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

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Abstract

Objective: Cognitive impairment and depression are among the most prevalent and most disabling non-motor symptoms in Parkinson’s disease (PD). The genetic factors that are associated with these symptoms remain uncertain. This systematic review aims to summarise the prevailing evidence from all genetic association studies investigating the genetic variants associated with cognitive impairment and depressive symptoms in people with PD.

Method: A systematic review using five online databases: PubMed, PsycINFO, CINAHL, EMBASE and OpenGrey (PROSPERO protocol: CRD42017067431). We completed the quality assessment using the Q-Genie tool.

Results: 2353 articles were screened, and 43 articles were found to be eligible to be included. A meta-analysis of studies investigating LRRK2 rs34637584 confirmed that the minor allele carriers had significantly less cognitive impairment (p = 0.015). Further meta-analyses showed that GBA variants rs76763715 (p < 0.001) and rs421016 (p = 0.001) were significantly associated with more cognitive impairment in people with PD. Minor alleles of GBA variants rs76763715, rs421016, rs387906315 and rs80356773 were associated with more depressive symptoms in PD. Moreover, APOE ε4 allele has been associated with more cognitive impairment in PD. BDNF (rs6265) and CRY1 (rs2287161) variants have been associated with more depressive symptoms in people with PD.

Conclusions: PD carriers of GBA variants are at high risk for cognitive decline and depression. Screening for these variants may facilitate early identification and effective management of these non-motor symptoms. The molecular mechanisms underlying favourable cognitive functioning in LRRK2 rs34637584 variant carriers warrant further investigation.

Summations:

1. Available evidence confirms that the LRRK2 variant rs34637584 is associated with less cognitive impairment in people with PD.
2. GBA variants rs76763715 and rs421016 are associated with more severe cognitive impairment in people with PD.
3. The GBA variants rs76763715, rs421016, rs387906315 and rs80356773 have been significantly associated with the onset of depressive symptoms in PD.

Considerations:

1. This systematic review has not included studies that were not published in English. It did not include gene expression and epigenetic studies.
2. Most of the included genetic association studies were small, and they were prone to type II error.
3. There was substantial heterogeneity among the included studies.

Introduction

Parkinson’s disease (PD) is a degenerative neurological disorder that comprises both motor and non-motor manifestations. Various non-motor symptoms emerge throughout the progression of PD, and they may become apparent even before the manifestation of motor symptoms. Such symptoms include insomnia, depression, anxiety and cognitive impairment, including Parkinson’s disease dementia (PDD) (Park & Stacy, 2009). Mild cognitive impairment (MCI) occurs early in the course of PD (Muslimovic et al., 2005), and it affects various cognitive domains including, visuospatial, attentional and executive (Pedersen et al., 2013). Up to 80% of
people with PD will progress from MCI to PDD, after having PD for 15–20 years (Aarsland & Kurz, 2010).

The understanding of cognitive decline in PD is important, because it has direct relations to quality of life, morbidity, nursing home placements and hospital admissions (Vossius et al., 2011). Therefore, many studies have investigated the associations between genetic variants and cognitive impairment in PD; for example, apolipoprotein E allele (APOE) has been associated with the early onset of PDD and more cognitive decline in PD (Morley et al., 2012; Gomperts et al., 2013). However, the results of studies investigating this genetic association have been inconsistent (Kurz et al., 2009; Williams-Gray et al., 2009). Other genetic correlates include microtubule-associated protein tau (MAPT) H1 haplotype (Goris et al., 2007) and variants in the glucosidase, beta acid (GBA) gene, which are not only predispositions to PD (Neumann et al., 2009) but have also been found to have associations with cognitive impairment in PD (Alcalay et al., 2012). Contrary to this, not all genetic variants, associated with PD, have relations to cognitive impairment in PD. For example, variants of leucine-rich repeat kinase 2 (LRRK2) are the most prevalent known cause of autosomal dominant PD, but a clear association has not been determined between the gene variants and cognition (Alcalay et al., 2015; Kalia et al., 2015; Somme et al., 2015).

