 dopamine are the two important neurotransmitters that are involved in the pathophysiology of  
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7 depression. Their levels in synaptic clefts are regulated by neurotransmitter transporters, and  
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9 it is the genetic variations of these transporters that are hypothesised as potential risk factors  
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11 for depression in PD. Where the serotonin transporter gene (*SLC6A4*) has been extensively  
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13 studied as a genetic risk factor for depression in people without PD (19), the dopamine  
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15 transporter gene (*SLC6A3*) has been examined as a potential candidate gene for depression in  
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17 PD (20). Additionally, variants in the parkin gene (*PARK2*) have also been shown to  
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19 contribute to a heightened risk of both depression and anxiety in people with PD, especially  
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21 to those with early onset PD (21).  
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27 There are currently no systematic reviews that comprehensively summarise the  
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29 relevant literature regarding the effects of genetic variants on non-motor symptoms in PD.  
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31 This systematic review will be the first to provide a cohesive summary of all genetic  
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33 association studies that have investigated the genetic factors associated with cognitive  
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35 impairment and depression in people with PD. This review aims to enhance the  
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37 understanding of the neurobiology underlying cognitive impairment and depression in people  
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39 with PD.  
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## 45 **Materials and Methods**

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48 **Study design:** The protocol of this systematic review has been registered (PROSPERO  
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50 protocol registration number: CRD42017067431), and is available online  
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52 ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42017067431](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017067431)).  
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55 **Inclusion Criteria:** All articles studying human participants with a clinical diagnosis of  
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57 Parkinson's disease, irrespective of their age, and gender, were considered. Animal studies  
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59 and invitro studies were excluded. Studies that investigated common and rare genetic  
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3 variations as well as cognitive impairment and/or depressive symptoms as outcome were  
4 included. Therefore, genetic association studies that did not include either of these as  
5 outcome variables were excluded. All relevant cohort studies, case controls, and case series  
6 were included. Studies were not excluded because of their controls or the lack of them.  
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12 **Search strategy:** A systematic search was carried out in January 2019 using the following  
13 five databases: PubMed (1996-Present), PsycINFO (1806-present), CINAHL (1981-present),  
14 EMBASE (1974-present) and OpenGrey. The search strategy was comprised of both  
15 'Population' AND 'Exposure' AND 'Outcome' terms. These terms were searched for in the  
16 titles, abstracts, and full texts. 'Parkinson\*' was the population search term. The exposure  
17 search terms that were included: 'Gene\*', OR 'LRRK2', OR 'GBA', OR 'SNCA'. The  
18 outcome search terms that were used included: ('Cognition' OR 'Cognitive' OR 'Memory')  
19 OR ('Depression' OR 'Depressive'). Articles that were not published in English were not  
20 included.  
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33 **Study selection:** All articles obtained following the search of key terms were screened for  
34 their eligibility. The duplicates were removed using Mendeley Desktop 1.17.1 (Mendeley  
35 Ltd., London, UK). Articles were initially screened by their titles. The abstracts of remaining  
36 articles were then screened for relevance and were evaluated for their eligibility. Articles that  
37 did not have cognition or depression as an outcome variable and/or did not include PD  
38 service users as participants were deemed ineligible. Full texts of the remaining pertinent  
39 articles were then retrieved and assessed. All eligible articles were included in this systematic  
40 review.  
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51 **Quality assessment:** The risk of bias and quality assessment of all eligible studies were  
52 carried out using the 'Q-Genie', a quality assessment tool for genetic association studies (22).  
53 The Q-Genie assesses the following 11 dimensions, (i) the rationale for study, (ii) selection  
54 and definition of outcome, (iii) selection and comparability of comparison groups, (iv)  
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3 technical classification of the genetic variant(s), (v) non-technical classification of the genetic  
4 variant(s), (vi) other sources of bias, (vii) sample size and power, (viii) a priori planning of  
5 statistical analyses, (ix) statistical methods and control for confounding, (x) tests of  
6 assumptions and inferences for the genetic analyses, and (xi) appropriate interpretation of the  
7 study results. Each dimension is scored on a scale from one (poor) to seven (excellent). For  
8 studies with control group, Q-Genie total scores  $\leq 35$  indicate poor quality, total scores more  
9 than 45 indicate good quality, and total scores between 36 and 45 indicate moderate quality.  
10 Total scores of  $\leq 35$  for studies with control groups and  $\leq 32$  for studies without control groups  
11 are rated having poor quality. Scores ranging between  $>35$  and  $\leq 45$  for studies with control  
12 groups and  $>32 \leq 40$  without are rated having moderate quality, and those with scores  $>45$  for  
13 with control groups and  $>42$  for without are deemed good quality. The reliability and validity  
14 of the Q-Genie tool has already been demonstrated (23).

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31 **Data extraction:** The data extracted from eligible studies were (i) Participants: The size of  
32 the cohort and their average age and standard deviation at the time of the study. Similarly, the  
33 corresponding Unified Parkinson's Disease Rating Scale (UPDRS) (24) scores for each  
34 subgroup were extracted for indicating the severity of PD. (ii) Exposure: Gene names and the  
35 investigated single-nucleotide variants were extracted with their 'rs' number, if stated. When  
36 the included studies have not reported the 'rs' numbers, we searched the dbSNP database  
37 (<https://www.ncbi.nlm.nih.gov/snp>) with the reported names of the variants. When our  
38 search could not establish a unique dbSNP identifier, we have reported the variant name as  
39 it was reported by the original study authors. (iii) Outcome: The outcome was classified as  
40 either 'cognition' or 'depression' to signify what was being measured. The measurement tool  
41 or test used to measure either outcome was recorded, for example 'Mini-mental State  
42 Examination' (MMSE) (25) or 'Beck Depression Inventory' (26). We obtained mean  
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3 differences between groups with statistical significance, as well as effect sizes and confidence  
4 intervals, if reported. Duration of follow-up was also obtained, if applicable.  
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8 **Data synthesis and analyses:** The data were firstly classified under the exposure variable  
9 (genes), and then classified under the outcome variables (cognition or depression). If three or  
10 more studies have investigated the association between a specific genetic variant and  
11 cognitive impairment or depression in PD, we combined the reported mean differences or  
12 effect sizes using fixed effect meta-analyses. Their degree of heterogeneity was assessed  
13 using Cochrane's Q statistics and Higgin's I<sup>2</sup>. We conducted the meta-analyses using the  
14 STATA 15.1 software (StataCorp LLC, TX, USA) and its "metan" command.  
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## 26 27 **Results**

