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

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in regards to the genetic associations of depression in the context of PD. Serotonin and dopamine are the two important neurotransmitters that are involved in the pathophysiology of depression. Their levels in synaptic clefts are regulated by neurotransmitter transporters, and it is the genetic variations of these transporters that are hypothesised as potential risk factors for depression in PD. Where the serotonin transporter gene (*SLC6A4*) has been extensively studied as a genetic risk factor for depression in people without PD (19), the dopamine transporter gene (*SLC6A3*) has been examined as a potential candidate gene for depression in PD (20). Additionally, variants in the parkin gene (*PARK2*) have also been shown to contribute to a heightened risk of both depression and anxiety in people with PD, especially to those with early onset PD (21).

There are currently no systematic reviews that comprehensively summarise the relevant literature regarding the effects of genetic variants on non-motor symptoms in PD. This systematic review will be the first to provide a cohesive summary of all genetic association studies that have investigated the genetic factors associated with cognitive impairment and depression in people with PD. This review aims to enhance the understanding of the neurobiology underlying cognitive impairment and depression in people with PD.

Materials and Methods

Study design: The protocol of this systematic review has been registered (PROSPERO protocol registration number: CRD42017067431), and is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017067431).

Inclusion Criteria: All articles studying human participants with a clinical diagnosis of Parkinson's disease, irrespective of their age, and gender, were considered. Animal studies and invitro studies were excluded. Studies that investigated common and rare genetic

variations as well as cognitive impairment and/or depressive symptoms as outcome were included. Therefore, genetic association studies that did not include either of these as outcome variables were excluded. All relevant cohort studies, case controls, and case series were included. Studies were not excluded because of their controls or the lack of them.

Search strategy: A systematic search was carried out in January 2019 using the following five databases: PubMed (1996-Present), PsycINFO (1806-present), CINAHL (1981-present), EMBASE (1974-present) and OpenGrey. The search strategy was comprised of both 'Population' AND 'Exposure' AND 'Outcome' terms. These terms were searched for in the titles, abstracts, and full texts. 'Parkinson*' was the population search term. The exposure search terms that were included: 'Gene*', OR 'LRRK2', OR 'GBA', OR 'SNCA'. The outcome search terms that were used included: ('Cognition' OR 'Cognitive' OR 'Memory') OR ('Depression' OR 'Depressive'). Articles that were not published in English were not included.

Study selection: All articles obtained following the search of key terms were screened for their eligibility. The duplicates were removed using Mendeley Desktop 1.17.1 (Mendeley Ltd., London, UK). Articles were initially screened by their titles. The abstracts of remaining articles were then screened for relevance and were evaluated for their eligibility. Articles that did not have cognition or depression as an outcome variable and/or did not include PD service users as participants were deemed ineligible. Full texts of the remaining pertinent articles were then retrieved and assessed. All eligible articles were included in this systematic review.

Quality assessment: The risk of bias and quality assessment of all eligible studies were carried out using the '*Q-Genie*', a quality assessment tool for genetic association studies (22). The Q-Genie assesses the following 11 dimensions, (i) the rationale for study, (ii) selection and definition of outcome, (iii) selection and comparability of comparison groups, (iv)

technical classification of the genetic variant(s), (v) non-technical classification of the genetic variant(s), (vi) other sources of bias, (vii) sample size and power, (viii) a priori planning of statistical analyses, (ix) statistical methods and control for confounding, (x) tests of assumptions and inferences for the genetic analyses, and (xi) appropriate interpretation of the study results. Each dimension is scored on a scale from one (poor) to seven (excellent). For studies with control group, Q-Genie total scores ≤35 indicate poor quality, total scores more than 45 indicate good quality, and total scores between 36 and 45 indicate moderate quality. Total scores of ≤35 for studies with control groups and ≤32 for studies without control groups are rated having poor quality. Scores ranging between >35 and ≤45 for studies with control groups and >32 ≤40 without are rated having moderate quality, and those with scores >45 for with control groups and >42 for without are deemed good quality. The reliability and validity of the Q-Genie tool has already been demonstrated (23).

Data extraction: The data extracted from eligible studies were (i) Participants: The size of the cohort and their average age and standard deviation at the time of the study. Similarly, the corresponding Unified Parkinson's Disease Rating Scale (UPDRS) (24) scores for each subgroup were extracted for indicating the severity of PD. (ii) Exposure: Gene names and the investigated single-nucleotide variants were extracted with their 'rs' number, if stated. When the included studies have not reported the 'rs' numbers, we searched the dbSNP database (https://www.ncbi.nlm.nih.gov/snp) with the reported names of the variants. When our search could not establish an unique dbSNP identifier, we have reported the variant name as it was reported by the original study authors. (iii) Outcome: The outcome was classified as either 'cognition' or 'depression' to signify what was being measured. The measurement tool or test used to measure either outcome was recorded, for example 'Mini-mental State Examination' (MMSE) (25) or 'Beck Depression Inventory' (26). We obtained mean

differences between groups with statistical significance, as well as effect sizes and confidence intervals, if reported. Duration of follow-up was also obtained, if applicable.

Data synthesis and analyses: The data were firstly classified under the exposure variable (genes), and then classified under the outcome variables (cognition or depression). If three or more studies have investigated the association between a specific genetic variant and cognitive impairment or depression in PD, we combined the reported mean differences or effect sizes using fixed effect meta-analyses. Their degree of heterogeneity was assessed using Cochrane's Q statistics and Higgin's I^2. We conducted the meta-analyses using the STATA 15.1 software (StataCorp LLC, TX, USA) and its "metan" command.

Results

Included studies: Figure-1 presents the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow chart that exhibits the process of identifying all eligible studies. Initial screening of the databases resulted in 2353 titles. 1647 were found in a joint search on PsychINFO and EMBASE, 685 on PubMed, five on CINAHL and 16 on OpenGrey. 43 articles were eligible to be included in this systematic review. Among them, 24 measured cognition as an outcome variable, 13 measured depression as an outcome variable, and six measured both. *LRRK2* and *GBA* were the most commonly investigated genes. Fourteen studies investigated PD service users, who are carriers of one of the *GBA* variants (rs76763715, rs75548401, rs421016, rs387906315 and rs80356773). Fourteen studies studied PD service users, who are carriers of *LRRK2* variants (rs34637584, rs33939927, rs11564148 and rs34778348). Other genes that have been investigated included *SNCA* (27), *APOE*, *BDNF* (rs6265), *SLC6A4*, *COMT* (Val158Met) and *MAPT*. Only 26 (60.5%) included studies have had sample sizes above 100. We present the quality assessment scores of the included studies in the supplementary information table-1. Their *Q-Genie* (22) total scores ranged

from 27 (28) to 55 (29) with main areas of concern being the technical and non-technical classification of the genetic exposure variables.