Another prevalent non-motor manifestation of PD is depression. The reported prevalence of depression in people with PD has varied from 40% to 90% (Cummings, 1991; Marsh, 2000). Despite there being an abundance of literature regarding the genetics of depression (Anguelova et al., 2003), research is sparse 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 (Wendland et al., 2006), the dopamine transporter gene (SLC6A3) has been examined as a potential candidate gene for depression in PD (Ohadi et al., 2006). In addition, 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 (Arabia et al., 2007).

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 PD, irrespective of their age and gender, were considered. Animal studies and in vitro 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 comprised 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 were: ‘Gene*’, OR ‘LRRK2’, OR ‘GBA’, OR ‘SNCA’. The outcome search terms that were used included were: (‘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 (Sohani et al., 2015). 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 (Sohani et al., 2016).
**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) (Martinez-Martin et al., 1994) 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) (Folstein et al., 1975) or ‘Beck Depression Inventory’ (Beck et al., 1996). 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 (LRRK2 variants, rs76763715), we conducted a meta-analysis of studies investigating this specific variant using different outcome measures and calculated their standardised mean difference (SMD) (95% CI 0.04–0.38) (Fig. 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 (Alcalay et al., 2010; Belbari et al., 2010; Shanker et al., 2011; Ben Sassi et al., 2012; Estanga et al., 2014; Zheng et al., 2015; Hong et al., 2017). Most of these studies were cross-sectional. They had relatively small sample sizes, and they have not reported power analyses (Hong et al., 2017). 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 (Belbari et al., 2010; Kasten et al., 2012). 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) (Gaig et al., 2014).

**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 (Alcalay et al., 2012; Malec-Litwinowicz et al., 2014; Wang et al., 2014; Zokaei et al., 2014; Brockmann et al., 2015; Davis et al., 2016; Mata et al., 2016, 2017). Alcalay et al. (2012) found that minor allele carriers of GBA variants rs76763715 and rs36806 obtained significantly less MMSE scores than the non-carriers. Moreover, a longitudinal study (Davis et al., 2016) 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. (2014) 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 (Mata et al., 2017). 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 (Alcalay et al., 2010; Brockmann et al., 2011). One of them was a longitudinal study including 3 years of follow-up, but it included only 13 people with GBA variants (Brockmann et al., 2011). We conducted meta-analyses of the studies investigating the effects of GBA rs76763715 (Fig. 3(A)) and rs421016 (Fig. 3(B)) variants on cognition in people with PD (Supplementary Figure 1). Our meta-analyses confirmed that both rs76763715

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Fig. 1. A PRISMA flowchart 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.
Table 1. Studies investigating the effects of \textit{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)        | 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)        | 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)        | 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)      | 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)        | 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)           | 1638 (223 \textit{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)        | 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)          | 54 (12 rs34637584, 15 rs33939927) | rs34637584 = 66.1 (11.1), rs33939927 = 62.1 (6.5) | rs34637584 = 29.8 (15.9), rs33939927 = 28.2 (8.4) | rs34637584, rs33939927 | MDRS II; RAVLT | \textit{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)      | 1355 (24 rs34637584, 5 rs33939927) | 67.9 (9.6)          | n/s                 | rs34637584, rs33939927   | MMSE; Letter-Number Sequencing Test | \textit{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)          | 90 (45 rs11564148) | 60.79 (10.19)       | 23.34 (9.88)        | rs11564148                | Stroop word colour test | Cognitive impairments did not correlate significantly with different \textit{LRRK2} rs11564148 variants in Chinese people with PD ($p = 0.051$) |
| Hong et al. (2017)           | 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; MDRS, Mattis Dementia Rating Scale; ADAS, 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.
(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 (Brockmann et al., 2011; Swan et al., 2014; Wang et al., 2014; Dan et al., 2016) and two studies that investigated GBA variant rs76763715 (Brockmann et al., 2011; Swan et al., 2014) 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 (Swan et al., 2014). However, a small longitudinal study following only 13 people with PD and GBA variants for 3 years has reported that mood symptoms did not differ significantly between the carriers and non-carriers during their follow-up (Brockmann et al., 2011). 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 (Brockmann et al., 2011). Another small longitudinal study investigating a heterogeneous PD group with one of several LRRK2 and GBA variants, including rs34637584, rs421016 and rs76763715, has reported them having significantly higher incidence and earlier onset of depressive symptoms than the non-carriers (Da Silva et al., 2017) 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 (Williams-Gray et al., 2009). Significantly more rapid cognitive decline, measured by the Hamilton Verbal Learning test (Mata et al., 2014) and the Mattis Dementia Rating Scale-II (Morley et al., 2012), has been reported in people with PD carrying APOE ε4 allele. However, there are negative studies that failed to replicate this association (Troster et al., 2006; Nombela et al., 2014). 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 (Williams-Gray et al., 2009).