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29 **Included studies:** Figure-1 presents the Preferred Reporting Items for Systematic Review  
30 and Meta-Analyses (PRISMA) flow chart that exhibits the process of identifying all eligible  
31 studies. Initial screening of the databases resulted in 2353 titles. 1647 were found in a joint  
32 search on PsychINFO and EMBASE, 685 on PubMed, five on CINAHL and 16 on  
33 OpenGrey. 43 articles were eligible to be included in this systematic review. Among them, 24  
34 measured cognition as an outcome variable, 13 measured depression as an outcome variable,  
35 and six measured both. *LRRK2* and *GBA* were the most commonly investigated genes.  
36 Fourteen studies investigated PD service users, who are carriers of one of the *GBA* variants  
37 (rs76763715, rs75548401, rs421016, rs387906315 and rs80356773). Fourteen studies studied  
38 PD service users, who are carriers of *LRRK2* variants (rs34637584, rs33939927, rs11564148  
39 and rs34778348). Other genes that have been investigated included *SNCA* (27), *APOE*,  
40 *BDNF* (rs6265), *SLC6A4*, *COMT* (Val158Met) and *MAPT*. Only 26 (60.5%) included studies  
41 have had sample sizes above 100. We present the quality assessment scores of the included  
42 studies in the supplementary information table-1. Their *Q-Genie* (22) total scores ranged  
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3 from 27 (28) to 55 (29) with main areas of concern being the technical and non-technical  
4 classification of the genetic exposure variables.  
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8 **LRRK2:** Table-1 summarises the findings of the studies that investigated the effects of  
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10 *LRRK2* variants on cognition in people with PD. Four of these studies have reported that  
11 carriers of minor allele of rs34637584 exhibited significantly less cognitive impairment,  
12 while comparing with PD non-carriers (14,15,30,31). We conducted a meta-analysis of  
13 studies investigating this specific variant using different outcome measures and calculated  
14 their standardised mean difference (SMD=0.21; 95%CI 0.04-0.38) (Figure-2)  
15 (Supplementary figure-1). The meta-analysis confirmed that people with PD, who carried the  
16 minor allele of rs34637584, had significantly less cognitive impairment than non-carriers  
17 ( $z=2.43$ ;  $p=0.015$ ). However, studies investigating the effects of other *LRRK2* variants, such  
18 as rs33939927, rs11564148, and rs33949390, did not report statistically significant difference  
19 on cognition between the carriers and non-carriers (28,32-37). Most of these studies were  
20 cross-sectional. They had relatively small sample sizes, and they have not reported power  
21 analyses (34). Moreover, three studies have investigated the associations between *LRRK2*  
22 variants and depressive symptoms in PD. Two of them have reported that depression was  
23 significantly more prevalent among the rs34637584 minor allele carriers with PD than the  
24 non-carriers (33,38). However, another study investigating the association between *LRRK2*  
25 variants and depressive symptoms in PD using the Hospital Anxiety and Depression Scale  
26 did not replicate this finding ( $p=0.54$ ) (39).  
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49 **GBA:** Table-2 provides a summary of findings of the studies that investigated the effects of  
50 *GBA* variants on cognition in people with PD. Several studies have reported that minor allele  
51 carriers of various *GBA* variants had significantly worse cognitive function than the non-  
52 carriers (12,31,40-45). Alcalay *et al* (12) found that minor allele carriers of *GBA* variants  
53 rs76763715 and rs36806 obtained significantly less MMSE scores than the non-carriers.  
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Moreover, a longitudinal study (41) investigating the effects of *GBA* variants including rs2230288 reported that significantly more carriers developed MCI or PDD, compared to non-carriers (OR=4.65; 95%CI 1.72-7.58; p=0.002). Malec-Litwinowicz *et al* (42) followed up only five people with PD and *GBA* variants, and found that minor allele carriers of rs76763715 developed significantly more cognitive impairment than non-carriers over time. *GBA* variant rs2230288 has been reported to be associated with significantly worse visuospatial abilities (45). However, there are studies that have reported that minor allele carriers of *GBA* variants rs76763715 and rs421016 did not differ significantly from non-carriers on their cognition (32,46). One of them was a longitudinal study including three years of follow-up, but it included only 13 people with *GBA* variants (46). We conducted meta-analyses of the studies investigating the effects of *GBA* rs76763715 (Figure-3A) and rs421016 (Figure-3B) variants on cognition in people with PD (Supplementary figure-1). Our meta-analyses confirmed that both rs76763715 ( $z=3.54$ ;  $p<0.001$ ) and rs421016 ( $z=3.45$ ;  $p=0.001$ ) variants were significantly associated with more cognitive impairment in people with PD.

Table-3 summarises the findings of five studies that investigated the associations between *GBA* variants and depressive symptoms in people with PD. Four studies that investigated *GBA* variant rs421016 (31,46-48), and two studies that investigated *GBA* variant rs76763715 (46,47) have consistently reported significantly more depressive symptoms in people with PD carrying minor alleles of these variants. *GBA* variants rs387906315 and rs80356773 have also been associated with significantly higher prevalence of depression among people with PD (47). However, a small longitudinal study following only 13 people with PD and *GBA* variants for three years has reported that mood symptoms did not differ significantly between the carriers and non-carriers during their follow-up (46). This study did not report relevant power analysis, and it did not consider the effects of potential confounders

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3 such as age and gender during their analyses (46). Another small longitudinal study  
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5 investigating a heterogeneous PD group with one of several *LRRK2* and *GBA* variants  
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7 including rs34637584, rs421016, and rs76763715 have reported them having significantly  
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9 higher incidence and earlier onset of depressive symptoms than the non-carriers (49)  
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11 supplementary information table-2.  
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15 ***APOE***: Most of the studies that investigated the effects of *APOE*  $\epsilon$ 4 allele on cognition in  
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17 people with PD have documented a weak association between the allele and cognitive  
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19 impairment in PD (8). Significantly more rapid cognitive decline, measured by the Hamilton  
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21 Verbal Learning test (50) and the Mattis Dementia Rating Scale-II (6), has been reported in  
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23 people with PD carrying *APOE*  $\epsilon$ 4 allele. However, there are negative studies that failed to  
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25 replicate this association (51,52). A prior meta-analysis of studies that investigated the  
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27 genetic association between *APOE*  $\epsilon$ 4 allele and cognitive impairment in PD has reported that  
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29 *APOE*  $\epsilon$ 4 allele significantly increases the risk of PDD (OR=1.74; 95%CI 1.36–2.23;  
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31 p=0.0001). However, this meta-analysis has documented significant heterogeneity of relevant  
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33 studies, and the possibility of publication bias (8).  
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38 ***SLC6A4***: Three studies have investigated the association between serotonin transporter gene  
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40 (*SLC6A4*) 5-HTTLPR variant and depressive symptoms in people with PD. Earliest and the  
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42 smallest (N=32) of them reported that people with PD carrying short allele of the 5-HTTLPR  
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44 variant scored significantly higher on depressive symptoms than corresponding non-carriers  
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46 (53). Later, two later relatively larger studies have clarified that people with PD carrying this  
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48 short allele did not differ significantly from non-carriers on their depressive symptoms  
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50 (29,54). Moreover, a recent large genetic association study using multiple population based  
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52 and case control samples regardless of their PD diagnoses has reported that the association  
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54 between *SLC6A4* 5-HTTLPR variant and depressive symptoms was not statistically  
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56 significant (55).  
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3 **Other genetic variants associated with cognitive impairment in PD:** Supplementary  
4 information table-3 provides an overview of the studies that investigated the associations  
5 between cognitive impairment in PD and various genetic variants. A recent study has  
6 investigated the associations between 249,336 genetic variants and various cognitive  
7 functions in 1105 people with PD, and it has reported false discovery rate adjusted  
8 statistically significant associations of 18 genetic variants with the results of one of the  
9 cognitive tests. These genetic variants include *PARP4* (rs9318600, rs9581094), *MDMI*  
10 (rs117673673), *ALS2CR11* (rs72939119), *FAT3* (rs75081660), *RYR1* (rs55876273), *IFT140*  
11 (rs146128830), *MTCL1* (rs34877994), *MOCS3* (rs7269297), *RASAL3* (rs56209154), and  
12 *ACSBG2* (rs79266675) (45). Most of these reported genetic associations have not been  
13 replicated so far, so they need to be interpreted with caution. People with PD carrying at least  
14 one Met allele of *BDNF* (rs6265) variant have been found to have significantly more  
15 cognitive impairment than non-carriers (56). Moreover, *MAPT* H1/H1 genotype has been  
16 reported to be an independent predictor of PDD (57). Low activity COMT (Val158Met)  
17 Met/Met genotype has been associated with cognitive impairment in PD(58), but another  
18 study failed to verify this association (51). Furthermore, a *PICALM* variant (rs3851179) has  
19 been reported to be associated with cognitive impairment in people with PD older than 70  
20 years (59), and this finding needs further replication.

