



Aquaporin-4 Polymorphisms Are Associated With Cognitive Performance in Parkinson's Disease

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Objective: Aquaporin-4 (AQP4) facilitates a sleep-enhanced interstitial brain waste clearance system. This study was conducted to determine the clinical implication of AQP4 polymorphisms in Parkinson's disease (PD).

Methods: Three-hundred and eighty-two patients with PD and 180 healthy controls with a mean follow-up time of 66.1 months from the Parkinson's Progression Marker Initiative study were analyzed. We examined whether AQP4 SNPs were associated with an altered rate of motor or cognitive decline using linear mixed model and Cox regression. We then investigated whether AQP4 SNPs were associated with A β burden as measured by ¹⁸F Florbetapir standard uptake values. Furthermore, we examined if AQP4 SNPs moderated the association between REM sleep behavior disorder (RBD) and CSF biomarkers.

Results: In patients with PD, AQP4 rs162009 (AA/AG vs. GG) was associated with slower dementia conversion, better performance in letter-number sequencing and symbol digit modalities, lower A β deposition in the putamen, anterior cingulum, and frontotemporal areas. In the subgroup of high RBD screening questionnaire score, rs162009 AA/AG had a higher CSF A β 42 level. rs162009 AA/AG also had better performance in semantic fluency in healthy controls. Besides, rs68006382 (GG/GA vs. AA) was associated with faster progression to mild cognitive impairment, worse performance in letter-number sequencing, semantic fluency, and symbol digit modalities in patients with PD.

Interpretation: Genetic variations of AQP4 and subsequent alterations of glymphatic efficacy might contribute to an altered rate of cognitive decline in PD. AQP4 rs162009 is likely a novel genetic prognostic marker of glymphatic function and cognitive decline in PD.

Keywords: Parkinson's disease, cognitive dysfunction, aquaporin-4, amyloid plaque, REM sleep behavior disorder

INTRODUCTION

Aquaporin-4 (AQP4) is a water channel that lies at the astrocytic endfeet around perivascular space in the brain (Nagelhus and Ottersen, 2013). AQP4 plays a central role in the glymphatic system, which facilitates exchange between cerebrospinal fluid (CSF) and interstitial fluid, and drains macromolecules from the brain to the periphery (Mestre et al., 2018). Strikingly, the AQP4-facilitated glymphatic system clears interstitial brain waste,

including amyloid β (A β ; Iliff et al., 2012), tau (Harrison et al., 2020), and α -synuclein (Zou et al., 2019) according to animal studies. The association between AQP4 and interstitial waste clearance was further validated by a postmortem study of aging human brains, which revealed a link between reduced perivascular localization of AQP4 and A β deposition (Zeppenfeld et al., 2017). In addition, Single Nucleotide Polymorphisms (SNPs) of the *AQP4* gene were associated with brain A β uptake on PET and the rate of cognitive decline in the spectrum of Alzheimer's disease (AD; Burfeind et al., 2017; Chandra et al., 2020).

Parkinson's disease (PD) is pathologically characterized by intraneuronal α -synuclein accumulation (Jakes et al., 1994), although extracellular α -synuclein is present and might contribute to the seeding of the disease (Lee et al., 2014). In addition, AD pathologies, including extracellular amyloid and tau aggregates, are also found in PD (Robinson et al., 2018). Amyloid deposition as measured by PET was positive in 34% of patients with PD dementia and 5% of patients with PD-mild cognitive impairment (MCI; Petrou et al., 2015). Furthermore, even subthreshold amyloid might contribute to cognitive decline in PD. In patients with PD, lower baseline CSF A β 42 is associated with a faster rate of cognitive decline (Compta et al., 2013; Alves et al., 2014; Bäckström et al., 2015), worse performance in executive function (Compta et al., 2009; Stav et al., 2015), and delayed memory recall (Hall et al., 2015). Therefore, it is likely that clearing efficacy of synuclein and AD co-pathology are associated with an altered rate of motor or cognitive progression in PD.

Glymphatic fluid transport is known to be sleep-enhanced (Xie et al., 2013) and regulated by circadian rhythms (Hablitz et al., 2020). Disrupted sleep is a potential mechanism accounting for glymphatic dysfunction in PD. REM sleep behavior disorder (RBD) is one of the most characteristic sleep disorders in PD (Xie et al., 2019). Concomitant RBD in patients with PD is associated with faster motor progression, and worse cognitive function (Pagano et al., 2018; Zhang et al., 2020). These patients exhibit elevated synuclein deposition across the brain according to a postmortem study (Postuma et al., 2015). Interestingly, they are also inclined to have lower CSF A β 42 and higher total tau/A β 42 levels (Pagano et al., 2018). The elevated synuclein and amyloid burden are potentially attributable to the reduced efficacy of the AQP4-facilitated glymphatic system as a result of sleep disturbance (Bohnen and Hu, 2019).

In this study, using longitudinal data from the Parkinson's Progression Marker Initiative (PPMI), we tested the hypothesis that *AQP4* SNPs were associated with altered CSF or PET biomarker values and rate of motor or cognitive decline in PD. We also studied if *AQP4* SNPs modulate the association between RBD and CSF biomarkers.

