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Large-scale Exploratory Genetic Analysis of Cognitive Impairment in Parkinson's Disease

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Abstract

Cognitive impairment is a common and disabling problem in Parkinson's disease (PD). Identification of genetic variants that influence the presence or severity of cognitive deficits in PD might provide a clearer understanding of the pathophysiology underlying this important nonmotor feature. We genotyped 1,105 PD patients from the PD Cognitive Genetics Consortium for 249,336 variants using the NeuroX array. Participants underwent assessments of learning and memory (Hopkins Verbal Learning Test–Revised [HVLT-R]), working memory/executive function (Letter-Number Sequencing and Trail Making Test [TMT] A and B), language processing (semantic and phonemic verbal fluency), visuospatial abilities (Benton Judgment of Line Orientation [JoLO]), and global cognitive function (Montreal Cognitive Assessment). For common variants we used linear regression to test for association between genotype and cognitive performance with adjustment for important covariates. Rare variants were analyzed using the optimal unified sequence kernel association test. The significance threshold was defined as a false discovery rate corrected *P*-value (P_{FDR}) of 0.05. Eighteen common variants in 13 genomic regions exceeded the significance threshold for one of the cognitive tests. These included *GBA* rs2230288 (E326K; $P_{FDR} = 2.7 \times 10^{-4}$) for JoLO, *PARP4* rs9318600 ($P_{FDR} = 0.006$) and rs9581094 ($P_{FDR} = 0.006$) for HVLT-R total recall, and *MTCL1* rs34877994 ($P_{FDR} = 0.01$) for TMT B-A. Analysis of rare variants did not yield any significant gene regions. We have conducted the first large-scale PD cognitive genetics analysis and nominated several new putative susceptibility genes for cognitive impairment in PD. These results will require replication in independent PD cohorts.

Introduction

Cognitive dysfunction is a common, debilitating, and difficult to treat problem in Parkinson's disease (PD).(Goldman and Weintraub, 2015, Meireles and Massano, 2012) The rate of decline in overall cognitive function and individual cognitive domains is highly variable for reasons that are not well understood.(Aarsland et al., 2004, Janvin et al., 2006) The identification of genetic variants that contribute to this phenotypic heterogeneity could reveal important insights into the pathophysiology of cognitive impairment in PD.

Using a candidate gene approach in cross-sectional studies, our group and others have identified variants in genes that are associated with either higher (*LRRK2*) or lower (*APOE*, *GBA*) overall cognitive performance among patients with PD.(Alcalay et al., 2012, Alcalay et al., 2015, Mata et al., 2016, Mata et al., 2014, Paul et al., 2016, Srivatsal et al., 2015)

Furthermore, we have shown that these genes have a differential impact on specific cognitive domains. For example, in PD patients without dementia the *APOE*ε4 allele is associated with lower performance on word list learning and semantic verbal fluency while *GBA* variants predict worse scores on tests of working memory/executive function and visuospatial abilities. Other studies have nominated variants in several other genes, including *COMT* and *MAPT*, as modifiers of cognitive dysfunction in PD,(Foltynie et al., 2004, Williams-Gray et al., 2009) but these results have not been uniformly replicated.(Hoogland et al., 2010, Mata et al., 2014, Paul et al., 2016)

Large scale genetic studies of cognition in PD have never been conducted. This is in part due to the limited availability of PD cohorts with detailed neuropsychological test data. Here we report the results of an exploratory analysis of genetic risk factors for cognitive impairment in PD in a multisite cohort using the NeuroX array that includes nearly 250,000 genetic markers.

Patients and Methods

Participants

The study population was comprised of 1,226 patients with PD enrolled at six sites from the PD Cognitive Genetics Consortium (PDCGC; Supplementary Materials). All participants met UK PD Society Brain Bank clinical diagnostic criteria for PD (Gibb and Lees, 1988) (modified so that having more than one affected relative was not considered an exclusion criterion), except those from University of California Los Angeles (UCLA) who satisfied clinical diagnostic criteria for PD as described elsewhere (Kang et al., 2005).

Standard protocol approvals, registrations, and patient consents were obtained. All study procedures were approved by the institutional review boards at each participating site.