LRRK2*:* Table-1 summarises the findings of the studies that investigated the effects of *LRRK2* variants on cognition in people with PD. Four of these studies have reported that carriers of minor allele of rs34637584 exhibited significantly less cognitive impairment, while comparing with PD non-carriers (14,15,30,31). We conducted a meta-analysis of studies investigating this specific variant using different outcome measures and calculated their standardised mean difference (SMD=0.21; 95%CI 0.04-0.38) (Figure-2) (Supplementary figure-1). The meta-analysis confirmed that people with PD, who carried the minor allele of rs34637584, had significantly less cognitive impairment than non-carriers (z=2.43; p=0.015). However, studies investigating the effects of other *LRRK2* variants, such as rs33939927, rs11564148, and rs33949390, did not report statistically significant difference on cognition between the carriers and non-carriers (28,32-37). Most of these studies were cross-sectional. They had relatively small sample sizes, and they have not reported power analyses (34). Moreover, three studies have investigated the associations between *LRRK2* variants and depressive symptoms in PD. Two of them have reported that depression was significantly more prevalent among the rs34637584 minor allele carriers with PD than the non-carriers (33,38). However, another study investigating the association between *LRRK2* variants and depressive symptoms in PD using the Hospital Anxiety and Depression Scale did not replicate this finding (p=0.54) (39).

GBA*:* Table-2 provides a summary of findings of the studies that investigated the effects of *GBA* variants on cognition in people with PD. Several studies have reported that minor allele carriers of various *GBA* variants had significantly worse cognitive function than the non-carriers (12,31,40-45). Alcalay *et al* (12) found that minor allele carriers of *GBA* variants rs76763715 and rs36806 obtained significantly less MMSE scores than the non-carriers.

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

such as age and gender during their analyses (46). Another small longitudinal study investigating a heterogeneous PD group with one of several *LRRK2* and *GBA* variants including rs34637584, rs421016, and rs76763715 have reported them having significantly higher incidence and earlier onset of depressive symptoms than the non-carriers (49) supplementary information table-2.

APOE: Most of the studies that investigated the effects of *APOE* ε4 allele on cognition in people with PD have documented a weak association between the allele and cognitive impairment in PD (8). Significantly more rapid cognitive decline, measured by the Hamilton Verbal Learning test (50) and the Mattis Dementia Rating Scale-II (6), has been reported in people with PD carrying *APOE* ε4 allele. However, there are negative studies that failed to replicate this association (51,52). A prior meta-analysis of studies that investigated the genetic association between *APOE* ε4 allele and cognitive impairment in PD has reported that *APOE* ε4 allele significantly increases the risk of PDD (OR=1.74; 95%CI 1.36–2.23; p=0.0001). However, this meta-analysis has documented significant heterogeneity of relevant studies, and the possibility of publication bias (8).

SLC6A4: Three studies have investigated the association between serotonin transporter gene (*SLC6A4*) 5-HTTLPR variant and depressive symptoms in people with PD. Earliest and the smallest (N=32) of them reported that people with PD carrying short allele of the 5-HTTLPR variant scored significantly higher on depressive symptoms than corresponding non-carriers (53). Later, two later relatively larger studies have clarified that people with PD carrying this short allele did not differ significantly from non-carriers on their depressive symptoms (29,54). Moreover, a recent large genetic association study using multiple population based and case control samples regardless of their PD diagnoses has reported that the association between *SLC6A4* 5-HTTLPR variant and depressive symptoms was not statistically significant (55).

Other genetic variants associated with cognitive impairment in PD*:* Supplementary information table-3 provides an overview of the studies that investigated the associations between cognitive impairment in PD and various genetic variants. A recent study has investigated the associations between 249,336 genetic variants and various cognitive functions in 1105 people with PD, and it has reported false discovery rate adjusted statistically significant associations of 18 genetic variants with the results of one of the cognitive tests. These genetic variants include *PARP4* (rs9318600, rs9581094), *MDM1* (rs117673673), *ALS2CR11* (rs72939119), *FAT3* (rs75081660), *RYR1* (rs55876273), *IFT140* (rs146128830), *MTCL1* (rs34877994), *MOCS3* (rs7269297), *RASAL3* (rs56209154), and *ACSBG2* (rs79266675) (45). Most of these reported genetic associations have not been replicated so far, so they need to be interpreted with caution. People with PD carrying at least one Met allele of *BDNF* (rs6265) variant have been found to have significantly more cognitive impairment than non-carriers (56). Moreover, *MAPT* H1/H1 genotype has been reported to be an independent predictor of PDD (57). Low activity COMT (Val158Met) Met/Met genotype has been associated with cognitive impairment in PD(58), but another study failed to verify this association (51). Furthermore, a *PICALM* variant (rs3851179) has been reported to be associated with cognitive impairment in people with PD older than 70 years (59), and this finding needs further replication.

Other genetic variants associated with depression in PD*:* Supplementary information table-4 summarises the findings of the studies that investigated the associations between various genetic variants and depressive symptoms in PD. *BDNF* (rs6265) variant has been associated with depression in people with PD, after accounting for the effects of potential confounders such as gender, disease progression, and motor symptoms (p=0.046) (60). *TEF* TT genotype (61), *CRY1* CC genotype (61), *SLC6A15* (rs1545843)(27), and *TPH2* (rs78162420) (27) have been associated with depression in people with PD, and these findings have not been

replicated so far. Moreover, people with PD carrying *SNCA* Rep1 (CA)12/12 genotype reportedly has a reduced risk of depression (p=0.02) (48). Another study has reported a significant association (p=0.003) between a specific *CNR1* genotype and reduced risk of depression in PD (62).

Discussion

For the first time, we systematically reviewed all studies that investigated the associations between various genetic variants and cognitive impairment and/or depressive symptoms in people with PD. The systematic review found that *LRRK2* variant rs34637584 has been associated with significantly less cognitive impairment in PD, and we confirmed it by a meta-analysis. More meta-analyses confirmed that *GBA* variants rs76763715 (p<0.001) and rs421016 (p=0.001) were significantly associated with more cognitive impairment in people with PD. Moreover, the systematic review has listed the genetic variants that have been associated with depression in PD, including *GBA* (rs76763715, rs421016, rs387906315 and rs80356773, *BDNF* (rs6265) and *CRY1* (rs2287161) variants.

The strengths of this systematic review include its broad inclusion criteria, searching multiple databases including grey literature, following PRISMA guidelines, and quality assessment using the *Q-Genie* instrument. Nonetheless, we must acknowledge the limitations of excluding the studies that were not published in English, not including gene expression and epigenetic studies, and of substantial heterogeneity among the included studies. Most of the included studies were small, and they have not reported sample size estimation or power analysis, so they were prone to type-II error. Moreover, there were only five longitudinal studies, and other studies did not evaluate the longitudinal changes in cognition and mood of their participants. Many studies have recruited participants only from specific ethnic groups, such as Ashkenazi Jews, and their findings have limited generalisability. Furthermore, there

are concerns over the validity of outcome measures like MMSE, employed by these studies, for assessing cognition and depressive symptoms in people with PD.

LRRK2 variants have the largest body of evidence in this topic. *LRRK2* variant rs34637584 may either delay or prevent cognitive decline on its own or because of its interactions with other genetic variants in people with PD (14,15,27,30). *LRRK2* encodes a kinase, and the minor allele of rs34637584 leads to increased expression and activity of LRRK2 (63) because of stabilising the kinase activation loop (64). Furthermore, the severity of Lewy body pathology correlates with the severity of cognitive impairment in PD (65), and *LRRK2* related PD can be with or without the presence of Lewy bodies (13). Overexpression of LRRK2 leads to enlarged lysosomes, lower endolysosomal pH, impaired autophagy, and diminished lysosomal degradation *in-vitro* (66), and these changes in the morphology and function of lysosomes could be reversed by LRRK2 kinase inhibitors *in-vitro* (66). A neuronal cell culture study using mouse embryos that were homozygous for *LRRK2* rs34637584 variant has replicated these findings (67). Despite the progress in the mechanistic understanding of LRRK2 overexpression leading to neurodegeneration in PD, the molecular mechanisms underlying relative preservation of cognitive functioning in people with PD carrying LRRK2 overexpressing variant rs34637584 remain uncertain.