MATERIALS AND METHODS

Study Participants

Major inclusion criteria for the PD cohort in the PPMI were as follows: (1) drug naïve; (2) diagnosed with PD within the past 2 years; (3) Hoehn and Yahr stage 1 or 2 at baseline; (4) age

TABLE 1 | Demographic information and clinical characteristics of patients and healthy controls.

	Patients	Healthy controls
Age, y	61.83 \pm 9.50	61.42 \pm 10.63
Sex, male, n (%)	252 (66.0%)	117 (65.0%)
Years of education	15.56 \pm 2.93	16.18 \pm 2.91
<i>APOE</i> ϵ 4 carriage	0.28 \pm 0.50	0.28 \pm 0.51
Baseline MDS-UPDRS I	5.43 \pm 4.14	2.84 \pm 2.80
Baseline MDS-UPDRS II	5.99 \pm 4.24	0.40 \pm 0.95
Baseline MDS-UPDRS III	20.96 \pm 8.92	1.71 \pm 2.16
Baseline MoCA	27.24 \pm 0.11	28.23 \pm 1.11
Baseline BJLOT	12.14 \pm 2.92	12.50 \pm 2.75
Baseline HVLt-total recall	45.84 \pm 10.61	49.72 \pm 9.78
Baseline LNS	11.59 \pm 2.63	11.78 \pm 2.76
Baseline SFT-T score	51.19 \pm 9.86	52.71 \pm 10.27
Baseline SDMT-T score	45.00 \pm 9.07	50.68 \pm 10.10
Baseline ESS	5.80 \pm 3.47	5.63 \pm 3.36
Baseline RBDSQ	4.53 \pm 2.87	2.78 \pm 2.29

MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; *MoCA*, Montreal Cognitive Assessment; *BJLOT*, Benton Judgment of line orientation test; *HVLt*, Hopkins verbal learning test; *LNS*, Letter-number sequencing; *SFT*, Semantic fluency test; *SDMT*, Symbol digit modalities; *ESS*, Epworth Sleepiness scale; *RBDSQ*, REM sleep behavior disorder screening questionnaire.

30 years or older; and (5) striatal dopaminergic dysfunction on SPECT.

To exclude the potential confounding effect of race and ethnicity, non-Hispanic Caucasian patients and healthy controls (HC) were included in our analysis. Causes of exclusion include: (1) no CSF biomarker study result; and (2) no whole-genome sequencing data. Overall, 382 patients and 180 HCs were included, their demographic information and clinical characteristics are presented in **Table 1**.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the institutional review board at each PPMI site. All patients signed an informed consent form before their participation in the PPMI study.

Clinical Assessment

Cognitive function was evaluated on a yearly basis. Cognitive tests included the Montreal Cognitive Assessment for global cognition, the Hopkins Verbal Learning Test (HVLt) for memory, the Benton Judgment of Line Orientation Test (BJLOT) for visuospatial perception, the Semantic Fluency Test (SFT) for executive function, the Letter-Number Sequencing (LNS) and the Symbol Digit Modality Test (SDMT) for working memory and attention-processing speed. Cognitive categorization of normal, MCI, and dementia was performed by investigators at each site in accordance with MDS criteria (Emre et al., 2007; Litvan et al., 2012).

Motor symptoms were evaluated at baseline, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, and 108 months. We analyzed Hoehn and Yahr stage that was rated during the off condition (levodopa/dopaminergic agonist withheld for at least 6 h prior to the visit).

RBD was evaluated with an RBD screening questionnaire (RBDSQ). The optimal cutoff value for probable RBD in PD is 6 (Stiasny-Kolster et al., 2007; Nomura et al., 2011). RBD

symptoms are time-varying. To study if *AQP4* modulates the association between RBD and CSF biomarker, we stratified patients into subgroups by their averaged RBDSQ score in the first 3 years, as CSF samples were collected from baseline to the 3rd year. Overall, there are four expected visits for RBDSQ evaluation during this time frame (baseline, 1st, 2nd, and 3rd-year). Patients who were absent for two or more of these scheduled visits were excluded due to insufficient available data to characterize RBD symptoms within this time frame ($N = 40$). Then we stratified patients into a high RBDSQ group if averaged 3-year RBDSQ lies in the top one-third ($\text{RBDSQ} \geq 5.5$, $N = 117$), and a low RBDSQ group if averaged 3-year RBDSQ lies in the least one-third ($\text{RBDSQ} \leq 3$, $N = 113$).

Genotyping and SNP Pruning

Whole-genome sequencing data were downloaded from the PPMI database. SNP pruning was undertaken using PLINK (Purcell et al., 2007). Genetic variants of *AQP4* underwent quality control procedures. Specifically, SNPs that were not in Hardy-Weinberg equilibrium ($p < 0.05$), had a minor allele frequency of $< 5\%$ were removed. Linkage disequilibrium-based SNP pruning was performed to reduce statistical redundancy and maintain coverage of the *AQP4* gene. SNP pruning parameters were as follows: window size 10, increment 5, and variance inflation factor 2. Two SNP pairs left after pruning were in high linkage disequilibrium (rs1058427 and rs12968026: $r^2 = 0.96$; rs335930 and rs455671: $r^2 = 0.86$). Therefore, rs12968026 and rs455671 were removed from further statistical analysis, leaving 11 SNPs. The information of these SNPs was displayed in **Table 2**, **Figure 1**, and **Supplementary Figure 1**.