Neuropsychological Assessment

All participants underwent detailed psychometric testing in the on state (if receiving medication). Seven tests that were administered by at least five of the six sites were defined as the “core battery” (Supplementary Table 1). We selected (a priori) nine variables for analysis from the core battery that represent the primary measures most commonly used in a clinical setting.

These “core variables” were: total scores for the Montreal Cognitive Assessment (MoCA); Letter-Number Sequencing Test (LNST); Trail Making Test (TMT) B-A, semantic and phonemic verbal fluency; Benton Judgment of Line Orientation (JoLO); Hopkins Verbal Learning Test-Revised (HVLT-R) total recall; HVLT-R delayed recall; and HVLT-R recognition discrimination index. Data from participants enrolled at four of the six PDCGC sites (Supplementary Materials) were reviewed at diagnostic consensus conferences and participants were classified as demented or nondemented, as previously described (Chahine et al., 2013, Cholerton et al., 2013). The nondemented group included participants with either no cognitive impairment or mild cognitive impairment (MCI).

Genotyping

Genomic DNA was extracted from peripheral blood using standard techniques. All DNA samples were genotyped on the NeuroX array at the Center for Applied Genomics, Children's Hospital of Philadelphia. NeuroX is a combination of the Illumina Human Exome array v1.1 (242,901 variants) and custom content (24,706 variants) focused on neurologic diseases. The exome array primarily (90%) contains nonsynonymous single nucleotide polymorphisms (SNPs). While the exome array contains a high proportion of rare variants (82% have a minor allele frequency [MAF] < 0.01), the majority (60%) of variants within the custom content are common and have a MAF between 0.05 and 0.50. Further details on the design and contents of the NeuroX array have been published elsewhere (Nalls et al., 2015) and are also provided in the Supplementary Materials. Automated allele calling was performed with Illumina GenomeStudio Software using a previously developed NeuroX-specific cluster file (Nalls et al., 2015), but none of the cluster plots were manually inspected.

Statistical Analysis

We excluded markers with genotyping call rates < 95% and those that were out of Hardy-Weinberg equilibrium (HWE) ($P < 0.0001$). To account for population structure we calculated eigenvectors from principal component analysis (PCA) using SNPStats based on 10,177 markers from the exome array with HapMap3 CEU, CHB, JPT, and YRI population samples as the reference. From visual inspection of scatter plots of the first two principal components we created a subjective boundary to define subjects of European ancestry (Supplementary Fig 1). We performed identity-by-descent estimation with the same markers to assess for erroneous duplicates and cryptic relatedness, using a threshold of Pi-hat > 0.40. The samples genotyped included one known duplicate and nine relatives. All of these individuals were correctly identified and removed, but no other duplicates or relatives were discovered.

Histograms were created for each of the nine core cognitive variables, and for those that were non-normally distributed (MoCA, JoLO, and HVLT-R recognition discrimination index), a squared transformation was employed to improve the fit to normality.

For common variants with MAF > 0.01 we performed linear regression to test for association between genotype and each of the core cognitive variables under an additive model. All models were adjusted for age, sex, disease duration, years of education, site, and the first three principal components from the PCA (to adjust for population structure). For rare variants with MAF < 0.01 we used the optimal unified sequence kernel association test (SKAT-O)(Lee et al., 2012) to test for association between all rare variants within each gene region (computing gene-level *P*-values) and the same cognitive variables adjusting for the same covariates. Because this was an exploratory study we used a liberal significance threshold defined as a false discovery rate (FDR) corrected *P*-value (P_{FDR}) of 0.05. For comparison, we also calculated the family wise error rate using the Holm–Bonferroni method (Holm, 1979). All analyses were performed using R 3.2.3.

Results

Of the 1,226 patients in the initial cohort, we excluded 121 individuals for the following reasons: 61 were of non-European ancestry, four failed genotyping, 19 were missing data for one or more covariates, 9 were related to another participant in the cohort, and 28 failed to complete at least half of the cognitive tests (this was done to reduce the influence of floor effects on cognitive test scores in patients with advanced dementia). The characteristics of the 1,105 participants included in the final analysis are summarized in Table 1. In the overall cohort the mean age was 68.8 ± 9.2 years, the mean disease duration was 8.4 ± 5.8 years, and 67.8% of the subjects were male.