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44 **Other genetic variants associated with depression in PD:** Supplementary information table-  
45 4 summarises the findings of the studies that investigated the associations between various  
46 genetic variants and depressive symptoms in PD. *BDNF* (rs6265) variant has been associated  
47 with depression in people with PD, after accounting for the effects of potential confounders  
48 such as gender, disease progression, and motor symptoms (p=0.046) (60). *TEF* TT genotype  
49 (61), *CRY1* CC genotype (61), *SLC6A15* (rs1545843)(27), and *TPH2* (rs78162420) (27) have  
50 been associated with depression in people with PD, and these findings have not been  
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3 replicated so far. Moreover, people with PD carrying *SNCA* Rep1 (CA)12/12 genotype  
4 reportedly has a reduced risk of depression ( $p=0.02$ ) (48). Another study has reported a  
5 significant association ( $p=0.003$ ) between a specific *CNRI* genotype and reduced risk of  
6 depression in PD (62).  
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## 15 Discussion

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18 For the first time, we systematically reviewed all studies that investigated the  
19 associations between various genetic variants and cognitive impairment and/or depressive  
20 symptoms in people with PD. The systematic review found that *LRRK2* variant rs34637584  
21 has been associated with significantly less cognitive impairment in PD, and we confirmed it  
22 by a meta-analysis. More meta-analyses confirmed that *GBA* variants rs76763715 ( $p<0.001$ )  
23 and rs421016 ( $p=0.001$ ) were significantly associated with more cognitive impairment in  
24 people with PD. Moreover, the systematic review has listed the genetic variants that have  
25 been associated with depression in PD, including *GBA* (rs76763715, rs421016, rs387906315  
26 and rs80356773, *BDNF* (rs6265) and *CRY1* (rs2287161) variants.  
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39 The strengths of this systematic review include its broad inclusion criteria, searching  
40 multiple databases including grey literature, following PRISMA guidelines, and quality  
41 assessment using the *Q-Genie* instrument. Nonetheless, we must acknowledge the limitations  
42 of excluding the studies that were not published in English, not including gene expression  
43 and epigenetic studies, and of substantial heterogeneity among the included studies. Most of  
44 the included studies were small, and they have not reported sample size estimation or power  
45 analysis, so they were prone to type-II error. Moreover, there were only five longitudinal  
46 studies, and other studies did not evaluate the longitudinal changes in cognition and mood of  
47 their participants. Many studies have recruited participants only from specific ethnic groups,  
48 such as Ashkenazi Jews, and their findings have limited generalisability. Furthermore, there  
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3 are concerns over the validity of outcome measures like MMSE, employed by these studies,  
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5 for assessing cognition and depressive symptoms in people with PD.  
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8 *LRRK2* variants have the largest body of evidence in this topic. *LRRK2* variant  
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10 rs34637584 may either delay or prevent cognitive decline on its own or because of its  
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12 interactions with other genetic variants in people with PD (14,15,27,30). *LRRK2* encodes a  
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14 kinase, and the minor allele of rs34637584 leads to increased expression and activity of  
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16 *LRRK2* (63) because of stabilising the kinase activation loop (64). Furthermore, the severity  
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18 of Lewy body pathology correlates with the severity of cognitive impairment in PD (65), and  
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20 *LRRK2* related PD can be with or without the presence of Lewy bodies (13). Overexpression  
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22 of *LRRK2* leads to enlarged lysosomes, lower endolysosomal pH, impaired autophagy, and  
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24 diminished lysosomal degradation *in-vitro* (66), and these changes in the morphology and  
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26 function of lysosomes could be reversed by *LRRK2* kinase inhibitors *in-vitro* (66). A  
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28 neuronal cell culture study using mouse embryos that were homozygous for *LRRK2*  
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30 rs34637584 variant has replicated these findings (67). Despite the progress in the mechanistic  
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32 understanding of *LRRK2* overexpression leading to neurodegeneration in PD, the molecular  
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34 mechanisms underlying relative preservation of cognitive functioning in people with PD  
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36 carrying *LRRK2* overexpressing variant rs34637584 remain uncertain.  
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43 *GBA* encodes lysosomal acid glucosylceramidase, and homozygous *GBA* variants  
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45 cause Gaucher's disease (GD) that is a lysosomal storage disorder. Minor alleles of *GBA*  
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47 variants rs76763715, rs421016, rs387906315 and rs80356773 lead to glucosylceramidase  
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49 protein misfolding that in turn may lead to either loss or gain of function (68).  
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51 Glucosylceramidase deficiency leads to autophagy impairment, lysosomal dysfunction, and  
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53 accumulation of  $\alpha$ -synuclein oligomers. These  $\alpha$ -synuclein oligomers disrupt misfolded  
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55 glucosylceramidase, and set off a vicious cycle leading to neurodegeneration and cognitive  
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57 impairment in people with PD carrying *GBA* variants (68). Prior studies have reported the  
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3 associations between these *GBA* variants and increased presence of cortical Lewy bodies  
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5 (69). Our systematic review and meta-analyses have confirmed the associations of these *GBA*  
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7 variants with cognitive impairment and depression in people with PD. There is a need for  
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9 further studies investigating the clinical utility and cost-effectiveness of screening for these  
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11 *GBA* variants for early identification of the non-motor symptoms. *GBA* variant rs421016 is  
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13 associated with more severe phenotype of PD and GD than rs76763715 variant (70), and  
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15 *LRRK2* rs34637584 leads to more benign PD phenotype than other *LRRK2* variants (71).  
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17 However, little is known about the differential effects of these variants on cognitive  
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19 impairment and depression in people with PD (43). Non-manifesting *LRRK2* rs34637584  
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21 carriers have been reported to have significantly more cognitive impairment than non-  
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23 manifesting carriers of *GBA* variants (72). Hence, further investigation focusing on the  
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25 effects of individual *LRRK2* and *GBA* variants on the non-motor symptoms of PD is  
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27 warranted.  
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33 Although there is substantial heterogeneity among the studies that investigated the  
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35 associations between genetic variants and depressive symptoms in PD, it is possible to derive  
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37 important conclusions. The studies differed widely on their participant characteristics,  
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39 assessment of depressive symptoms, threshold for diagnosing depression, and their analyses  
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41 addressing potential confounders. Statistically significant associations between depression in  
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43 PD and *BDNF* (rs6265), *TEF* TT genotype (61), *CRY1* CC genotype (61), *SLC6A15* variant  
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45 rs1545843 (27), and *TPH2* variant rs78162420 (27) have been reported. These reported  
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47 genetic associations are only tentative, and they need further replication. Further larger  
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49 studies including structured diagnostic interviews and detailed assessment of confounding  
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51 psychosocial variables are needed for verifying these reported genetic associations. Unlike  
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53 the progressive cognitive decline in PD, depressive symptoms in people with PD are often  
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55 episodic and responsive to treatment with antidepressant medications. However, most of the  
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3 genetic association studies investigating depression in PD are cross-sectional, and they have  
4 not added any information on the longitudinal course of depressive symptoms, and their  
5 response to antidepressant medications in PD. Further longitudinal studies are needed for  
6 addressing this issue. Moreover, a *SNCA* genotype (48), and a *CNR1* genotype (62) have been  
7 associated with reduced risk of depression in PD. There is a need for investigating whether  
8 these two genetic associations can be replicated. If they can be replicated, investigating  
9 underlying molecular mechanisms may facilitate identifying novel therapeutic targets.