A dominant model was used for all *AQP4* SNPs.

A β Retention by PET

Overall, 36 patients who met the inclusion criteria of the current study underwent a Florbetaben (FBB) PET imaging for *in vivo* imaging of A β plaques. We analyzed standard uptake values (SUVs) downloaded from the PPMI dataset. SUV ratios (SUVRs) were calculated using the cerebellar cortex as reference.

Measurement of CSF Biomarkers

CSF was collected at baseline, 6, 12, 24, and 36 months. Levels of CSF A β 42, total tau (*t*-tau), and phosphorylated tau (*p*-tau) at threonine 181 position were measured using Elecsys electrochemiluminescence immunoassays on the cobas e 601 analysis platform. CSF α -synuclein concentrations were analyzed using commercially available enzyme-linked immunosorbent assay kits. These values were downloaded from the PPMI database.

Statistical Analysis

Clinical and biomarker data were downloaded from the PPMI database in December 2020. Statistical analysis was performed using SPSS (IBM Corp, Armonk NY, USA). Graphs were plotted using GraphPad (San Diego, CA, USA).

For longitudinal cognitive test score analysis, mixed models with random slope and intercept and unstructured covariance were used. Fixed effects include age at baseline, sex, baseline MoCA score, years of education, Apolipoprotein-E (*APOE*

$\epsilon 4$ carriage, and *AQP4* SNP of interest. The *AQP4* SNP by time interaction effect was also included as a fixed effect in separate models. Time was treated as a continuous variable. The patient number was listed as a random effect.

Cox proportional hazards regressions were performed to study if *AQP4* polymorphisms were associated with the rate of motor and cognitive deterioration. We defined events separately as: (1) progression to MCI for the first time; (2) progression to dementia for the first time; and (3) progression of Hoehn and Yahr stage for the first time. Age, sex, *APOE* $\epsilon 4$ carriage, years of education, and baseline MoCA score were covaried for conversion to MCI or dementia. Age, sex, baseline MDS-UPDRS-III, and levodopa equivalent dose were covaried for motor progression. Kaplan-Meier curves were plotted, and log-rank test results were presented.

APOE $\epsilon 4$ (Mata et al., 2014), glucocerebrosidase (*GBA*) variants (Alcalay et al., 2012), and Catechol-O-methyltransferase (*COMT*) Val¹⁵⁸Met (rs4680; Egan et al., 2001; Williams-Gray et al., 2009) are previously established genetic markers of cognition in PD. *COMT* rs4680 data was extracted from whole-genome sequencing data. *GBA* variant summary from across different sequencing platforms was directly downloaded. Their distribution on *AQP4* SNPs was tested using the Chi-Square test.

The association between *AQP4* SNPs and SUVrs was examined using linear regression. Covariates included age, sex, *APOE* $\epsilon 4$ carriage, and disease duration at the time of PET scan.

CSF biomarkers (α -synuclein, A β , *t*-tau, *p*-tau) did not follow a normal distribution and were, therefore, log10 transformed in the statistical analysis. To determine whether CSF biomarkers differed with respect to *AQP4* polymorphisms across time, linear mixed models with random intercept were used. Fixed effects included age at baseline, sex, time, and *AQP4* SNP of interest. For CSF A β 42, *APOE* $\epsilon 4$ carriage was also covaried. To determine whether *AQP4* SNPs moderate the association between RBD and CSF biomarkers, the RBDSQ subgroup by *AQP4* SNP interaction effect was tested.

To correct for multiple comparisons, the Benjamini-Hochberg procedure with a false discovery rate at 0.10 was used given the exploratory nature of this study. $p < 0.05$ was used as the threshold for statistical significance.

RESULT

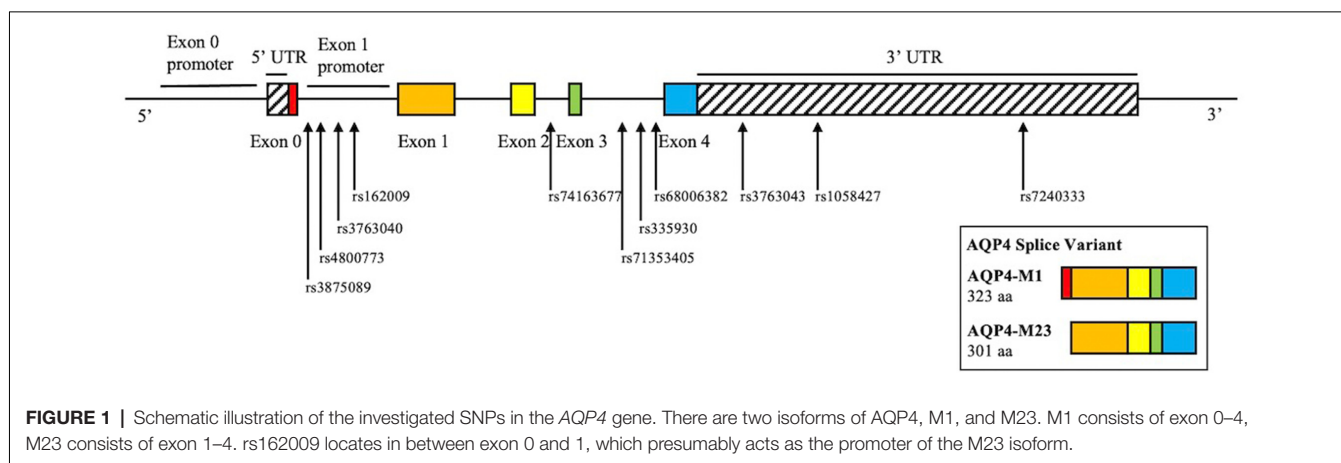
AQP4 SNPs and Conversion to MCI and Dementia

We did not observe a significant association between *AQP4* SNPs and motor progression as reflected by MDS-UPDRS-III score increment in mixed model and Hoehn and Yahr stage progression in Cox regression.