After restricting the marker set to autosomal single nucleotide substitutions, and excluding variants that failed genotyping (n = 11,350) or were out of HWE (n = 796), 249,336 variants remained available for analysis, of which 46,871 were common and 202,465 were rare. Single-marker analyses of the common variants yielded 18 markers in 13 genomic regions that exceeded the significance threshold for one of the cognitive tests, and none of these variants were significant for more than one test (Table 2). Sixteen of the variants occurred within or in close proximity to a known gene, and two were located within an intergenic region. Across all cognitive measures the strongest associations observed were for transformed JoLO scores and markers within *GBA* (rs2230288 [E326K]; $P_{FDR} = 2.7 \times 10^{-4}$) and *ACSBG2* (rs79266675; $P_{FDR} = 8.3 \times 10^{-4}$), and for TMT B-A and variants in *RYR1* (rs55876273; $P_{FDR} = 6.4 \times 10^{-4}$) and *IFT140* (rs146128830; $P_{FDR} = 6.4 \times 10^{-4}$). None of the common variants examined were significantly associated with semantic or phonemic verbal fluency, LNST, transformed MoCA, or HVLT-R recognition discrimination index scores. Manhattan plots for the four cognitive variables associated with at least one variant are presented in Fig 1 and plots for the remaining five variables are shown in Supplementary Fig 2. The top 50 variants for each of the core cognitive variables, ranked by *P*-value, are presented in Supplementary Tables 2–10. Inspection of the QQ plots for each cognitive variable (Supplementary Fig 3) indicated that most of the observed associations lay close to the expected distribution, suggesting that there was no substantial inflation in the test statistics due to population structure or other sources.

One of the variants that failed genotyping on the NeuroX array was rs429358, which differentiates the *APOE* ε3 and ε4 alleles. Because *APOE* ε4 is known to influence cognitive performance in PD (Mata et al., 2014, Morley et al., 2012, Paul et al., 2016), we separately genotyped rs429358 on all subjects using a TaqMan assay as previously described (Mata et al., 2014) and analyzed the ε4 allele using the methods employed for all other common variants. After correction for multiple testing, *APOE* ε4 was not associated with any of the core cognitive variables (Supplementary Table 11). However, it did approach significance for HVLT-R total recall ($P = 6.1 \times 10^{-05}$; $P_{FDR} = 0.36$) (Supplementary Table 5).

Because some studies have reported that common variants in *COMT* and *MAPT*, and rare missense mutations and multiplications of *SNCA*, are associated with cognitive performance or dementia in PD (Foltynie et al., 2004, Monchi et al., 2016, Williams-Gray et al., 2009), we present the results for these three genes separately. The final dataset included 1 common

(rs4680; V158M) and 2 rare variants for *COMT*, 102 common and 6 rare variants for *MAPT*, and 45 common and no rare variants for *SNCA*. However, none of these variants approached significance for any of the cognitive tests in single marker analyses (Supplementary Tables 12–14) or analyses of rare variants using SKAT-O (data not shown).

The analysis of rare variants using a gene-centric approach did not yield any genes that exceeded the significance threshold (data not shown). However, *PERP* was marginally associated with HVLT-R delayed recall scores ($P = 3.7 \times 10^{-7}$; $P_{FDR} = 0.053$) based on results for two rare markers.

Discussion

This study represents the first large-scale genetic analysis of cognition in PD. We have nominated several genetic variants as putative susceptibility or protective factors for cognitive impairment in PD, and the vast majority of the genes in which they occur have not previously been linked to PD motor or cognitive phenotypes. A major strength of the study was that the analysis was based on performance on an extensive neuropsychological battery, which provided an opportunity to discern genetic effects within individual cognitive domains. Recent studies suggest that this is a substantially more sensitive approach than relying solely on global screening assessments of cognition, such as the MoCA or Mini Mental State Examination (MMSE), since the anticipated effects for each gene likely vary by cognitive domain (Alcalay et al., 2012, Mata et al., 2016, Mata et al., 2014).