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19 Non-motor symptoms of PD have devastating consequences to the service users, their  
20 families, and societies. Early identification, and appropriate multidisciplinary management of  
21 non-motor symptoms may improve the quality of life of people with PD (73). The importance  
22 of further systematic research investigating the genetics and molecular biology of non-motor  
23 symptoms of PD cannot be overemphasised. Despite the studies highlighting the association  
24 between Lewy body pathology and cognitive impairment in PD (65), there is a conspicuous  
25 gap in the available literature for studies investigating the associations between *SNCA* variants  
26 and non-motor symptoms in PD. Moreover, poor replication, and inconsistent findings of  
27 reported genetic associations can be explained by small sample of size, lack of study power,  
28 and by the differences in outcome measures. Larger multi-centre international collaborations  
29 are necessary for conducting future genetic association studies with adequate statistical  
30 power. Developing a consensus for standardised assessment of non-motor symptoms in PD  
31 will help larger international collaborations and will enhance the generalisability of the study  
32 findings. Furthermore, future studies should consider investigating the pharmacogenetic  
33 associations between the genetic variants and clinical responses to various medications  
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**Authors' contributions:**

APR conceived this study, and both APR and TD designed the review protocol. TD reviewed the literature, identified eligible studies, and completed the quality assessment. TD and APR interpreted the findings of the included studies. APR performed necessary statistical analyses. TD wrote the initial draft. Both authors are involved in further revisions of the manuscript, and they have approved the final submitted version of the manuscript.

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**Statement of interest:**

Both authors declare that they do not have any competing interests.

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3 **Figure Legends:**  
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5 **Figure-1:** A PRISMA flow-chart illustrating the selection process of the 43 articles obtained  
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7 with reasons for exclusion.  
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10 PD = Parkinson's Disease, \*Cannot obtain full text of grey literature and author(s) could not  
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12 be contacted  
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17 **Figure-2:** The meta-analysis of five studies investigating the association between *LRRK2*  
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19 variant rs34637584 and cognitive impairment in people with PD  
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24 **Figure-3:** The meta-analyses of studies investigating the associations between cognitive  
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26 impairment in people with PD and *GBA* variants rs76763715 (Figure-3A), and rs421016  
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28 (Figure-3B).  
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**Table-1: Studies investigating the effects of *LRRK2* variants on cognition in people with PD**

Article	Sample Size	Mean Age (SD) years	Mean UPDRS-III (SD)	variants	Outcome	Findings
Alcalay et al. (2010) (32)	699 (20 rs34637584)	54.9 (7.9)	19.8 (14.7)	rs34637584	MMSE	MMSE scores did not differ significantly among the study groups.
Belarbi et al. (2010) (33)	71 (23 rs34637584)	High-education = 52.14 (7.22) Low-education = 57.88 (5.78)	n/s	rs34637584	MMSE; MDRS	Low MMSE scores were significantly more frequent in rs34637584 carriers than in non-carriers within the low-educational level group ( $p=0.04$ ), but not in the other group.
Shanker et al. (2011) (36)	42 (21 rs34637584)	58.7 (9.7)	9.5 (5.6)	rs34637584	MMSE; HVLT; JLO; FAB	Those with rs34637584 minor allele scored significantly higher on JLO ( $p=0.01$ ) and frontal assessment battery ( $p=0.01$ ).
Ben Sassi et al. (2012) (35)	110 (55 rs34637584)	61.9 (11.8)	n/s	rs34637584	MMSE; MoCA; FAB	Cognitive functions did not differ significantly among PD patients with and without rs34637584 variant.
Estanga et al. (2014) (28)	60 (30 rs33939927)	69.97 (10.64)	18.86 (10.61)	rs33939927	Boston Naming Test	Carriers performed significantly worse in the Boston Naming test ( $p=0.03$ ).
Wang et al. (2014) (31)	1638 (223 <i>LRRK2</i> )	61.61 (10.90)	22.53 (14.17)	rs34778348, rs33949390	MMSE; ADAS	Cognitive impairment did not differ significantly between carriers and non-carriers ( $p=0.371$ ).
Alcalay et al. (2015) (14)	236 (116 rs34637584)	66.7 (10.0)	21.4 (12.2)	rs34637584	Stroop Word Reading; Stroop Interference; Category Fluency	rs34637584 carriers performed significantly better in stroop word reading ( $p=0.001$ ), stroop interference ( $p=0.01$ ) and in category fluency ( $p=0.026$ ).

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Somme et al. (2015) (15)	54 (12 rs34637584, 15 rs33939927)	rs34637584 = 66.1 (11.1), rs33939927 = 62.1 (6.5)	rs34637584 = 29.8 (15.9) rs33939927 = 28.5 (8.4)	rs34637584, rs33939927	MDRS II; RAVLT	<i>LRRK2</i> carriers showed significantly less cognitive impairment (MDRS: 131.2 (10.9) vs. 119 (24.0); $p=0.02$ ), (RAVLT, immediate recall: 39.2 (9.5) vs. 27.6 (12.8); $p<0.001$ ), (RAVLT, delayed recall: 7.2 (3.7) vs. 4.7 (4.0); $p=0.022$ ).
Srivatsal et al. (2015) (30)	1355 (24 rs34637584, 5 rs33939927)	67.9 (9.6)	n/s	rs34637584, rs33939927	MMSE; Letter-Number Sequencing Test	<i>LRRK2</i> carriers were found to exhibit significantly better performance on MMSE ( $p=0.03$ ) and Letter number sequencing test ( $p=0.005$ ).
Zheng et al. (2015) (37)	90 (45 rs11564148)	60.79 (10.19)	23.34 (9.88)	rs11564148	Stroop word colour test	Cognitive impairments did not correlate significantly with different <i>LRRK2</i> rs11564148 variants in Chinese people with PD ( $p=0.051$ ).
Hong et al. (2017) (34)	299 (23 rs33949390)	67.7 (7.8)	30.8 (20.7)	rs33949390	MMSE; MoCA	rs33949390 was not significantly associated with cognitive impairment measured by MMSE (carriers=25.6 (4.4), non-carriers=25.0 (4.0), $p=0.442$ ).