GBA encodes lysosomal acid glucosylceramidase, and homozygous *GBA* variants cause Gaucher's disease (GD) that is a lysosomal storage disorder. Minor alleles of *GBA* variants rs76763715, rs421016, rs387906315 and rs80356773 lead to glucosylceramidase protein misfolding that in turn may lead to either loss or gain of function (68). Glucosylceramidase deficiency leads to autophagy impairment, lysosomal dysfunction, and accumulation of α-synuclein oligomers. These α-synuclein oligomers disrupt misfolded glucosylceramidase, and set off a vicious cycle leading to neurodegeneration and cognitive impairment in people with PD carrying *GBA* variants (68). Prior studies have reported the

associations between these *GBA* variants and increased presence of cortical Lewy bodies (69). Our systematic review and meta-analyses have confirmed the associations of these *GBA* variants with cognitive impairment and depression in people with PD. There is a need for further studies investigating the clinical utility and cost-effectiveness of screening for these *GBA* variants for early identification of the non-motor symptoms. *GBA* variant rs421016 is associated with more severe phenotype of PD and GD than rs76763715 variant (70), and *LRRK2* rs34637584 leads to more benign PD phenotype than other *LRRK2* variants (71). However, little is known about the differential effects of these variants on cognitive impairment and depression in people with PD (43). Non-manifesting *LRRK2* rs34637584 carriers have been reported to have significantly more cognitive impairment than non-manifesting carriers of *GBA* variants (72). Hence, further investigation focusing on the effects of individual *LRRK2* and *GBA* variants on the non-motor symptoms of PD is warranted.

Although there is substantial heterogeneity among the studies that investigated the associations between genetic variants and depressive symptoms in PD, it is possible to derive important conclusions. The studies differed widely on their participant characteristics, assessment of depressive symptoms, threshold for diagnosing depression, and their analyses addressing potential confounders. Statistically significant associations between depression in PD and *BDNF* (rs6265), *TEF* TT genotype (61), *CRY1* CC genotype (61), *SLC6A15* variant rs1545843 (27), and *TPH2* variant rs78162420 (27) have been reported. These reported genetic associations are only tentative, and they need further replication. Further larger studies including structured diagnostic interviews and detailed assessment of confounding psychosocial variables are needed for verifying these reported genetic associations. Unlike the progressive cognitive decline in PD, depressive symptoms in people with PD are often episodic and responsive to treatment with antidepressant medications. However, most of the

genetic association studies investigating depression in PD are cross-sectional, and they have not added any information on the longitudinal course of depressive symptoms, and their response to antidepressant medications in PD. Further longitudinal studies are needed for addressing this issue. Moreover, a *SNCA* genotype (48), and a *CNR1* genotype (62) have been associated with reduced risk of depression in PD. There is a need for investigating whether these two genetic associations can be replicated. If they can be replicated, investigating underlying molecular mechanisms may facilitate identifying novel therapeutic targets.

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

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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.

Figure Legends:

Figure-1: A PRISMA flow-chart illustrating the selection process of the 43 articles obtained with reasons for exclusion.

PD = Parkinson's Disease, *Cannot obtain full text of grey literature and author(s) could not be contacted

Figure-2: The meta-analysis of five studies investigating the association between *LRRK2* variant rs34637584 and cognitive impairment in people with PD

Figure-3: 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).

References

1. Park A, Stacy M. Non-motor symptoms in Parkinson's disease. J Neurol. 2009;256 Suppl 3:293-8.
2. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005;65(8):1239-45.
3. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol. 2013;70(5):580-6.
4. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol. 2010;20(3):633-9.
5. Vossius C, Larsen JP, Janvin C, Aarsland D. The economic impact of cognitive impairment in Parkinson's disease. Mov Disord. 2011;26(8):1541-4.
6. Morley JF, Xie SX, Hurtig HI, Stern MB, Colcher A, Horn S, et al. Genetic influences on cognitive decline in Parkinson's disease. Mov Disord. 2012;27(4):512-8.
7. Gomperts SN, Locascio JJ, Rentz D, Santarlasci A, Marquie M, Johnson KA, et al. Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. Neurology. 2013;80(1):85-91.
8. Williams-Gray CH, Goris A, Saiki M, Foltynie T, Compston DA, Sawcer SJ, et al. Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. J Neurol. 2009;256(3):493-8.
9. Kurz MW, Dekomien G, Nilsen OB, Larsen JP, Aarsland D, Alves G. APOE alleles in Parkinson disease and their relationship to cognitive decline: a population-based, longitudinal study. J Geriatr Psychiatry Neurol. 2009;22(3):166-70.

10. Goris A, Williams-Gray CH, Clark GR, Foltynie T, Lewis SJ, Brown J, et al. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol. 2007;62(2):145-53.
11. Neumann J, Bras J, Deas E, O'sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain. 2009;132(Pt 7):1783-94.
12. Alcalay RN, Caccappolo E, Mejia-Santana H, Tang M, Rosado L, Orbe Reilly M, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology. 2012;78(18):1434-40.
13. Kalia LV, Lang AE, Hazrati LN, Fujioka S, Wszolek ZK, Dickson DW, et al. Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. JAMA Neurol. 2015;72(1):100-5.
14. Alcalay RN, Mejia-Santana H, Mirelman A, Saunders-Pullman R, Raymond D, Palmese C, et al. Neuropsychological performance in LRRK2 G2019S carriers with Parkinson's disease. Parkinsonism Relat Disord. 2015;21(2):106-10.
15. Somme JH, Molano Salazar A, Gonzalez A, Tijero B, Berganzo K, Lezcano E, et al. Cognitive and behavioral symptoms in Parkinson's disease patients with the G2019S and R1441G mutations of the LRRK2 gene. Parkinsonism Relat Disord. 2015;21(5):494-9.
16. Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics. 2000;41(1):15-23.
17. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry. 1992;149(4):443-54.
18. Anguelova M, Benkelfat C, Turecki G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. Mol Psychiatry. 2003;8(7):646-53.

19. Wendland JR, Martin BJ, Kruse MR, Lesch KP, Murphy DL. Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. Mol Psychiatry. 2006;11(3):224-6.

20. Ohadi M, Shirazi E, Tehranidoosti M, Moghimi N, Keikhaee MR, Ehssani S, et al. Attention-deficit/hyperactivity disorder (ADHD) association with the DAT1 core promoter -67 T allele. Brain Res. 2006;1101(1):1-4.

21. Arabia G, Grossardt BR, Geda YE, Et Al. Increased risk of depressive and anxiety disorders in relatives of patients with parkinson disease. Archives of General Psychiatry. 2007;64(12):1385-92.

22. Sohani ZN, Meyre D, De Souza RJ, Joseph PG, Gandhi M, Dennis BB, et al. Assessing the quality of published genetic association studies in meta-analyses: the quality of genetic studies (Q-Genie) tool. BMC Genet. 2015;16:50.

23. Sohani ZN, Sarma S, Alyass A, De Souza RJ, Robiou-Du-Pont S, Li A, et al. Empirical evaluation of the Q-Genie tool: a protocol for assessment of effectiveness. BMJ Open. 2016;6(6):e010403.

24. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord. 1994;9(1):76-83.