However, after adjusting for age, sex, *APOE* $\epsilon 4$ carriage, and baseline MoCA score, minor allele carrier status of rs68006382 was associated with accelerated conversion to MCI (HR = 1.973, 95% CI = 1.246–3.123, $p = 0.004$; **Figure 2A**), but not dementia (HR = 1.512, 95% CI = 0.753–3.034, $p = 0.245$). In addition, minor allele carrier status of rs162009 was associated with slower conversion to MCI (HR = 0.646, 95%

TABLE 2 | AQP4 SNPs being investigated in the current study.

	Annotation	Position (GRCh38)	Minor allele frequency	Previously reported associations
rs7240333 C/T	3'-UTR	18:26852848	0.098	
rs1058427 G/T	3'-UTR	18:26855131	0.115	Risk of cerebral edema (Appelboom et al., 2015)
rs3763043 C/T	3'-UTR	18:26855854	0.318	Risk of intracerebral hemorrhage (Dardiotis et al., 2019) and schizophrenia (Wu et al., 2020)
rs68006382 A/G	intron	18:26856555	0.205	
rs335930 A/C	intron	18:26856961	0.228	
rs71353405 C/T	intron	18:26857429	0.061	
rs74163677 G/A	intron	18:26861697	0.055	
rs162009 G/A	M23 promoter	18:26864250	0.344	
rs3763040 G/A	M23 promoter	18:26864410	0.192	Rate of cognitive decline in AD (Burfeind et al., 2017)
rs4800773 G/A	M23 promoter	18:26865017	0.356	
rs3875089 T/C	M23 promoter	18:26865469	0.149	Rate of cognitive decline in AD (Burfeind et al., 2017)



CI = 0.409–1.019, $p = 0.060$), and dementia (HR = 0.473, 95% CI = 0.234–0.956, $p = 0.037$), although these effects were marginal (Figures 3A,B).

AQP4 SNPs and Performance in Cognitive Subdomains

The association between AQP4 SNPs and cognitive subdomains is presented in Table 3.

Briefly, minor allele carrier status of rs68006382 was associated with worse performance in executive function, working memory, and attention (SFT: $p = 0.001$; LNS: $p = 0.003$; SDMT: $p = 0.002$; Figures 2B–D).

Minor allele carrier status of rs162009, on the other hand, was protective, with better performance in working memory and attention (LNS: $p = 0.009$; SDMT: $p = 0.006$; Figures 3C,D).

In addition, minor allele carrier status of rs3763043 and rs3763040 were associated with worse executive function (SFT: $p = 0.003$) and better visuospatial function (BJLOT: $p = 0.007$), respectively. Minor allele carrier of rs7240333 was associated with better memory (HVL: $p = 0.047$), which was not significant after correction for multiple comparisons.

There was no significant SNP by time interaction effect in any of the tests. Notably, there was no significant main effect of time in HVL ($p = 0.457$), LNS ($p = 0.068$), and SFT ($p = 0.518$), indicating the absence of decreasing scores in these subdomains over time. This was likely attributable to the high education level in the PPMI cohort, which amounts to an average of

15.56 years of education. Patients with a higher level of education are likely to have higher cognitive reserve and therefore slower cognitive decline in PD (Meng and D'Arcy, 2012; Hindle et al., 2014).

Association Between AQP4 and APOE ε4, COMT Val¹⁵⁸Met, GBA Variants

Chi-Square test indicated that the distribution of COMT variants on rs3763043 minor allele carriers and non-carriers was statistically different ($p = 0.027$), indicating a potential confounding effect of COMT variants on the observed association between rs3763043 and SFT. The distribution of APOE ε4, COMT Val¹⁵⁸Met, GBA variants on other AQP SNPs minor allele carrier vs. non-carrier was not significant (Supplementary Table 1).

AQP4 SNPs and ¹⁸F Florbetapir SUVR

Of the 36 patients who underwent ¹⁸F Florbetapir imaging, six (16.7%) were amyloid positive, if a cut-off of 1.43 for composite SUVR was used (Bullich et al., 2017; Fiorenzato et al., 2018). The average disease duration at the time of PET imaging was 4.73 ± 1.71 years. There was no statistically significant association between SNPs and composite SUVRs, although rs162009 was marginally associated lower composite SUVRs ($\beta = -0.076$, SE = 0.044, $p = 0.094$).

