**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 |

|  |  |  |
| --- | --- | --- |
|  | | |
| **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 2:** Genetic variants and associated amino acid changes

**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 *pc*=6.0 × 10−5), delayed recall (*p* = .001; *pc*=.009), and recognition discrimination Index (*p*=.004; *pc*=.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 | | | | | | |

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