Loss-of-function mutations in the *GBA* gene are well-established risk factors for cognitive impairment and dementia in PD (Alcalay et al., 2012, Mata et al., 2016, Winder-Rhodes et al., 2013, Zokaei et al., 2014). In addition, *GBA* contains a functional polymorphism, E326K (rs2230288), that decreases glucocerebrosidase activity in vitro (Montfort et al., 2004). In a recent analysis focused on *GBA* variants, conducted in a cohort that largely overlapped with the one studied here, we found that among PD patients *GBA* E326K predicted lower performance on tests of working memory/executive function (LNST and TMT B-A) and visuospatial abilities (JoLO) (Mata et al., 2016). In the present study, we again observed that this SNP was associated with lower JoLO scores, and this was one of the strongest associations observed across all markers and all cognitive measures (Table 2). Viewed in the context of an exome-wide analysis, these results provide a new perspective on the importance of *GBA*-associated cognitive deficits in PD.

While the results of our study will require replication in independent PD cohorts before firm conclusions can be drawn, two of the candidate genes we have nominated are particularly intriguing from a biological standpoint. Two SNPs in the *PARP4* gene, one nonsynonymous (rs9318600) and the other intronic (rs9581094), were associated with HVLT-R total recall scores (Table 2). PARP4 (VPARP) catalyzes the reversible addition of multiple branched chains of ADP-ribose to target proteins, including actin (De Maio et al., 2013). Through inhibition of actin polymerization, PARP4 is thought to regulate neuronal plasticity and experiments in animal models suggest that it might play a role in memory consolidation (De Lisa et al., 2012, De Maio et al., 2013). Rs34877994, a nonsynonymous SNP within the *MTCL1* gene, was associated with performance on TMT B-A. *MTCL1* is preferentially

expressed in brain (Nagase et al., 1998) and encodes microtubule crosslinking factor 1. This protein interacts with microtubule affinity regulating kinase 2 (MARK2) to maintain the correct temporal balance between dynamic and stable microtubules.(Sato et al., 2013) MARK2 also phosphorylates microtubule-associated protein tau at multiple sites which alters tau's affinity for microtubules; (Schwalbe et al., 2013) the *MAPT* gene, which encodes tau, is a well-established susceptibility for PD.

Our data failed to validate two genes previously implicated in modulating cognitive function in PD. The *COMT* gene encodes catechol-O-methyltransferase which metabolizes dopamine and other catecholamines. It contains a functional polymorphism, V158M, with nearly equal allele frequencies in populations of European origin. Individuals homozygous for the V allele display higher COMT activity and lower dopaminergic signaling in the prefrontal cortex (PFC) than subjects homozygous for the M allele (Weinberger et al., 2001). Two studies of partially overlapping PD cohorts found that individuals with the high activity V allele performed significantly better on the Tower of London (ToL), a frontostriatally based executive task (Foltynie et al., 2004, Williams-Gray et al., 2009). However, a subsequent study failed to replicate these findings using several measures of attention and executive function including the ToL, TMT B, Stroop Color Word test, and Wisconsin Card Sorting Test (Hoogland et al., 2010). In the present study of a much larger PD cohort, we did not observe an association between *COMT* V158M and any of the cognitive variables assessed including two tests of working memory/executive function, LNST and TMT B-A (Supplementary Table 12). This was true even without correction for multiple comparisons. However, our psychometric battery did not include the ToL which limits direct comparisons across studies. *MAPT* is frequently cited as a risk factor for dementia in PD. This is largely based on sequential publications from a longitudinal study in the UK, which reported that PD patients with the *MAPT* H1 haplotype experienced a more rapid decline in MMSE score and faster conversion to dementia than patients with the alternate H2 haplotype (Goris et al., 2007, Williams-Gray et al., 2009). Although patients in that study underwent detailed neuropsychological assessments, association tests between the H1 haplotype and change over time in the other cognitive measures were not performed. In contrast, a recent longitudinal study of 246 PD patients from the Parkinson's Environment and Gene Study observed no association between the *MAPT* H1 haplotype and change in MMSE score over time (Paul et al., 2016). We recently reported that the *MAPT* H1 haplotype was not associated with any of the PDCGC core cognitive variables in a PD cohort that largely overlapped with the one studied here (Mata et al., 2014). In the present study, we extend these findings in that despite having much more extensive marker coverage across the *MAPT* region we still did not observe any significant associations with cognitive performance (Supplementary Table 13).