25. Folstein MF, Folstein SE, Mchugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.

26. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996;78:490–8.

27. Zheng J, Yang X, Zhao Q, Tian S, Huang H, Chen Y, et al. Association between gene polymorphism and depression in Parkinson's disease: A case-control study. J Neurol Sci. 2017;375:231-4.

28. Estanga A, Rodriguez-Oroz MC, Ruiz-Martinez J, Barandiaran M, Gorostidi A, Bergareche A, et al. Cognitive dysfunction in Parkinson's disease related to the R1441G mutation in LRRK2. Parkinsonism Relat Disord. 2014;20(10):1097-100.

29. Burn DJ, Tiangyou W, Allcock LM, Davison J, Chinnery PF. Allelic variation of a functional polymorphism in the serotonin transporter gene and depression in Parkinson's disease. Parkinsonism & Related Disorders. 2006;12(3):139-41.

30. Srivatsal S, Cholerton B, Leverenz JB, Wszolek ZK, Uitti RJ, Dickson DW, et al. Cognitive profile of LRRK2-related Parkinson's disease. Mov Disord. 2015;30(5):728-33.

31. Wang C, Cai Y, Gu Z, Ma J, Zheng Z, Tang BS, et al. Clinical profiles of Parkinson's disease associated with common leucine-rich repeat kinase 2 and glucocerebrosidase genetic variants in Chinese individuals. Neurobiol Aging. 2014;35(3):725 e1-6.

32. Alcalay RN, Mejia-Santana H, Tang MX, Rakitin B, Rosado L, Ross B, et al. Self-report of cognitive impairment and mini-mental state examination performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease. J Clin Exp Neuropsychol. 2010;32(7):775-9.

33. Belarbi S, Hecham N, Lesage S, Kediha MI, Smail N, Benhassine T, et al. LRRK2 G2019S mutation in Parkinson's disease: a neuropsychological and neuropsychiatric study in a large Algerian cohort. Parkinsonism Relat Disord. 2010;16(10):676-9.

34. Hong JH, Kim YK, Park JS, Lee JE, Oh MS, Chung EJ, et al. Lack of association between LRRK2 G2385R and cognitive dysfunction in Korean patients with Parkinson's disease. J Clin Neurosci. 2017;36:108-13.

35. Ben Sassi S, Nabli F, Hentati E, Nahdi H, Trabelsi M, Ben Ayed H, et al. Cognitive dysfunction in Tunisian LRRK2 associated Parkinson's disease. Parkinsonism Relat Disord. 2012;18(3):243-6.

36. Shanker V, Groves M, Heiman G, Palmese C, Saunders-Pullman R, Ozelius L, et al. Mood and cognition in leucine-rich repeat kinase 2 G2019S Parkinson's disease. Mov Disord. 2011;26(10):1875-80.

37. Zheng Y, Pei Z, Liu Y, Zhou H, Xian W, Fang Y, et al. Cognitive Impairments in LRRK2-Related Parkinson's Disease: A Study in Chinese Individuals. Behavioural Neurology. 2015;2015:5.

38. Kasten M, Kertelge L, Tadic V, Bruggemann N, Schmidt A, Van Der Vegt J, et al. Depression and quality of life in monogenic compared to idiopathic, early-onset Parkinson's disease. Mov Disord. 2012;27(6):754-9.

39. Gaig C, Vilas D, Infante J, Sierra M, Garcia-Gorostiaga I, Buongiorno M, et al. Nonmotor symptoms in LRRK2 G2019S associated Parkinson's disease. PLoS One. 2014;9(10):e108982.

40. Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord. 2015;30(3):407-11.

41. Davis MY, Johnson CO, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, et al. Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease. JAMA Neurol. 2016;73(10):1217-24.

42. Malec-Litwinowicz M, Rudzinska M, Szubiga M, Michalski M, Tomaszewski T, Szczudlik A. Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients. Neurol Neurochir Pol. 2014;48(4):258-61.

43. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, et al. GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord. 2016;31(1):95-102.

44. Zokaei N, Mcneill A, Proukakis C, Beavan M, Jarman P, Korlipara P, et al. Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. Brain. 2014;137(Pt 8):2303-11.

45. Mata IF, Johnson CO, Leverenz JB, Weintraub D, Trojanowski JQ, Van Deerlin VM, et al. Large-scale exploratory genetic analysis of cognitive impairment in Parkinson's disease. Neurobiol Aging. 2017;56:211 e1- e7.

46. Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T, et al. GBA-associated PD presents with nonmotor characteristics. Neurology. 2011;77(3):276-80.

47. Swan M, Ortega R, Barrett M, Soto-Valencia J, Boschung S, Deik Acosta Madiedo A, et al. Neuropsychiatric Features of GBA-Associated Parkinson Disease. Neurology. 2014;82(10 Supplement):P2.024.

48. Dan X, Wang C, Zhang J, Gu Z, Zhou Y, Ma J, et al. Association between common genetic risk variants and depression in Parkinson's disease: A dPD study in Chinese. Parkinsonism Relat Disord. 2016;33:122-6.

49. Da Silva CP, De MaG, Cabello Acero PH, Campos MJ, Pereira JS, De ARSR, et al. Clinical profiles associated with LRRK2 and GBA mutations in Brazilians with Parkinson's disease. J Neurol Sci. 2017;381:160-4.

50. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Hurtig HI, Van Deerlin VM, et al. APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. JAMA Neurol. 2014;71(11):1405-12.

51. Nombela C, Rowe JB, Winder-Rhodes SE, Hampshire A, Owen AM, Breen DP, et al. Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain. 2014;137(Pt 10):2743-58.

52. Troster AI, Fields JA, Paolo AM, Koller WC. Absence of the apolipoprotein E epsilon4 allele is associated with working memory impairment in Parkinson's disease. J Neurol Sci. 2006;248(1-2):62-7.

53. Menza MA, Palermo B, Dipaola R, Sage JI, Ricketts MH. Depression and anxiety in Parkinson's disease: possible effect of genetic variation in the serotonin transporter. J Geriatr Psychiatry Neurol. 1999;12(2):49-52.

54. Dissanayaka NNW, Silburn PA, O'sullivan JD, Mellick GD. Serotonin and dopamine transporter genes do not influence depression in Parkinson's disease. Movement Disorders. 2009;24(1):111-5.

55. Border R, Johnson EC, Evans LM, Smolen A, Berley N, Sullivan PF, et al. No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples. Am J Psychiatry. 2019;176(5):376-87.

56. Altmann V, Schumacher-Schuh AF, Rieck M, Callegari-Jacques SM, Rieder CR, Hutz MH. Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. Neurosci Lett. 2016;615:88-91.

57. Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009;132(Pt 11):2958-69.

58. Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain. 2008;131(Pt 2):397-408.

59. Barrett MJ, Koeppel AF, Flanigan JL, Turner SD, Worrall BB. Investigation of Genetic Variants Associated with Alzheimer Disease in Parkinson Disease Cognition. J Parkinsons Dis. 2016;6(1):119-24.

60. Cagni FC, Campelo C, Coimbra DG, Barbosa MR, Junior LGO, Neto ABS, et al. Association of BDNF Val66MET Polymorphism With Parkinson's Disease and Depression and Anxiety Symptoms. J Neuropsychiatry Clin Neurosci. 2017;29(2):142-7.