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UPDRS: Unified Parkinson’s Disease Rating Scale; HVLT: Hamilton Verbal Learning Test; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; ADAS: MDRS: Mattis Dementia Rating Scale; The Alzheimer’s Disease Assessment Scale – Cognitive; RAVLT: Rey's auditory verbal learning test; JLO: Judgment of Line Orientation test; FAB: Frontal assessment battery; n/s: Not specified.

**Table-2: Studies investigating the effects of *GBA* variants on cognition in people with PD**

Article	Sample Size	Mean Age (SD) years	Mean UPDRS-III severity (SD)	variants	Outcome	Findings
Alcalay et al. (2010) (32)	699 (37 <i>GBA</i> )	54.4 (4.9)	23.8 (11.3)	rs76763715 rs421016	MMSE	MMSE scores did not differ significantly among the study groups.
Brockmann et al. (2011) (46)	40 (6 rs76763715, 14 rs421016)	<i>GBA</i> -PD= 62.75 (10.4); Sporadic PD= 67.60 (9.3)	<i>GBA</i> -PD= 34.75 (14.1); Sporadic PD= 27.85 (7.5).	rs76763715, rs421016	MoCA	Cognitive impairment was significantly more frequent (45% vs 30%) and more severe (22.53 vs 26.53 MoCA points) among <i>GBA</i> -PD compared to sporadic PD (p=0.02).
Alcalay et al. (2012) (12)	71 (24 <i>GBA</i> )	59.0 (6.7)	35.1 (11.5)	rs76763715, rs421016, rs387906315, rs80356773	MMSE, CVLT-II, BVRT, COWAT, WMS-R	<i>GBA</i> variant carriers performed significantly worse on MMSE (p=0.035), visual memory (p<0.001), and visuospatial ability (p=0.025).
Brockmann et al. (2015) (40)	47	62.75 (10.4)	34.75 (14.1)	rs76763715, rs421016	MoCA	<i>GBA</i> variant carriers developed significantly more cognitive decline than non-carriers over three years follow-up period (p=0.01)
Malec-Litwinowicz et al. (2014) (42)	138 (16 <i>GBA</i> )	57.2 (2.8)	36.4 (18.5)	rs76763715, rs75548401	MMSE	<i>GBA</i> rs76763715 carriers were significantly more likely to develop dementia (MMSE score<26) (p=0.03).
Wang et al. (2014) (31)	1638 (49 <i>GBA</i> )	61.61 (10.90)	22.53 (14.17)	rs421016	MMSE; ADAS	Cognitive impairment did not differ significantly between carriers and non-carriers (p=0.474).

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Zokaei et al. (2014) (44)	67 (15 <i>GBA</i> )	61.0 (9.0)	n/s	rs76763715, rs421016	VSTM	<i>GBA</i> -positive people with showed significantly worse recall than other study groups (p<0.005)
Davis et al. (2016) (41)	733 (58 <i>GBA</i> )	64.0 (9.0)	31.8 (10.6)	<i>GBA</i> coding region variants, rs2230288	“Detailed cognitive testing”	A significantly higher proportion of rs2230288 carriers (p=0.01) and of other <i>GBA</i> variant carriers (p=0.04) progressed to mild cognitive impairment or dementia.
Mata et al. (2016) (43)	1369 (125 <i>GBA</i> )	57.3 (12.3)	30.4 (12.3)	<i>GBA</i> coding region variants, rs2230288	MoCA, Letter-Number sequencing, trail making, JLO	<i>GBA</i> carriers had a higher prevalence of dementia (p=9.7×10 <sup>-6</sup> ) and lower performance on letter-number sequencing, trail making, and JLO (p=0.0045).
Mata et al. (2017) (45)	1105	68.8 (9.2)	n/s	NeuroX array (249,336 variants)	HVLT-R, MoCA, JLO, language processing and executive function tests	18 common variants in 13 genomic regions exceeded the genome-wide significance threshold for one of the cognitive tests. They included <i>GBA</i> rs2230288 (PFDR = 2.7 × 10 <sup>-4</sup> ) for JLO.
Liu et al. (2017) (74)	3200 (308 <i>GBA</i> )	n/s	n/s	n/s	MMSE	A multivariable cognitive risk score including the <i>GBA</i> variants could predict dementia or disabling cognitive impairment with an area under curve of 0.88 (95%CI 0.79–0.94) and negative predictive value of 0.92 (95%CI 0.88–0.95).

UPDRS: Unified Parkinson’s Disease Rating Scale; MMSE: Mini-Mental State Examination; CVLT-II: California Verbal Learning Test-II; BVRT: Benton Visual Retention Test; COWAT: Controlled Oral Word Association Test; WMS-R: Wechsler Memory Scale–Revised; MoCA: Montreal Cognitive Assessment; ADAS: The Alzheimer’s Disease Assessment Scale - Cognitive; VSTM: Experimental visual short-term memory task; JLO: Benton Judgment of Line Orientation; HVLT-R: Hamilton Verbal Learning Test-Revised; n/s: Not specified.

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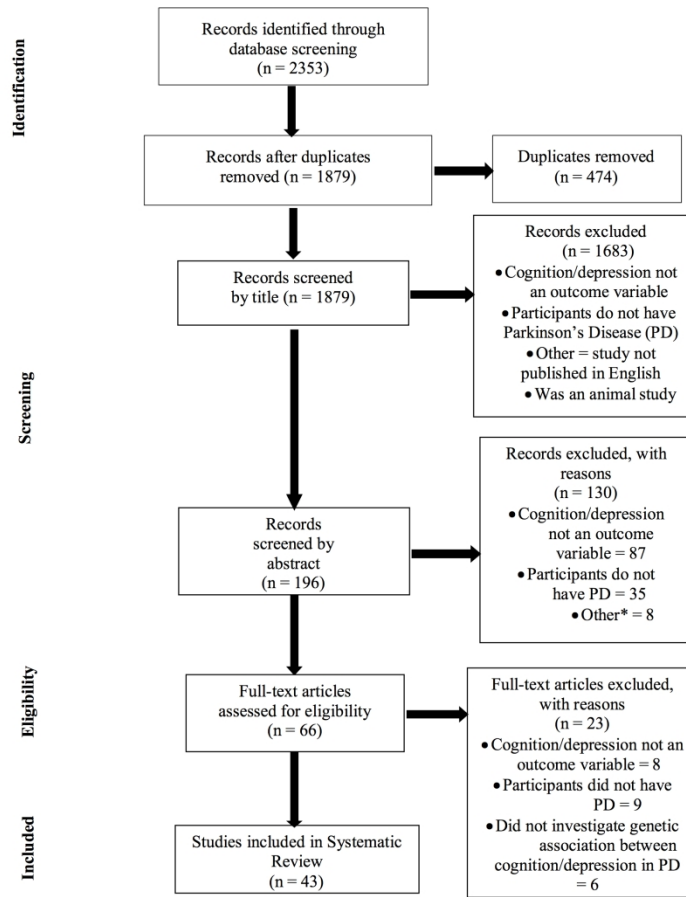
**Table-3: Studies investigating the effects of *GBA* variants on depressive symptoms in people with PD**