Prior candidate gene studies have shown that *APOE* ε4 is associated with lower cognitive performance in PD across multiple cognitive domains (Morley et al., 2012, Paul et al., 2016) and in a previous study from the PDCGC the most significant difference in performance observed between ε4 carriers and non-carriers was for HVLT-R total recall (Mata et al., 2014). In the present study, *APOE* ε4 did not reach significance for any of the cognitive tests, but for HVLT-R total recall the results were suggestive of association ($P = 6.1 \times 10^{-05}$) and ε4 ranked 8th among all variants tested in single-marker analyses (Supplementary Table

5). One possible explanation for this result is that we used a much more stringent significance threshold in comparison to all previous studies in which no more than a handful of candidate genes were examined.

Bras and colleagues nominated *SNCA* as a susceptibility locus for dementia with Lewy bodies (DLB) (Bras et al., 2014). They reported that the strongest association signal came from variants at the 5′ end of the gene (top SNPs rs894280 and rs7687945) in contrast to a large PD meta-analysis where the peak SNP (rs356182) was located 3′ of *SNCA* (Nalls et al., 2014). Thus, the authors suggested that PD and DLB might have distinct association profiles. A subsequent case-control study which included both a PD and a DLB cohort replicated this finding (Guella et al., 2016). As shown in Supplementary Table 14, none of the *SNCA* SNPs in our study were associated with cognitive performance after correction for multiple testing. However, it is interesting to note that among the 45 *SNCA* SNPs we examined, the two with the lowest *P*-values for any cognitive measures (HVLT-R total recall, rs894280, $P = 6.1 \times 10^{-4}$; rs7687945, $P = 5.4 \times 10^{-4}$) were also the top-two ranked DLB SNPs reported by Bras et al. In contrast, the highest-ranked PD SNP (rs356182) observed in the meta-analysis by Nalls and colleagues did not display any association signal in our dataset, with $P \geq 0.06$ for all cognitive tests (data not shown).

Our study had several limitations. Most importantly, we did not have an independent PD cohort with comparable neuropsychological data available for replication. Given the large number of statistical tests performed, it is likely that some of our findings represent false positive errors. Though the cohort we studied was large in comparison to previous PD cognitive genetic studies, we were still likely underpowered to detect signals for rare variants with small to modest effects. Participants in our study had a higher-than-average level of education, a known contributor to performance across most cognitive measures. Thus, our sample might not be fully representative of all patients with PD. Some of the cognitive measures used rely, in part, on motor function, and thus motor symptoms might have interfered with performance on these tests. However, this was not an issue for HVLT-R and JoLO, which do not require drawing/writing and do not have time limits for responses. Furthermore, we corrected TMT B for motor impairment by subtracting the TMT A score. Therefore, it is unlikely that motor symptoms impacted our findings on the tests (HVLT-R total and delayed recall, TMT B-A, JoLO) for which significant associations were observed. In addition, participants taking medications completed testing in the on state to lessen the impact of motor dysfunction on test performance.

The identification and characterization of genetic risk factors for cognitive impairment in PD has the potential to reveal novel therapeutic targets, but could also have more immediate clinical applications. For example, a priori screening of key genes could be used to better predict prognosis and identify patients who are at risk of faster cognitive decline for earlier interventions. Additionally, PD patients enrolled in clinical trials of neuroprotective agents or cognitive enhancing drugs could be stratified based on genotype to create more homogeneous groups, thus increasing power to detect treatment effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- 18 common variants in 13 genomic regions were associated with cognitive performance
- Most of the genes identified have not been linked to PD motor or cognitive phenotypes
- *PARP4*, which effects memory in animals, was associated with word list learning
- *GBA* E326K was associated with visuospatial abilities, consistent with previous work
- There was no relationship between *MAPT* and any of the cognitive tests examined