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 (Menza et al., 1999). Later, two relatively larger studies have clarified that people with PD carrying this short allele did not differ significantly from non-carriers on their depressive symptoms (Burn et al., 2006; Dissanayaka et al., 2009). 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 (Border et al., 2019).

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), Fig. 2. The meta-analysis of five studies investigating the association between LRRK2 variant rs34637584 and cognitive impairment in people with PD.

| Study ID | SMD (95% CI) | Weight |
|----------|--------------|--------|
| Shanker et al. (2011) | -0.30 (0.92) | 7.91 |
| Ben Sassi et al. (2012) | -0.26 (0.49) | 20.93 |
| Alcalay et al. (2015) | -0.13 (0.39) | 44.88 |
| Somme et al. (2015) | -0.20 (1.18) | 6.17 |
| Srivatsal et al. (2015) | -0.00 (0.76) | 20.12 |
| Overall (I-squared = 0.0%, p = 0.717) | 0.21 (0.04, 0.38) | 100.00 |

(−1.5, −1.0, −0.5, 0, 0.5, 1.5) More impairment Less impairment
### Table 2. Studies investigating the effects of GBA variants on cognition in people with PD

| Sample size | Mean age (SD) years | Mean UPDRS-III severity (SD) | Variants | Outcome | Findings |
|-------------|---------------------|-----------------------------|----------|---------|----------|
| Alcalay et al. (2010) | 699 (37 GBA) | 54.4 (4.9) | rs76763715 rs421016 | MMSE | MMSE scores did not differ significantly among the study groups |
| Brockmann et al. (2011) | 40 (6 rs76763715, 14 rs421016) | GBA-PD = 62.75 (10.4); Sporadic PD = 67.60 (9.3) | 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) | 71 (24 GBA) | 59.0 (6.7) | 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) | 47 | 62.75 (10.4) | rs76763715, rs421016 | MoCA | GBA variant carriers developed significantly more cognitive decline than non-carriers over 3-year follow-up period ($p = 0.01$) |
| Malec-Litwinowicz et al. (2014) | 138 (16 GBA) | 57.2 (2.8) | rs76763715, rs75548401 | MMSE | GBA rs76763715 carriers were significantly more likely to develop dementia (MMSE score < 26) ($p = 0.03$) |
| Wang et al. (2014) | 1638 (49 GBA) | 61.61 (10.30) | rs421016 | MMSE; ADAS | Cognitive impairment did not differ significantly between carriers and non-carriers ($p = 0.474$) |
| Zokaei et al. (2014) | 67 (15 GBA) | 61.0 (9.0) | n/s | VSTM | GBA-positive people with showed significantly worse recall than other study groups ($p < 0.005$) |
| Davis et al. (2016) | 733 (58 GBA) | 64.0 (9.0) | 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) | 1369 (125 GBA) | 57.3 (12.3) | GBA coding region variants, rs2230288 | MoCA, Letter-Number sequencing, trail making, JLO | GBA carriers had a higher prevalence of dementia ($p = 9.7 \times 10^{-6}$) and lower performance on letter-number sequencing, trail making and JLO ($p = 0.0045$) |
| Mata et al. (2017) | 1105 | 68.8 (9.2) | n/s | NeuroX array (249,336 variants) | 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) | 3200 (308 GBA) | 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.
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 (Altmann et al., 2016). Moreover, MAPT H1/H1 genotype has been reported to be an independent predictor of PDD (Williams-Gray et al., 2009). Low-activity COMT (Val158Met) Met/Met genotype has been associated with cognitive impairment in PD (Williams-Gray et al., 2008), but another study failed to verify this association (Nombela et al., 2014). Furthermore, a PICALM variant (rs3851179) has been reported to be associated with cognitive impairment in people with PD older than 70 years (Barrett et al., 2016), 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 ($p = 0.046$) (Cagni et al., 2017). TEF TT genotype (Hua et al., 2012), CRY1 CC genotype (Hua et al., 2012), SLC6A15 (rs1545843) (Zheng et al., 2017) and TPH2 (rs78162420) (Zheng et al., 2017) 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 ($p = 0.02$) (Dan et al., 2016). Another study has
reported a significant association \(p = 0.003\) between a specific \(CNR1\) genotype and reduced risk of depression in PD (Barrero et al., 2005).