Article	Sample Size	Mean Age (SD) years	Mean UPDRS-III severity (SD)	variants	Outcome	Findings
Brockmann et al. (2011) (46)	40 (6 rs76763715, 14 rs421016)	GBA-PD= 62.75 (10.4); Sporadic PD= 67.60 (9.3)	GBA-PD= 34.75 (14.1); Sporadic PD= 27.85 (7.5)	rs76763715, rs421016	BDI-II	GBA-PD people had significantly more depressive symptoms (BDI II: 12.05 Vs 7.10) than people with sporadic PD (p= 0.03).
Brockmann et al. (2015) (40)	47	62.75 (10.4)	34.75 (14.1)	rs76763715, rs421016	BDI-II	<i>GBA</i> variant carriers did not differ significantly on their depressive symptoms than non-carriers over three years follow-up period.
Swan et al. (2014) (47)	86 (31 <i>GBA</i> )	65.6 (12.5)	16.7 (8.7)	rs76763715, rs421016, rs387906315, rs80356773	BDI	<i>GBA</i> variant carriers had significantly higher prevalence of depression (33.3%) than non-carriers (13.2%) (p=0.03)
Wang et al. (2014) (31)	1638 (49 <i>GBA</i> )	61.61 (10.90)	22.53 (14.17)	rs421016	CES-D	<i>GBA</i> variant carriers had significantly higher CES-D scores above 16 than other study groups (p=0.048).
Dan et al. (2016) (48)	1047 (40 <i>GBA</i> )	With depression= 61.66 (9.98) Without depression= 62.05 (10.20)	With depression = 30.01 (16.16) Without depression = 22.00 (12.64)	rs421016	HDRS	rs421016 was associated with significantly increased risk of depression (Odds Ratio=2.69, 95%CI 1.31-5.53; p=0.007).

UPDRS: Unified Parkinson's Disease Rating Scale; BDI-II: Beck's Depression Inventory II; CES-D: Center for Epidemiologic Studies-Depression; HDRS – Hamilton Depression Scale; n/s: Not specified.

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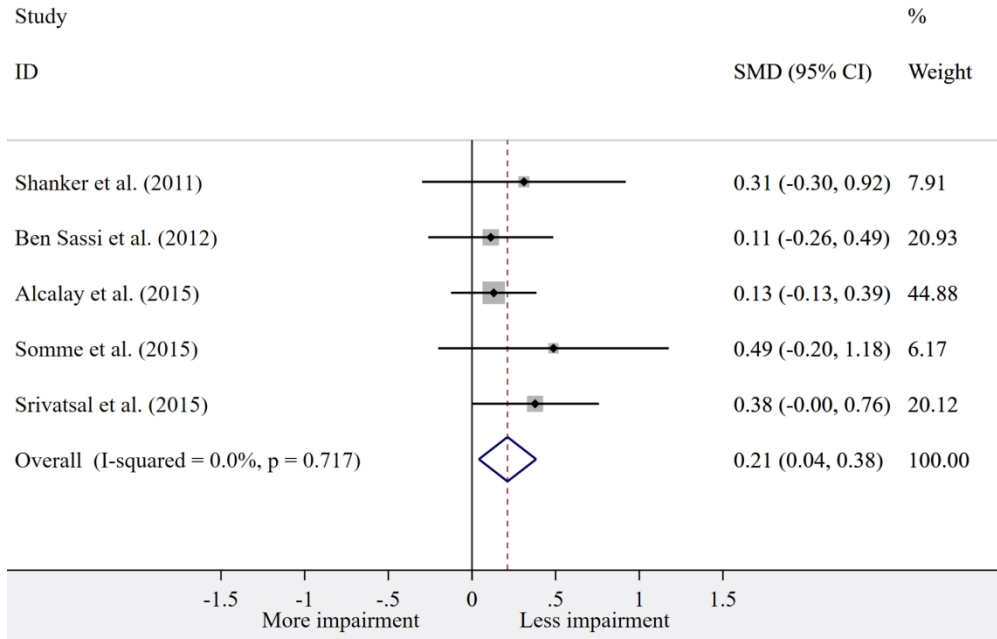
**Figure 1: PRISMA flowchart demonstrating the selection process of obtaining studies**



*\*Cannot obtain full text of grey literature and author cannot be contacted*

A PRISMA flow-chart illustrating the selection process of the 43 articles obtained with reasons for exclusion.

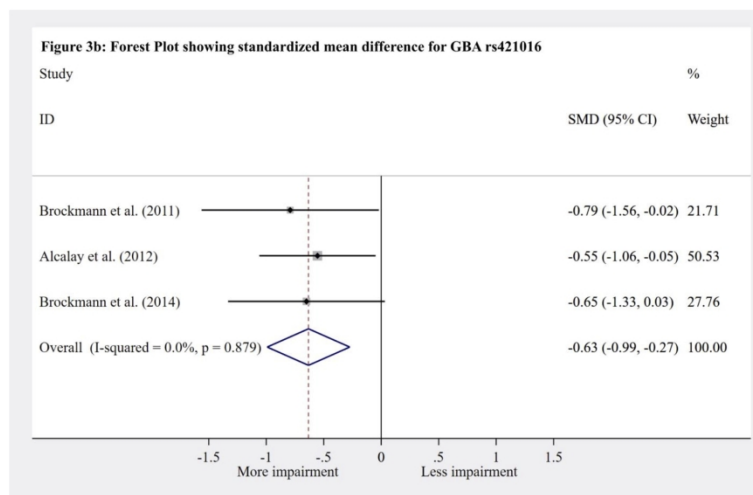
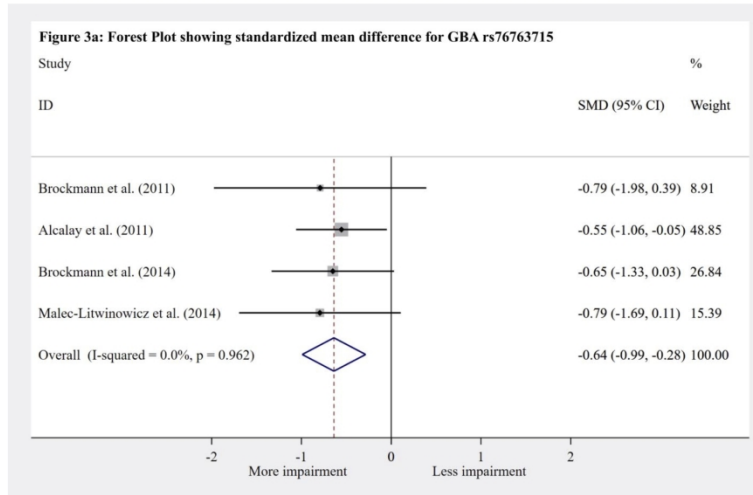
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The meta-analysis of five studies investigating the association between LRRK2 variant rs34637584 and cognitive impairment in people with PD

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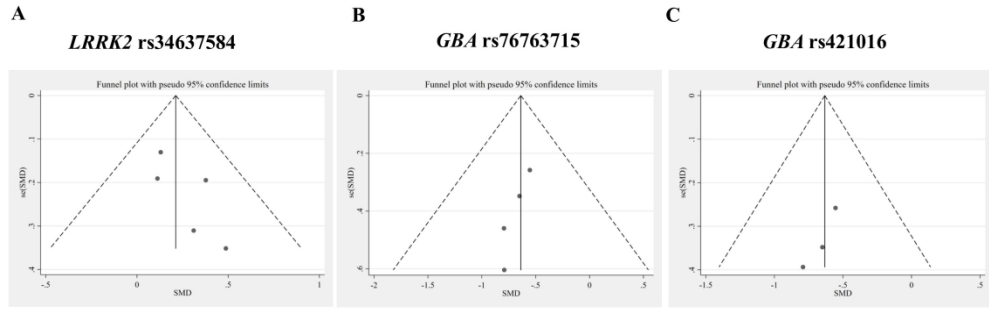
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The meta-analyses of studies investigating the associations between cognitive impairment in people with PD and GBA variants rs76763715 (Figure-3A), and rs421016 (Figure-3B).