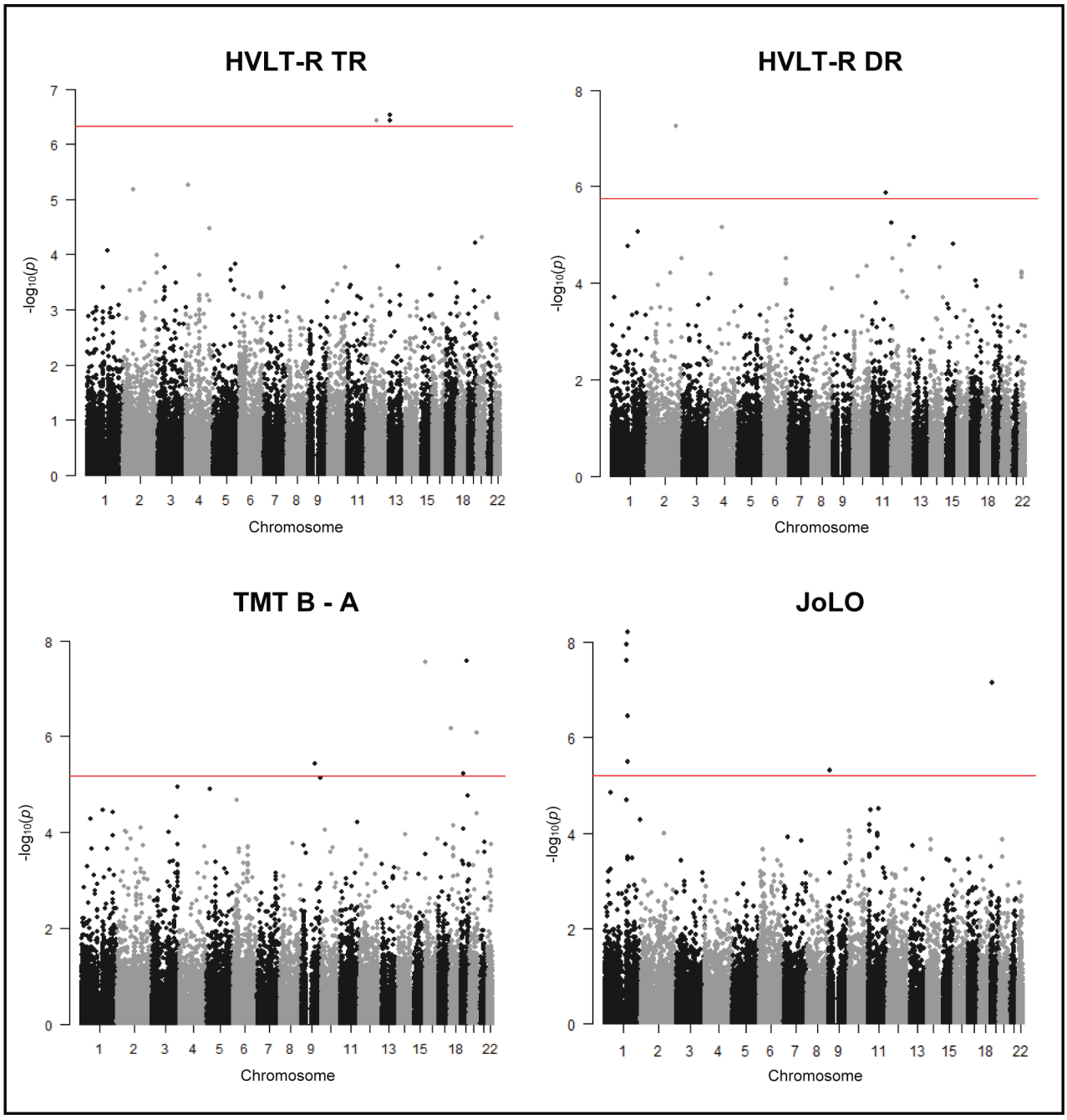

Figure 1. Manhattan Plots for all tests with significant associations

The values on the y axis represent −log10 of the uncorrected *p*-values from linear regression. The red line indicates the significance threshold defined as a FDR-corrected *p*-value of 0.05 for each test.

HVLT-R, Hopkins Verbal Learning Test-Revised; DR, delayed recall; TR, total recall; JoLO, Benton Judgment of Line Orientation; TMT, Trail Making Test