Given the observed association between minor allele carriers of rs162009 and more preserved cognitive performance,

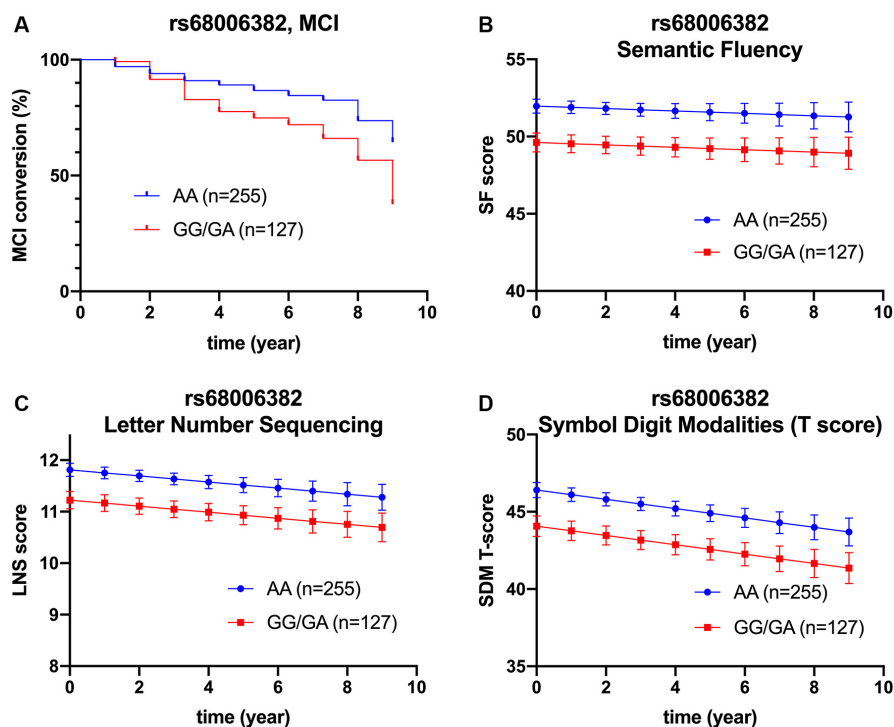


FIGURE 2 | Association between rs68006382 and cognition. rs68006382 (GG/GA vs. AA) had faster conversion to MCI (HR = 1.973, 95% CI = 1.246–3.123, $p = 0.004$) (A). rs68006382 GG/GA genotype also had worse performance in semantic fluency test ($\beta = -2.357$, SE = 0.691, $p = 0.001$) (B), letter-number sequencing ($\beta = -0.587$, SE = 0.193, $p = 0.003$) (C), and symbol digit modalities test ($\beta = -2.339$, SE = 0.193, $p = 0.002$) (D). Covariates for cox regression and linear mixed model included age, sex, *APOE* $\epsilon 4$ carriage, years of education, and baseline MoCA score. Lines in Panels (B–D) represent the estimated marginal mean from the mixed model. MCI, mild cognitive impairment.

we explored its association with SUVRs in cortical and subcortical regions of interest (Table 4). There were decreased SUVRs in putamen ($p = 0.012$) and anterior cingulum ($p = 0.048$) even with a limited sample size ($n = 36$; Figure 3E). In addition, minor allele carriers of rs162009 were marginally associated with lower amyloid burden in the temporal ($p = 0.070$) and frontal ($p = 0.072$) cortex.

The Interaction Between *AQP4* SNPs, Sleep Disturbance, and CSF Biomarkers

There was no significant association between *AQP4* SNPs and CSF biomarkers in the whole cohort. Then we examined the association between RBD and CSF biomarkers. Our analysis concurs with a previous study that RBD is associated with lower CSF A β 42 using the same PPMI database (Pagano et al., 2018). There was no such association between RBD and α -synuclein or tau. Given the proposed role of *AQP4* in solute drainage during sleep, we examined if *AQP4* SNPs modulate this association. After controlling for *APOE* $\epsilon 4$ carriage, age, sex and time, minor allele of rs162009 was associated with higher CSF A β 42 level in the high RBDSQ subgroup ($\beta = 0.081$, SE = 0.033, $p = 0.017$), but not in the low RBDSQ subgroup (subgroup by SNP interaction effect: $\beta = -0.056$, SE = 0.023, $p = 0.014$; Figure 3F).

AQP4 SNPs and Cognitive Performance in Healthy Controls

The association between *AQP4* SNP and cognitive scales was demonstrated in Table 5. Notably, minor allele carrier status of rs162009 was associated with higher semantic fluency test performance ($\beta = 2.209$, SE = 0.913, $p = 0.016$), validating the association between rs162009 and cognitive performance observed in patients with PD.

In addition, multiple *AQP4* SNPs (rs3763043, rs68006382, and rs74163677) were associated with HVLIT performance. However, these associations were likely attributable to the fact that *AQP4* plays a role in synaptic plasticity and therefore learning and memory (Hubbard et al., 2018; Woo et al., 2018).

During follow-up, 6/180 (3.33%) and 1/180 (0.56%) HCs developed MCI and dementia, respectively. Therefore, we did not perform Cox regressions in HCs.

Besides, there was no significant distribution difference of *AQP4* SNPs in PD and HCs.