61. Hua P, Liu W, Kuo SH, Zhao Y, Chen L, Zhang N, et al. Association of Tef polymorphism with depression in Parkinson disease. Mov Disord. 2012;27(13):1694-7.

62. Barrero FJ, Ampuero I, Morales B, Vives F, De Dios Luna Del Castillo J, Hoenicka J, et al. Depression in Parkinson's disease is related to a genetic polymorphism of the cannabinoid receptor gene (CNR1). Pharmacogenomics J. 2005;5(2):135-41.

63. West AB, Moore DJ, Biskup S, Bugayenko A, Smith WW, Ross CA, et al. Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. Proc Natl Acad Sci U S A. 2005;102(46):16842-7.

64. Gilsbach BK, Kortholt A. Structural biology of the LRRK2 GTPase and kinase domains: implications for regulation. Front Mol Neurosci. 2014;7:32.

65. Irwin DJ, White MT, Toledo JB, Xie SX, Robinson JL, Van Deerlin V, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol. 2012;72(4):587-98.

66. Henry AG, Aghamohammadzadeh S, Samaroo H, Chen Y, Mou K, Needle E, et al. Pathogenic LRRK2 mutations, through increased kinase activity, produce enlarged lysosomes with reduced degradative capacity and increase ATP13A2 expression. Hum Mol Genet. 2015;24(21):6013-28.

67. Schapansky J, Khasnavis S, Deandrade MP, Nardozzi JD, Falkson SR, Boyd JD, et al. Familial knockin mutation of LRRK2 causes lysosomal dysfunction and accumulation of endogenous insoluble alpha-synuclein in neurons. Neurobiol Dis. 2018;111:26-35.

68. Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol. 2012;11(11):986-98.

69. Clark LN, Kartsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, et al. Association of glucocerebrosidase mutations with dementia with lewy bodies. Arch Neurol. 2009;66(5):578-83.

70. Gan-Or Z, Amshalom I, Kilarski LL, Bar-Shira A, Gana-Weisz M, Mirelman A, et al. Differential effects of severe vs mild GBA mutations on Parkinson disease. Neurology. 2015;84(9):880-7.

71. Li JQ, Tan L, Yu JT. The role of the LRRK2 gene in Parkinsonism. Mol Neurodegener. 2014;9:47.

72. Chahine LM, Urbe L, Caspell-Garcia C, Aarsland D, Alcalay R, Barone P, et al. Cognition among individuals along a spectrum of increased risk for Parkinson's disease. PLoS One. 2018;13(8):e0201964.

73. Barone P, Erro R, Picillo M. Quality of Life and Nonmotor Symptoms in Parkinson's Disease. Int Rev Neurobiol. 2017;133:499-516.

74. Liu G, Locascio JJ, Corvol JC, Boot B, Liao Z, Page K, et al. Prediction of cognition in Parkinson's disease with a clinical-genetic score: a longitudinal analysis of nine cohorts. Lancet Neurol. 2017;16(8):620-9.

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 *LRRK2*)	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).

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	*LRRK2* 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	*LRRK2* 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 LRRK2 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).

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 *GBA*)	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)	*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	MoCA	Cognitive impairment was significantly more frequent (45% vs 30%) and more severe (22.53 vs 26.53 MoCA points) among *GBA*-PD compared to sporadic PD (p=0.02).
Alcalay et al. (2012) (12)	71 (24 *GBA)*	59.0 (6.7)	35.1 (11.5)	rs76763715, rs421016, rs387906315, rs80356773	MMSE, CVLT-II, BVRT, COWAT, WMS-R	*GBA* 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	*GBA* 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 *GBA*)	57.2 (2.8)	36.4 (18.5)	rs76763715, rs75548401	MMSE	*GBA* rs76763715 carriers were significantly more likely to develop dementia (MMSE score<26) (p=0.03).
Wang et al. (2014) (31)	1638 (49 *GBA*)	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*)*.

Zokaei et al. (2014) (44)	67 (15 *GBA*)	61.0 (9.0)	n/s	rs76763715, rs421016	VSTM	*GBA*-positive people with showed significantly worse recall than other study groups ($p<0.005$)
Davis et al. (2016) (41)	733 (58 *GBA*)	64.0 (9.0)	31.8 (10.6)	*GBA* coding region variants, rs2230288	"*Detailed cognitive testing*"	A significantly higher proportion of rs2230288 carriers ($p=0.01$) and of other *GBA* variant carriers ($p=0.04$) progressed to mild cognitive impairment or dementia.
Mata et al. (2016) (43)	1369 (125 *GBA*)	57.3 (12.3)	30.4 (12.3)	*GBA* coding region variants, rs2230288	MoCA, Letter-Number sequencing, trail making, JLO	*GBA* carriers had a higher prevalence of dementia ($p=9.7\times10^{-6}$) 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 *GBA* rs2230288 ($PFDR = 2.7 \times 10^{-4}$) for JLO.
Liu et al. (2017) (74)	3200 (308 *GBA*)	n/s	n/s	n/s	MMSE	A multivariable cognitive risk score including the *GBA* 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).

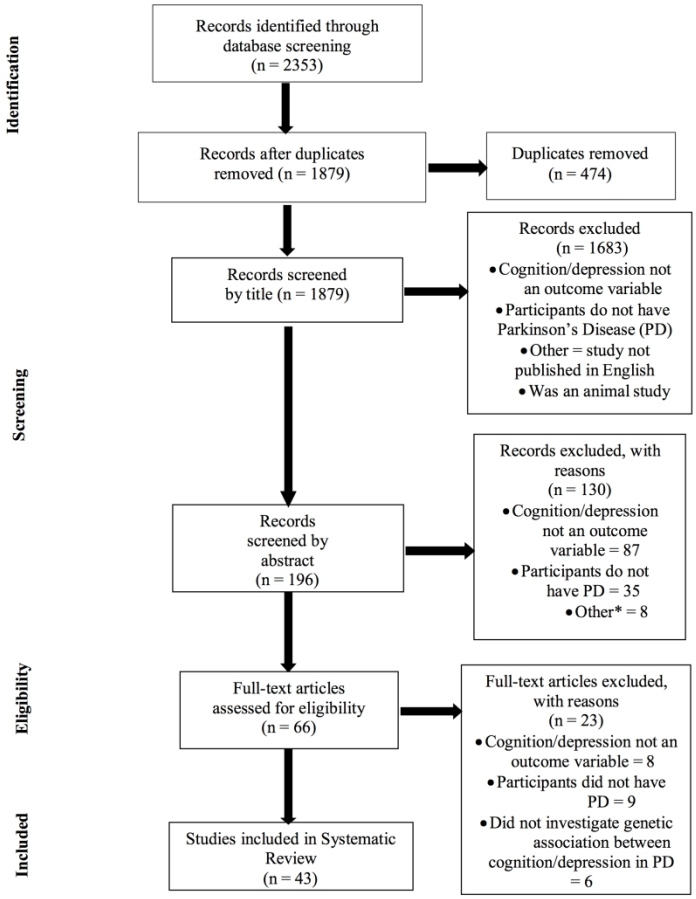
UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; CVLT-II: California Verbal Learning Test-II; BVRT: Benton Visual Retention Test; COWAT: Controlled Oral Word Association Test; WMS-R: Wechsler Memory Scale–Revised; MoCA: Montreal Cognitive Assessment; ADAS: The Alzheimer's 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.