Table 1

Characteristics of the Study Population

Site	N	Male, n (%)	Age, y			Disease Duration	Years of Education	Demented, n (%)
			At Testing mean ± SD	At Diagnosis mean ± SD	At Disease Onset mean ± SD			
Emory University	142	93 (65.5)	65.2 ± 9.1	59.4 ± 9.8	57.7 ± 9.8	7.5 ± 4.5	15.7 ± 2.4	NA
PANUC (Portland)	119	105 (88.2)	68.4 ± 8.0	61.0 ± 10.6	58.6 ± 11.3	9.9 ± 6.7	15.6 ± 2.9	27 (22.7)
PANUC (Seattle)	432	279 (64.6)	67.8 ± 9.5	60.7 ± 11.1	58.3 ± 11.4	9.5 ± 6.6	15.8 ± 2.5	85 (19.7)
UCLA	163	94 (57.7)	72.6 ± 9.5	67.2 ± 9.7	NC	5.4 ± 2.4	14.4 ± 2.8	NA
U. Cincinnati	30	24 (80.0)	63.6 ± 7.7	59.9 ± 8.2	57.2 ± 8.2	6.4 ± 3.2	15.3 ± 2.8	3 (10.0)
U. Pennsylvania	219	154 (70.3)	71.0 ± 7.5	64.2 ± 8.4	62.6 ± 8.8	8.4 ± 5.2	15.9 ± 2.4	25 (11.4)
Total	1105	749 (67.8)	68.8 ± 9.2	62.2 ± 10.4	59.2 ± 10.6	8.4 ± 5.8	15.5 ± 2.6	140 (17.5)

NA, not applicable; NC, not collected; PANUC, Pacific Northwest Udall Center; UCLA, University of California, Los Angeles

Table 2

Association of common variants with cognitive performance

Test	Gene Region	Chr	Position (hg19)	SNP	Type	MAF	N	β	SE	*P*	P_{FDR}	P_{FWE}
HVLT-R TR	*PARP4*	13	25068808	rs9318600	missense	0.10	1039	1.88	0.37	2.9×10^{-7}	0.0059	0.014
	MDM1	12	68720534	rs117673673	missense	0.01	1040	−3.62	0.71	3.7×10^{-7}	0.0059	0.017
	PARP4	13	25082630	rs9581094	intronic	0.15	1040	1.65	0.32	3.8×10^{-7}	0.0059	0.018
HVLT-R DR	*ALS2CR11*	2	202352480	rs72939119	missense	0.02	1038	1.66	0.31	5.7×10^{-8}	0.0027	0.003
	FAT3	11	92577659	rs75081660	missense	0.01	1038	2.07	0.43	1.4×10^{-6}	0.032	0.06
TMT B-A[a]	*RYR1*	19	39018347	rs55876273	missense	0.02	867	−34.84	6.26	2.6×10^{-78}	6.4×10^{-4}	0.001
	IFT140	16	1652418	rs146128830	missense	0.01	867	−37.05	6.67	2.7×10^{-08}	6.4×10^{-4}	0.001
	MTCL1	18	8806925	rs34877994	missense	0.01	867	−41.13	8.27	6.7×10^{-7}	0.0096	0.03
	MOCS3	20	49576664	rs7269297	missense	0.01	867	−36.47	7.40	8.2×10^{-7}	0.0096	0.04
	Intergenic	9	97314741	rs16910061	intergenic	0.02	867	−28.13	6.07	3.6×10^{-6}	0.034	0.17
	RASAL3	19	15565646	rs56209154	missense	0.02	867	−29.23	6.46	6.0×10^{-6}	0.047	0.28
JoLO[b,c]	*GBA*[d]	1	155206167	rs2230288	missense	0.03	919	−143.61	25.16	1.2×10^{-8}	2.7×10^{-4}	2.8×10^{-4}
	ACSBG2	19	6141593	rs79266675	missense	0.02	919	159.86	29.67	7.1×10^{-8}	8.3×10^{-4}	0.003
	Intergenic	9	8230433	rs1984216	intergenic	0.43	919	−44.12	9.66	4.9×10^{-6}	0.033	0.23

Key: Chr, chromosome; HVLT-R, Hopkins Verbal Learning Test-Revised; DR, delayed recall; TR, total recall; JoLO, Benton Judgment of Line Orientation; MAF, minor allele frequency; MoCA, Montreal Cognitive Assessment; P_{FDR}, false discovery rate-corrected *P*-value; P_{FWE}, family wise error-corrected P-value; TMT, Trail Making Test.

[a] Not administered at University of Pennsylvania

[b] Not administered at University of California, Los Angeles

[c] Based on square-transformed scores.

[d] Not shown are results from four SNPs in neighboring genes (rs71628662 [*ASH1L*], rs12726330 [*SLC50A1*], rs71630614 [*LMNA*], rs34372695 [*RAB25*]) that were each highly correlated with *GBA* rs2230288 (see Supplementary Materials for details).