DISCUSSION

Given the previously established association between *AQP4* and cognitive performance in the spectrum of AD, we explored this association in a cohort of patients with PD. We found that

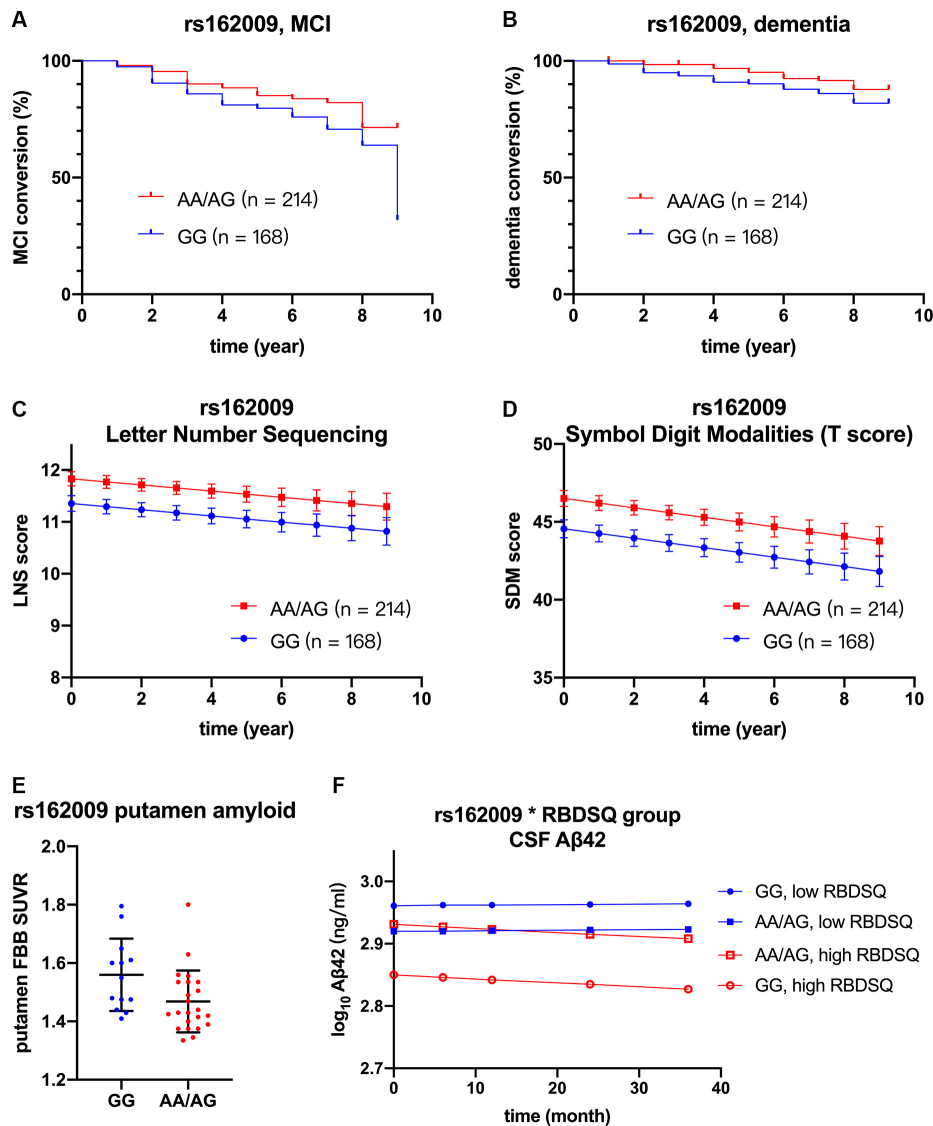


FIGURE 3 | Association between rs162009, cognition, and biomarkers. rs162009 (AA/AG vs. GG) had slower conversion to MCI (HR = 0.646, 95% CI = 0.409–1.019, $p = 0.060$) (A) and dementia (HR = 0.473, 95% CI = 0.234–0.957, $p = 0.037$) (B), better performance in letter-number sequencing ($\beta = 0.477$, SE = 0.183, $p = 0.009$) (C), and symbol digit modalities test ($\beta = 2.401$, SE = 1.953, $p = 0.006$) (D). rs162009 AA/AG genotype also had lower putamen FBB SUVRs ($\beta = -0.105$, SE = 0.039, $p = 0.012$) (E). In the subgroup of patients with high RBDSQ score (averaged score during the first 3 year ≥ 5.5 , $N = 117$), patients with rs162009 AA/AG genotype had higher CSF A β 42 levels ($\beta = 0.081$, SE = 0.033, $p = 0.017$), indicating its protective effect on A β deposition (F). Covariates for cox regression and linear mixed model included age, sex, APOE $\epsilon 4$ carriage, years of education, and baseline MoCA score. Lines in Panels (C,D,F) represent the estimated marginal mean from the mixed model. FBB, ^{18}F Florbetaben; MCI, mild cognitive impairment; RBDSQ, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SUVRs, standard uptake value ratios.

rs162009 was associated with slower dementia conversion, better performance in LNS and SDMT, and lower amyloid burden in the putamen and anterior cingulum. This variant was also associated with higher CSF A β in the subgroup with a high RBDSQ score. Besides, rs68006382 was associated with faster MCI conversion and worse performance in LNS, SFT, and SDMT.