### 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 \(GBA\) \(rs76763715\), \(rs421016\), \(rs80356773\), and \(BDNF\) \(rs6265\) and \(CRI1\) \(rs2287161\) 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, of 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 (Alcalay et al., 2015; Somme et al., 2015; Srivatsal et al., 2015; Zheng et al., 2017). \(LRRK2\) encodes a kinase, and the minor allele of \(rs34637584\) leads to increased expression and activity of \(LRRK2\) (West et al., 2005) because of stabilising the kinase activation loop (Gilsbach & Kortholt, 2014). Furthermore, the severity of Lewy body pathology correlates with the severity of cognitive impairment in PD (Irwin et al., 2012), and \(LRRK2\) related PD can be with or without the presence of Lewy bodies (Kalia et al., 2015). Overexpression of \(LRRK2\) leads to enlarged lysosomes, lower endolysosomal pH, impaired autophagy and diminished lysosomal degradation in vitro (Henry et al., 2015), and these changes in the morphology and function of lysosomes could be reversed by \(LRRK2\) kinase inhibitors in vitro (Henry et al., 2015). A neuronal cell culture study using mouse embryos that were homozygous for \(LRRK2\) \(rs34637584\) variant has replicated these findings (Schapansky et al., 2018). 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 (Sidransky & Lopez, 2012). 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 (Sidransky & Lopez, 2012). Prior studies have reported the associations between these GBA variants and increased presence of cortical Lewy bodies (Clark et al., 2009). 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 (Jan-Or et al., 2015), and LRRK2 rs34637584 leads to benign PD phenotype than other LRRK2 variants (Li et al., 2014). However, little is known about the differential effects of these variants on cognitive impairment and depression in people with PD (Mata et al., 2016). Non-manifesting LRRK2 rs34637584 carriers have been reported to have significantly more cognitive impairment than non-manifesting carriers of GBA variants (Chahine et al., 2018). 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 (Hua et al., 2012), CRY1 CC genotype (Hua et al., 2012), SLC6A15 variant rs1545843 (Zheng et al., 2017) and TPH2 variant rs78162420 (Zheng et al., 2017) 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, an SNCA genotype (Dan et al., 2016), and a CNR1 genotype (Barrero et al., 2005) 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 (Barone et al., 2017). 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 (Irwin et al., 2012), 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 a 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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