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	*GBA* 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 *GBA*)	65.6 (12.5)	16.7 (8.7)	rs76763715, rs421016, rs387906315, rs80356773	BDI	*GBA* 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 *GBA*)	61.61 (10.90)	22.53 (14.17)	rs421016	CES-D	*GBA* variant carriers had significantly higher CES-D scores above 16 than other study groups (p=0.048).
Dan et al. (2016) (48)	1047 (40 *GBA*)	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.

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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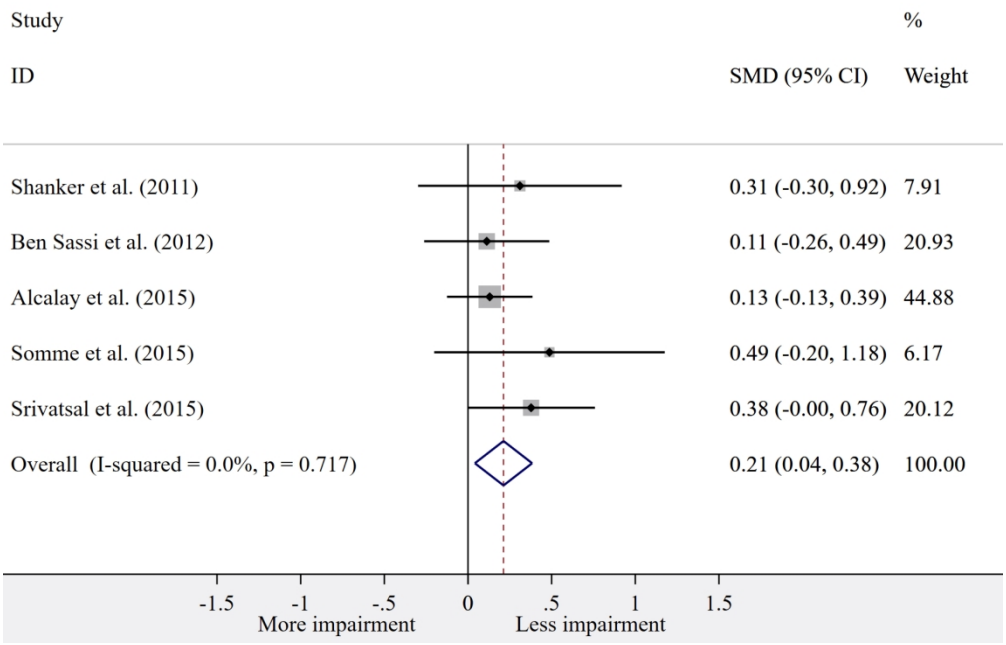
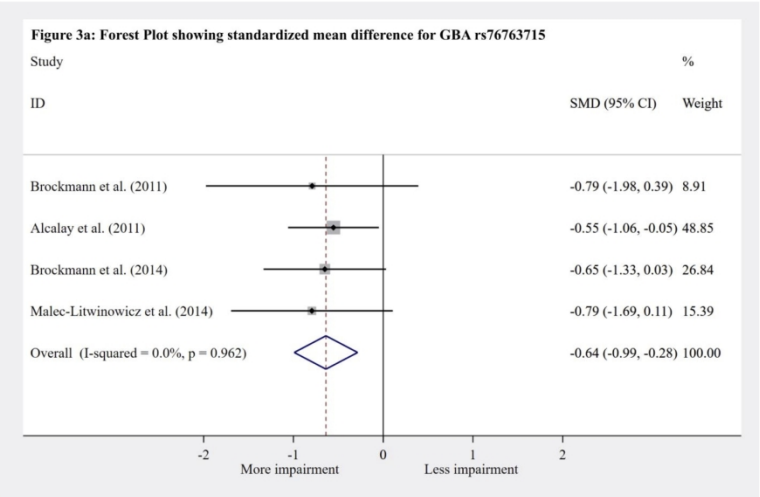
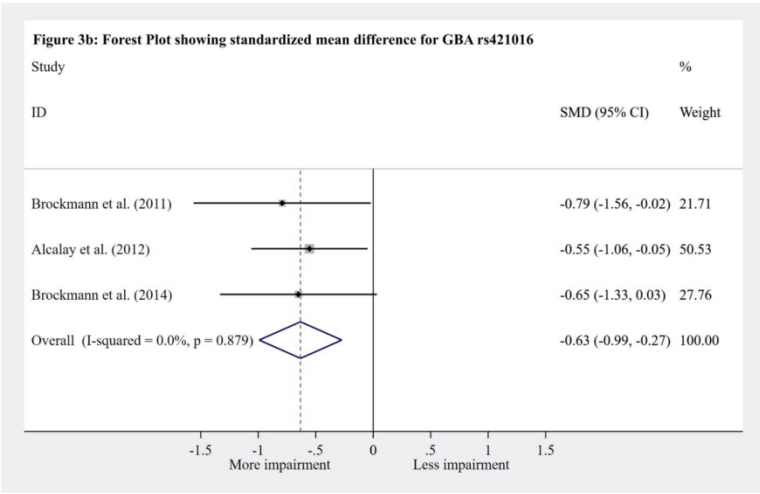


The meta-analysis of five studies investigating the association between LRRK2 variant rs34637584 and cognitive impairment in people with PD

659x423mm (300 x 300 DPI)





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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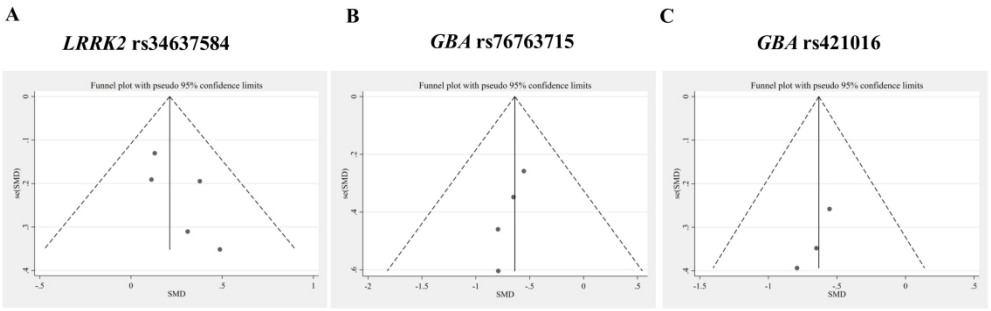

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Supplementary Information Table 1: Quality assessment of included studies using 'Q-Genie' quality assessment tool

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

Williams-Gray et al. (2008) (22)	3	3	4	3	2	3	4	4	4	3	4	37
Barrero et al. (2005) (23)	4	4	3	3	3	2	4	3	4	3	3	36
Belarbi et al. (2010) (24)	3	3	4	4	4	2	4	3	3	4	2	36
Davis et al. (2016) (25)	4	3	3	5	4	3	2	3	4	4	3	36
Srivastava et al. (2011) (26)	4	3	2	2	2	2	5	4	4	3	3	36
Gaig et al. (2014) (27)	3	3	3	2	3	4	4	4	3	3	3	35
Shanker et al. (2011) (28)	2	3	4	2	5	4	3	3	3	3	3	35
Da Silva et al. (2017) (29)	3	4	4	3	2	3	2	3	2	4	5	35
Brockmann et al. (2011) (30)	3	3	4	2	3	3	3	3	4	3	3	34
Hua et al. (2012) (31)	4	3	n/a	2	2	3	4	4	5	4	3	34
Zheng et al. (2017) (32)	3	4	4	3	3	2	2	3	4	3	3	34
Altmann et al. (2016) (33)	4	3	n/a	3	2	3	4	3	4	3	4	33
Malec-Litwinowicz et al. (2014) (34)	3	3	3	2	2	3	4	3	3	3	3	32
Menza et al. (1999) (35)	4	4	3	3	2	3	2	3	3	2	3	32
Ben Sassi et al. (2012) (36)	4	4	3	2	2	3	3	4	2	2	3	32
Srivatsal et al. (2015) (37)	3	3	3	2	2	3	3	4	4	2	3	32
Hong et al. (2017) (38)	4	3	4	5	4	3	3	4	4	4	3	31
Somme et al. (2015) (39)	4	2	4	2	2	3	2	3	3	3	3	31
Kasten et al. (2012) (40)	3	2	4	2	2	3	2	4	3	2	3	30
Brockmann et al. (2015) (41)	2	2	3	3	4	2	2	3	2	3	3	29
Zheng et al. (2015) (42)	4	3	n/a	2	3	2	2	4	3	2	3	28
Estanga et al. (2014) (43)	5	3	3	1	1	2	1	3	3	3	2	27