The implication of rs162009 AA/AG genotype was more compelling as this variant was associated with both better cognitive performance and lower amyloid deposition in multiple

regions. In addition, its protective effect on cognition was also seen in HCs. One of the potential mechanisms to back up these clinical findings is that rs162009 likely increases the transcription of AQP4-M23 isoform and improves the glymphatic fluid circulation. There are two AQP4 splice variants, the M1 and M23. The M1 variant tends to be evenly distributed across the astrocytic membrane, while the M23 variant primarily locates at the astrocytic endfeet (Smith et al., 2014). rs162009 locates between exon 0 and exon 1 of the AQP4 gene (Figure 1), and putatively acts

TABLE 3 | AQP4 SNPs and cognition in patients with PD.

	Hazard ratio (95% CI)		Cognitive subdomains (β estimate)				
	MCI	Dementia	BJLOT	HVLT	LNS	SF	SDMT
rs7240333	0.677 (0.355, 1.293)	0.556 (0.194, 1.595)	0.213	1.626	0.308	0.171	0.367
rs1058427	0.668 (0.347, 1.285)	0.564 (0.195, 1.637)	0.038	0.035	0.280	0.457	0.950
rs3763043	1.435 (0.899, 2.292)	1.295 (0.643, 2.606)	-0.089	-0.161	-0.068	-1.931^a	-0.981
rs68006382	1.973 (1.246, 3.123)	1.512 (0.753, 3.034)	-0.229	-1.162	-0.587^a	-2.357^a	-2.339^a
rs335930	0.932 (0.584, 1.485)	0.748 (0.366, 1.530)	-0.178	-0.017	-0.009	-0.387	0.235
rs71353405	0.971 (0.417, 2.258)	0.737 (0.174, 3.120)	-0.063	-1.085	0.150	0.499	-0.243
rs74163677	0.737 (0.365, 1.489)	0.529 (0.160, 1.750)	0.056	0.154	-0.126	-0.964	-0.600
rs162009	0.646 (0.409, 1.019)	0.473 (0.234, 0.957)	-0.129	0.583	0.477^a	1.108	1.953^a
rs3763040	0.784 (0.481, 1.277)	0.735 (0.348, 1.553)	0.465^a	1.146	0.333	0.768	0.950
rs4800773	0.896 (0.560, 1.431)	1.034 (0.506, 2.112)	0.141	0.183	0.276	-0.388	-0.486
rs3875089	0.858 (0.490, 1.503)	1.001 (0.440, 2.279)	-0.026	-0.366	0.061	-0.537	0.049

^aSignificant after correction of multiple comparisons. Covariates include age, sex, APOE ϵ 4 carriage, years of education, and baseline MoCA score. BJLOT, Benton Judgment of line orientation test; HVLT, Hopkins verbal learning test (total recall); LNS, Letter-number sequencing; SFT, Semantic fluency test; SDMT, Symbol digit modalities test. Bold values are statistically significant.

TABLE 4 | Association between rs162009 and ¹⁸F Florbetapir SUVRs.

Regions of interest	β	SE	p	Adjusted r^2
putamen	-0.105	0.039	0.012	0.159
Anterior cingulum	-0.122	0.059	0.048	0.066
orbitofrontal	-0.084	0.042	0.056	0.077
Mesial temporal cortex	-0.065	0.034	0.068	0.046
Lateral temporal cortex	-0.067	0.036	0.070	0.082
Temporal cortex	-0.066	0.035	0.070	0.069
Frontal cortex	-0.084	0.045	0.072	0.102
Parietal cortex	-0.081	0.048	0.102	0.095
Rectus	-0.084	0.050	0.104	0.046
Occipital cortex	-0.062	0.041	0.139	0.018
Posterior cingulum	-0.078	0.066	0.245	-0.002
Thalamus	-0.040	0.052	0.449	-0.037
Caudate	-0.038	0.055	0.494	0.021
Pons	0.023	0.071	0.746	-0.132

FBB, ¹⁸F Florbetaben; SUVRs, standard uptake value ratios. Bold values are statistically significant.

as a promoter for the AQP4-M23 splice variant, which potentially facilitates the glymphatic fluid circulation (Iliff et al., 2012). However, this was primarily speculative, more mechanistic study is needed to explore the physiological effect of AQP4 SNPs.

The current findings add weight to previous observations that even subthreshold amyloid contributes to cognitive decline in non-demented PD. Interestingly, we observed a link between rs162009 and decreased putamen amyloid deposition. Increased striatal amyloid deposition was a prominent feature in PD-dementia autopsy (Kalaitzakis et al., 2008; Hepp et al., 2016). PD patients with combined amyloid pathology in cortex and striatum were associated with worse cognition than those with cortical amyloid pathology alone (Shah et al., 2016). In line with AD, it has been proposed that amyloid deposits in the neocortex first and striatum later (Shah et al., 2016). Therefore, the association between rs162009 and putamen SUVR might correspond to the slowed dementia conversion. The lower amyloid burden in the anterior cingulum (Petersen and Posner, 2012) and frontotemporal area (Randolph et al., 1993; Forn et al., 2009) in rs162009 minor allele carriers might correspond to better attention and working memory performance in these patients. However, AQP4 might modulate cognition in PD through other mechanisms such as synaptic plasticity (Hubbard et al., 2018; Woo et al., 2018), and neuroimmunological regulation (Ikeshima-Kataoka, 2016; Tamtaji et al., 2019).