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**Supplementary Information Table 1:** Quality assessment of included studies using ‘Q-Genie’ quality assessment tool

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score
Burn et al. (2006) (1)	4	4	4	5	4	5	5	5	5	4	5	55
Chahine et al. (2018) (2)	4	5	5	4	5	4	4	6	5	4	5	51
Wang et al. (2016) (3)	4	5	4	5	5	4	4	5	4	5	5	50
Nombela et al. (2014) (4)	5	5	4	5	5	4	5	4	3	4	5	49
Dan et al. (2016) (5)	5	5	3	2	2	4	5	5	4	4	4	47
Williams-Gray et al. (2009) (6)	4	5	4	4	4	3	5	4	4	5	5	47
Zokaei et al. (2014) (7)	5	5	4	5	4	3	4	5	4	4	4	47
Alcalay et al. (2010) (8)	4	4	5	5	5	3	5	4	4	3	4	46
Dissanayaka et al. (2009) (9)	4	4	5	5	4	4	5	4	3	3	4	45
Tröster et al. (2006) (10)	4	6	5	2	4	3	3	5	4	4	4	44
Mata et al. (2017) (11)	5	6	n/a	5	4	3	4	5	3	4	5	44
Barrett et al. (2016) (12)	3	3	4	6	4	3	5	4	4	4	3	43
Alcalay et al. (2015) (13)	3	4	5	2	3	5	5	4	3	4	4	42
Cagni et al. (2017) (14)	4	3	4	5	3	3	5	4	4	3	4	42
Beavan et al. (2015) (15)	4	3	4	3	2	3	4	5	4	3	4	39
Mata et al. (2014) (16)	4	5	n/a	5	5	6	5	5	5	5	5	39
Morley et al. (2012) (17)	3	3	2	3	4	4	5	3	4	4	4	39
Wang et al. (2014) (18)	4	4	n/a	5	4	4	5	3	3	4	3	39
Alcalay et al. (2012) (19)	3	3	4	3	2	4	4	4	4	3	4	38
Mata et al. (2016) (20)	3	3	4	4	3	3	5	3	3	3	4	38
Swan et al. (2014) (21)	3	2	3	4	3	3	4	4	3	4	4	37



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**Supplementary Information Table 2:** Genetic variants and associated amino acid changes

<b>Gene</b>	<b>Amino acid changes</b>	<b>rs number</b>
<i>LRRK2</i>	G2019S	rs34637584
	G2385R	rs34778348
	R1441C	rs33939927
	R1441G	rs33939927
	S1647T	rs11564148
<i>GBA</i>	84GG	rs387906315
	E326K	rs2230288
	L444P	rs421016
	N370S	rs76763715
	R496H	rs80356773
	T369M	rs75548401

For Peer Review

**Supplementary Information Table 3:** Studies investigating the genetic associations between cognitive impairment in people with Parkinson's disease and various genetic variants

Article	Sample Size	Mean Age (SD)	Mean Severity of PD (SD)	Variants	Outcome	Follow up duration	Findings
Tröster et al. (2006) (10)	208 (20 <i>APOE</i> )	65.6 (8.2)	n/s	<i>APOE</i> ( $\epsilon$ 4 allele)	MDRS; WMS—Revised; WCST	n/s	Carriers and non-carriers differed in their cognitive performance (BNT: carriers = 49.7 (11.7), non-carriers = 52.0 (6.4), $p=0.001$ , WCST: carriers = 3.4 (2.4), non-carriers = 3.1 (2.6), $p=0.001$ ), however this was not significant after controlling for age.
Williams-Gray et al. (2008) (22)	29	Val = 64.8 (10.4), Met = 64.0 (9.4)	n/s	<i>COMT</i> (rs6265)	Modified CANTAB ID/ED task	n/s	People with high activity <i>COMT</i> genotypes (val/val) adopted an approach of preferentially shifting attention within dimensions rather than between. Those with low activity genotypes (met/met) did not, which suggests an inability to form an attentional 'set'.
Williams-Gray et al. (2009) (6)	528 (107 from incident cohort)	62.5 (11.8)	n/s	<i>APOE</i> ( $\epsilon$ 4 and $\epsilon$ 2 allele)	MMSE	Incident cohort = 5 years ( $\pm 0.7$ )	A case-control study comparing PD patients and healthy controls found no significant difference between the two groups in relation genotype distribution of <i>APOE</i> . No significant difference in "change in MMSE per year" was found (Mann-Whitney U test, $p=0.27$ ).
Morley et al. (2012) (17)	269	71.0 (7.4)	UPDRS-III 23.0 (11.0)	<i>APOE</i> ( $\epsilon$ 4 allele)	MDRS version II	1 year	The $\epsilon$ 4 allele of <i>APOE</i> was associated with more rapid decline (loss of 2.9 more points/year, $p<0.001$ ) in total score and an increased risk of a $\geq 10$ points drop during the follow-up period (HR=2.8, $p=0.003$ ).
Mata et al. (2014) (16)	1079	68.8 (9.1)	n/s	<i>APOE</i> ( $\epsilon$ 4 allele), <i>MAPT</i> variants, <i>SNCA</i> (rs356219)	HVLT-R; Letter-Number Sequencing Test and Trail Making Test; MoCA	n/s	The <i>APOE</i> $\epsilon$ 4 allele was associated with lower performance on the HVLT-R total recall ( $p=6.7 \times 10^{-6}$ ; corrected $p_c=6.0 \times 10^{-5}$ ), delayed recall ( $p=.001$ ; $p_c=.009$ ), and recognition discrimination Index ( $p=.004$ ; $p_c=.04$ ).

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Nombela et al. (2014) (4)	235 (49 PD from cohort 1 (C1) and 102 from cohort 2 (C2) and 49 controls from C1 and 35 from C2)	PD C1 = 65.36 (7.9), PD C2 = 64.81 (11.1), Controls C1 = 63.83 (5.8), Controls C2 = 66.23 (8.4)	UPDRS-III PD C1 = 29.28 (11.02 ) PD C2 = 25.36 (10.7)	<i>COMT</i> and <i>MAPT</i> variants, and <i>APOE</i> ( $\epsilon 4$ allele)	Tower of London task; Spatial Rotations Task; MMSE	n/s	A repeated measures ANCOVA revealed no effect of disease or interaction between disease and site on accuracy in the Tower of London Task. For the Spatial Rotations Task, there was a trend towards a disease effect [F(1,207) = 3.319, $p < 0.07$ , lower score in patients] but no significant interaction.
Altmann et al. (2016) (33)	175	68.8. (9.3)	n/s	<i>BDNF</i> (rs62665)	MMSE	n/s	Carriers of at least one <i>BDNF</i> Met allele presented with more cognitive impairment ( $p = 0.005$ ).
Barrett et al. (2016) (12)	1468 (471 from the GenePD cohort and 997 for the NGRC cohort)	GenePD = 62.0 (10.5) NGRC = 58.5 (11.9)	n/s	Variants in <i>BINI</i> , <i>CLU</i> , <i>ABCA7</i> , <i>CR1</i> , <i>PICALM</i> , <i>MS4A6A</i> , <i>CD33</i> , <i>MS4A4E</i> , <i>CD2AP</i>	MMSE	n/s	<i>PICALM</i> rs3851179 was associated with cognitive impairment (MMSE < 24) in PD subjects > 70 years old but not in PD subjects $\leq$ 70 years old.
Wang et al. (2016) (3)	296	62.60 (9.40)	UPDRS-III 22.62 (13.83)	<i>SNCA</i> (rs11931074, rs894278) <i>MAPT</i> (rs242557, rs3744456)	MMSE	4 years	Increased severity of cognitive impairment was associated with <i>MAPT</i> H1c haplotype ( $p = 0.05$ ) with none of the risk alleles chosen associated with survival to the cognitive cutoff ( $p > 0.05$ ).