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

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

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 *APOE*)	65.6 (8.2)	n/s	*APOE* (ε4 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	*COMT* (rs6265)	Modified CANTAB ID/ED task	n/s	People with high activity COMT 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	*APOE* (ε4 and ε2 allele)	MMSE	Incident cohort = 5 years (±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 APOE. 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)	*APOE* (ε4 allele)	MDRS version II	1 year	The ε4 allele of *APOE* 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 ≥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	*APOE* (ε4 allele), *MAPT* variants, *SNCA* (rs356219)	HVLT-R; Letter-Number Sequencing Test and Trail Making Test; MoCA	n/s	The *APOE* ε4 allele was associated with lower performance on the HVLT-R total recall (p=6.7 × 10^{-6}; corrected p_C=6.0 × 10^{-5}), delayed recall (p = .001; p_C=.009), and recognition discrimination Index (p=.004; p_C=.04).

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)	*COMT* and *MAPT* variants, and *APOE* (ε4 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	*BDNF* (rs6265)	MMSE	n/s	Carriers of at least one BDNF 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 *BIN1*, *CLU*, *ABCA7*, *CR1*, *PICALM*, *MS4A6A*, *CD33*, *MS4A4E*, *CD2AP*	MMSE	n/s	*PICALM* rs3851179 was associated with cognitive impairment (MMSE < 24) in PD subjects>70 years old but not in PD subjects≤70 years old.
Wang et al. (2016) (3)	296	62.60 (9.40)	UPDRS-III 22.62 (13.83)	*SNCA* (rs11931074, rs894278) MAPT (rs242557, rs3744456)	MMSE	4 years	Increased severity of cognitive impairment was associated with *MAPT* H1c haplotype (p=0.05) with none of the risk alleles chosen associated with survival to the cognitive cutoff (p>0.05).

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	*5-HTTLPR (SLC6A4)*	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)	*CNR1* variants	HDRS	The presence of two long alleles in the *CNR1* gene was associated with a reduced prevalence of depression (p=0.003).
Burn et al. (2006) (1)	190 (108 *5-HTTLPR*)	71.1 (8.2)	n/s	*5-HTTLPR (SLC6A4)*	MADRS; GDS-15	No association between *5-HTTLPR* 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	*SLC6A3* and *SLC6A4* variants	GDS-15	There were no significant differences in haplotype frequencies between depressed people and not depressed groups; SLC6A4 (p=0.69) and SLC6A3 (p=0.41).
Srivastava et al. (2011) (26)	88	51.8 (9.7)	UPDRS-III 19.75 (7.25)	*PRKN* 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 *PRKN* variants.
Hua et al. (2012) (31)	408	65.3 (10.2)	UPDRS-III = 25.7 (15.1)	*Cry1 (*rs2287161), *Cry2* (rs10838524) and *Tef (*rs738499) variants.	HDRS	Higher HDRS scores were found in the TT genotype group in *Tef* rs738499 (p<0.01) and the CC genotype group in Cry1 rs2287161 (p<0.01). There was no difference in HDRS scores between the *CRY2* AA genotype and AG genotype (rs10838524).
Kasten et al. (2012) (40)	42 (2 *SNCA*, 8 *PRKN*, 9 *PINK1* and 4 *LRRK2*)	Carriers = 44 (13) (MMC),	UPDRS-III 16.7 (13.9) (MMC)	Variants in *SNCA, Parkin, PINK1, LRRK2*	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.

Cagni et al. (2017) (14)	200 (104 *BDNF*)	64.32 (11.71)	UPDRS-III Carriers (G/G) = 21.72 (10.8) Carriers = (A/G +A/A) = 21.07 (8.07)	*BDNF* (rs6265)	BDI	People with PD presented more prevalent and severe depression symptoms, measured by BDI (7.18 (7.80) versus 16.22 (9.52), p=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	*SNCA* variants	HDRS	Significant differences between the two groups in minor allele frequency of *SLC6A15* rs1545843 and in frequencies of genotypes and minor alleles of rs78162420 in *TPH2*.

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

References:

1. Burn DJ, Tiangyou W, Allcock LM, Davison J, Chinnery PF. Allelic variation of a functional polymorphism in the serotonin transporter gene and depression in Parkinson's disease. Parkinsonism & Related Disorders. 2006;12(3):139-41.
2. Chahine LM, Urbe L, Caspell-Garcia C, Aarsland D, Alcalay R, Barone P, et al. Cognition among individuals along a spectrum of increased risk for Parkinson's disease. PLoS One. 2018;13(8):e0201964.
3. Wang G, Huang Y, Chen W, Chen S, Wang Y, Xiao Q, et al. Variants in the SNCA gene associate with motor progression while variants in the MAPT gene associate with the severity of Parkinson's disease. Parkinsonism Relat Disord. 2016;24:89-94.
4. Nombela C, Rowe JB, Winder-Rhodes SE, Hampshire A, Owen AM, Breen DP, et al. Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain. 2014;137(Pt 10):2743-58.
5. Dan X, Wang C, Zhang J, Gu Z, Zhou Y, Ma J, et al. Association between common genetic risk variants and depression in Parkinson's disease: A dPD study in Chinese. Parkinsonism Relat Disord. 2016;33:122-6.
6. Williams-Gray CH, Goris A, Saiki M, Foltynie T, Compston DA, Sawcer SJ, et al. Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. J Neurol. 2009;256(3):493-8.
7. Zokaei N, Mcneill A, Proukakis C, Beavan M, Jarman P, Korlipara P, et al. Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. Brain. 2014;137(Pt 8):2303-11.
8. Alcalay RN, Mejia-Santana H, Tang MX, Rakitin B, Rosado L, Ross B, et al. Self-report of cognitive impairment and mini-mental state examination performance in PRKN,

LRRK2, and GBA carriers with early onset Parkinson's disease. J Clin Exp Neuropsychol. 2010;32(7):775-9.