The association between rs162009 and CSF A β 42 in the subgroup of high RBDSQ score provides a novel insight into

TABLE 5 | AQP4 SNPs and cognition in healthy controls.

	BJLOT		HVLT		LNS		SF		SDMT	
	β	p	β	p	β	p	β	p	β	p
rs7240333	0.063	0.819	-0.451	0.676	-0.464	0.091	0.502	0.636	-0.961	0.379
rs1058427	0.046	0.872	-1.781	0.108	0.235	0.406	0.810	0.458	0.317	0.778
rs3763043	0.217	0.380	2.000	0.038	-0.025	0.921	-0.006	0.995	-0.135	0.891
rs68006382	0.150	0.543	2.954	0.002^a	0.305	0.216	-0.119	0.900	-0.247	0.801
rs335930	0.178	0.473	-0.519	0.593	-0.093	0.708	0.903	0.345	-0.380	0.701
rs71353405	-0.278	0.441	-0.118	0.933	-0.320	0.377	0.578	0.678	1.231	0.391
rs74163677	0.702	0.122	-4.060	0.022	-0.510	0.262	-2.640	0.130	0.737	0.683
rs162009	0.241	0.315	0.087	0.926	0.162	0.499	2.209	0.016	0.895	0.348
rs3763040	-0.022	0.929	-0.847	0.379	-0.280	0.255	-0.269	0.777	-1.977	0.042
rs4800773	-0.003	0.991	-1.654	0.091	0.000	0.999	0.329	0.733	-1.382	0.164
rs3875089	0.152	0.556	-1.246	0.216	0.126	0.624	1.138	0.251	1.017	0.320

^aSignificant after correction of multiple comparisons. BJLOT, Benton Judgment of line orientation test; HVLT, Hopkins verbal learning test (total recall); LNS, Letter-number sequencing; SFT, Semantic fluency test; SDMT, Symbol digit modalities test. Bold values are statistically significant.

the interaction between RBD and AQP4-facilitated glymphatic clearance. Although glymphatic efficacy peaks during slow-wave sleep (Hablitiz et al., 2019), changes in the EEG signature of non-REM sleep have been observed in patients with RBD (Sunwoo et al., 2020). Therefore, it is reasonable to assume that RBD reduces glymphatic capacity. In patients with high RBDSQ scores, disrupted sleep architecture likely reduced the clearing capacity of the glymphatic system, which is attributable to the *AQP4* polymorphisms. The absence of significant association in the low RBDSQ subgroup likely reflected a situation where the glymphatic capacity exceeds the clearing need due to intact sleep. This finding provides indirect evidence that amyloid deposition as a result of disrupted glymphatic clearance might contribute to cognitive decline in RBD. This finding also highlights the prospects of targeting amyloid with immunotherapy in a subgroup of patients with PD (for instance, RBD and non-carriers of rs162009 minor allele).

We did not observe a significant association between *AQP4* and motor progression or CSF α -synuclein. This was likely because α -synuclein was primarily intracellular, the need for interstitial clearance might be low when compared with extracellular A β . Although significant α -synuclein aggregation was reported in *Aqp4* knockout mice (Xue et al., 2019), single nucleotide polymorphisms in humans likely exert a much smaller effect than genetic knockout.

The major limitations of the current study are as follows: (1) Significant associations observed in the current study are likely to be false positive. More work in other cohorts is needed to verify the effect of *AQP4* SNPs on PD. (2) We observed a marginally significant effect of rs162009 on FBB SUVs in a limited number of patients ($n = 36$). Future studies to validate the finding by expanding the patient sample size would be necessary. Besides, such a small number of patients who underwent FBB-PET would limit the statistical power to detect *AQP4* variants that are potentially associated with FBB SUV, especially for those SNPs that have low minor allele frequency. (3) Caution must be taken when interpreting the interaction effect between rs162009 and RBDSQ subgroup. It is also likely that abnormal neuronal activation as a result of sleep disturbance causes elevated production and release of A β (Ovsepian and O'Leary, 2016; Lucey, 2020). As A β measured by CSF or PET represents the balance of production and clearance, future studies to measure glymphatic activity *in vivo* would be necessary. (4) Measuring RBD symptoms with RBDSQ is prone to subjectivity (Halsband et al., 2018). More studies are warranted to validate and explore the effect of various types of sleep disturbance with objective sleep assessment equipment such as polysomnography and actigraphy.

CONCLUSIONS

Genetic variations of *AQP4* likely alter the glymphatic clearance of A β in the brain and subsequently the rate of cognitive decline in PD. *AQP4* rs162009 is likely a novel prognostic marker of cognitive decline in PD. Our findings also provide indirect evidence that in PD, AQP4-facilitated clearance of interstitial

amyloid might be disrupted in patients with probable REM sleep behavior disorder.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: <https://www.ppmi-info.org/access-data-specimens/download-data>.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because this study obtained and analyzed data from the PPMI dataset. Ethical approval was obtained at each individual PPMI participating site. The patients/participants provided their written informed consent to participate in the PPMI study.

AUTHOR CONTRIBUTIONS

YF, JP, and BZ contributed to the conception and design of the study. YF, SD, and CJ performed the statistical analysis. YF and SD wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIALS

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnagi.2021.740491/full#supplementary-material>.

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