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PD: Parkinson’s disease; UPDRS: Unified Parkinson’s Disease Rating Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; HVLt-R: Hamilton Verbal Learning Test–Revised; WMS: Wechsler Memory Scale; WCST: Wisconsin Card Sorting Test; MDRS: Mattis Dementia Rating Scale; CANTAB ID/ED: Cambridge Neuropsychological Test Automated Battery intra-dimensional/ extra-dimensional; BNT: Boston Naming Test; NGRC: Genome-Wide Association Study of Parkinson Disease: Genes and Environment

**Supplementary Information Table 4:** Studies investigating the genetic associations between depressive symptoms in people with Parkinson's disease and various genetic variants

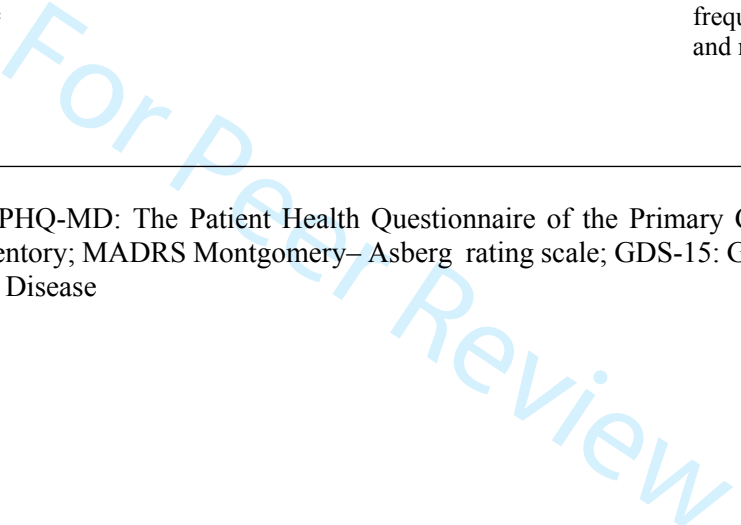
Article	Sample Size	Mean Age (SD)	Mean Severity of PD (SD)	Variants	Outcome	Findings
Menza et al. (1999) (35)	32	67.0	n/s	<i>5-HTTLPR</i> ( <i>SLC6A4</i> )	HDRS	Those with the short allele of the serotonin transporter promoter scored significantly higher on depression ( $p < 0.004$ ).
Barrero et al. (2005) (23)	89	Men = 67.2 (11); Women = 73.4 (6.3)	UPDRS 56.4 (30.5)	<i>CNR1</i> variants	HDRS	The presence of two long alleles in the <i>CNR1</i> gene was associated with a reduced prevalence of depression ( $p = 0.003$ ).
Burn et al. (2006) (1)	190 (108 <i>5-HTTLPR</i> )	71.1 (8.2)	n/s	<i>5-HTTLPR</i> ( <i>SLC6A4</i> )	MADRS; GDS-15	No association between <i>5-HTTLPR</i> genotype or the presence of the S allele and the risk of depression measured by MADRS or GDS-15.
Dissanayaka et al. (2009) (9)	190 (95 with depression and 95 without depression)	With depression = n/s, without depression = 69.9 (8.0)	n/s	<i>SLC6A3</i> and <i>SLC6A4</i> variants	GDS-15	There were no significant differences in haplotype frequencies between depressed people and not depressed groups; <i>SLC6A4</i> ( $p = 0.69$ ) and <i>SLC6A3</i> ( $p = 0.41$ ).
Srivastava et al. (2011) (26)	88	51.8 (9.7)	UPDRS-III 19.75 (7.25)	<i>PRKN</i> variants	PHQ-MD; BDI-II	Only compound heterozygotes had a significantly high BDI-II score and BDI-II total depression score ( $b = 8.4$ ; 95% CI 2.4-11.3) compared to those without <i>PRKN</i> variants.
Hua et al. (2012) (31)	408	65.3 (10.2)	UPDRS-III = 25.7 (15.1)	<i>Cry1</i> (rs2287161), <i>Cry2</i> (rs10838524) and <i>Tef</i> (rs738499) variants.	HDRS	Higher HDRS scores were found in the TT genotype group in <i>Tef</i> rs738499 ( $p < 0.01$ ) and the CC genotype group in <i>Cry1</i> rs2287161 ( $p < 0.01$ ). There was no difference in HDRS scores between the <i>CRY2</i> AA genotype and AG genotype (rs10838524).
Kasten et al. (2012) (40)	42 (2 <i>SNCA</i> , 8 <i>PRKN</i> , 9 <i>PINK1</i> and 4 <i>LRRK2</i> )	Carriers = 44 (13) (MMC),	UPDRS-III 16.7 (13.9) (MMC)	Variants in <i>SNCA</i> , <i>Parkin</i> , <i>PINK1</i> , <i>LRRK2</i>	BDI	Frequency of depression was increased in all PD groups, particularly the MMC (0.44) and EOPD (0.31) groups. However the treated disease controls had the highest proportion of at least moderate depressive symptoms at 0.63.

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Cagni et al. (2017) (14)	200 (104 <i>BDNF</i> )	64.32 (11.71)	UPDRS-III Carriers (G/G) = 21.72 (10.8) Carriers = (A/G + A/A) = 21.07 (8.07)	<i>BDNF</i> (rs6265)	BDI	People with PD presented more prevalent and severe depression symptoms, measured by BDI (7.18 (7.80) versus 16.22 (9.52), <i>p</i> =0.0001), when compared with controls.
Zheng et al. (2017) (32)	330 (125 depression and 205 without depression)	With depression = 62.3 (10.3), Without = 61.8 (11.6)	n/s	<i>SNCA</i> variants	HDRS	Significant differences between the two groups in minor allele frequency of <i>SLC6A15</i> rs1545843 and in frequencies of genotypes and minor alleles of rs78162420 in <i>TPH2</i> .

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UPDRS: Unified Parkinson’s Disease Rating Scale; PHQ-MD: The Patient Health Questionnaire of the Primary Care Evaluation of Mental Disorders; HDRS: Hamilton Depression Rating Scale; BDI: Beck’s Depression Inventory; MADRS Montgomery–Asberg rating scale; GDS-15: Geriatric Depression Scale – 15 items; MMC: Early-Onset Manifesting Carriers; EOPD: Early-Onset Parkinson’s Disease





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