9. Dissanayaka NNW, Silburn PA, O'sullivan JD, Mellick GD. Serotonin and dopamine transporter genes do not influence depression in Parkinson's disease. Movement Disorders. 2009;24(1):111-5.
10. Troster AI, Fields JA, Paolo AM, Koller WC. Absence of the apolipoprotein E epsilon4 allele is associated with working memory impairment in Parkinson's disease. J Neurol Sci. 2006;248(1-2):62-7.
11. Mata IF, Johnson CO, Leverenz JB, Weintraub D, Trojanowski JQ, Van Deerlin VM, et al. Large-scale exploratory genetic analysis of cognitive impairment in Parkinson's disease. Neurobiol Aging. 2017;56:211 e1- e7.
12. Barrett MJ, Koeppel AF, Flanigan JL, Turner SD, Worrall BB. Investigation of Genetic Variants Associated with Alzheimer Disease in Parkinson Disease Cognition. J Parkinsons Dis. 2016;6(1):119-24.
13. Alcalay RN, Mejia-Santana H, Mirelman A, Saunders-Pullman R, Raymond D, Palmese C, et al. Neuropsychological performance in LRRK2 G2019S carriers with Parkinson's disease. Parkinsonism Relat Disord. 2015;21(2):106-10.
14. Cagni FC, Campelo C, Coimbra DG, Barbosa MR, Junior LGO, Neto ABS, et al. Association of BDNF Val66MET Polymorphism With Parkinson's Disease and Depression and Anxiety Symptoms. J Neuropsychiatry Clin Neurosci. 2017;29(2):142-7.
15. Beavan M, Mcneill A, Proukakis C, Hughes DA, Mehta A, Schapira AH. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA Neurol. 2015;72(2):201-8.

16. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Hurtig HI, Van Deerlin VM, et al. APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. JAMA Neurol. 2014;71(11):1405-12.

17. Morley JF, Xie SX, Hurtig HI, Stern MB, Colcher A, Horn S, et al. Genetic influences on cognitive decline in Parkinson's disease. Mov Disord. 2012;27(4):512-8.

18. Wang C, Cai Y, Gu Z, Ma J, Zheng Z, Tang BS, et al. Clinical profiles of Parkinson's disease associated with common leucine-rich repeat kinase 2 and glucocerebrosidase genetic variants in Chinese individuals. Neurobiol Aging. 2014;35(3):725 e1-6.

19. Alcalay RN, Caccappolo E, Mejia-Santana H, Tang M, Rosado L, Orbe Reilly M, et al. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology. 2012;78(18):1434-40.

20. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, et al. GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord. 2016;31(1):95-102.

21. Swan M, Ortega R, Barrett M, Soto-Valencia J, Boschung S, Deik Acosta Madiedo A, et al. Neuropsychiatric Features of GBA-Associated Parkinson Disease. Neurology. 2014;82(10 Supplement):P2.024.

22. Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain. 2008;131(Pt 2):397-408.

23. Barrero FJ, Ampuero I, Morales B, Vives F, De Dios Luna Del Castillo J, Hoenicka J, et al. Depression in Parkinson's disease is related to a genetic polymorphism of the cannabinoid receptor gene (CNR1). Pharmacogenomics J. 2005;5(2):135-41.

24. Belarbi S, Hecham N, Lesage S, Kediha MI, Smail N, Benhassine T, et al. LRRK2 G2019S mutation in Parkinson's disease: a neuropsychological and neuropsychiatric study in a large Algerian cohort. Parkinsonism Relat Disord. 2010;16(10):676-9.

25. Davis MY, Johnson CO, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, et al. Association of GBA Mutations and the E326K Polymorphism With Motor and Cognitive Progression in Parkinson Disease. JAMA Neurol. 2016;73(10):1217-24.

26. Srivastava A, Tang MX, Mejia-Santana H, Rosado L, Louis ED, Caccappolo E, et al. The relation between depression and parkin genotype: the CORE-PD study. Parkinsonism Relat Disord. 2011;17(10):740-4.

27. Gaig C, Vilas D, Infante J, Sierra M, Garcia-Gorostiaga I, Buongiorno M, et al. Nonmotor symptoms in LRRK2 G2019S associated Parkinson's disease. PLoS One. 2014;9(10):e108982.

28. Shanker V, Groves M, Heiman G, Palmese C, Saunders-Pullman R, Ozelius L, et al. Mood and cognition in leucine-rich repeat kinase 2 G2019S Parkinson's disease. Mov Disord. 2011;26(10):1875-80.

29. Da Silva CP, De MaG, Cabello Acero PH, Campos MJ, Pereira JS, De ARSR, et al. Clinical profiles associated with LRRK2 and GBA mutations in Brazilians with Parkinson's disease. J Neurol Sci. 2017;381:160-4.

30. Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T, et al. GBA-associated PD presents with nonmotor characteristics. Neurology. 2011;77(3):276-80.

31. Hua P, Liu W, Kuo SH, Zhao Y, Chen L, Zhang N, et al. Association of Tef polymorphism with depression in Parkinson disease. Mov Disord. 2012;27(13):1694-7.

32. Zheng J, Yang X, Zhao Q, Tian S, Huang H, Chen Y, et al. Association between gene polymorphism and depression in Parkinson's disease: A case-control study. J Neurol Sci. 2017;375:231-4.

33. Altmann V, Schumacher-Schuh AF, Rieck M, Callegari-Jacques SM, Rieder CR, Hutz MH. Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. Neurosci Lett. 2016;615:88-91.

34. Malec-Litwinowicz M, Rudzinska M, Szubiga M, Michalski M, Tomaszewski T, Szczudlik A. Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients. Neurol Neurochir Pol. 2014;48(4):258-61.

35. Menza MA, Palermo B, Dipaola R, Sage JI, Ricketts MH. Depression and anxiety in Parkinson's disease: possible effect of genetic variation in the serotonin transporter. J Geriatr Psychiatry Neurol. 1999;12(2):49-52.

36. Ben Sassi S, Nabli F, Hentati E, Nahdi H, Trabelsi M, Ben Ayed H, et al. Cognitive dysfunction in Tunisian LRRK2 associated Parkinson's disease. Parkinsonism Relat Disord. 2012;18(3):243-6.

37. Srivatsal S, Cholerton B, Leverenz JB, Wszolek ZK, Uitti RJ, Dickson DW, et al. Cognitive profile of LRRK2-related Parkinson's disease. Mov Disord. 2015;30(5):728-33.

38. Hong JH, Kim YK, Park JS, Lee JE, Oh MS, Chung EJ, et al. Lack of association between LRRK2 G2385R and cognitive dysfunction in Korean patients with Parkinson's disease. J Clin Neurosci. 2017;36:108-13.

39. Somme JH, Molano Salazar A, Gonzalez A, Tijero B, Berganzo K, Lezcano E, et al. Cognitive and behavioral symptoms in Parkinson's disease patients with the G2019S and R1441G mutations of the LRRK2 gene. Parkinsonism Relat Disord. 2015;21(5):494-9.

40. Kasten M, Kertelge L, Tadic V, Bruggemann N, Schmidt A, Van Der Vegt J, et al. Depression and quality of life in monogenic compared to idiopathic, early-onset Parkinson's disease. Mov Disord. 2012;27(6):754-9.

41. Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord. 2015;30(3):407-11.

42. Zheng Y, Pei Z, Liu Y, Zhou H, Xian W, Fang Y, et al. Cognitive Impairments in LRRK2-Related Parkinson's Disease: A Study in Chinese Individuals. Behavioural Neurology. 2015;2015:5.

43. Estanga A, Rodriguez-Oroz MC, Ruiz-Martinez J, Barandiaran M, Gorostidi A, Bergareche A, et al. Cognitive dysfunction in Parkinson's disease related to the R1441G mutation in LRRK2. Parkinsonism Relat Disord. 2014;20(10):1097-100.