Alpha-synuclein seed amplification assay performance in 1,145 cases: results from the PPMI Study

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Parkinson's Progression Markers Initiative

Abstract

Background: Biomarkers that confirm early diagnosis or indicate risk for Parkinson's disease (PD) are needed for clinical care and to accelerate therapeutic development.

Objective: To evaluate alpha-synuclein seed amplification assay (SAA) performance in CSF samples from a large cohort of patients with PD, individuals at-risk for PD and healthy controls.

Methods: The Parkinson Progression Marker Initiative (PPMI) study is a multi-national observational study of deeply phenotyped PD patients and individuals at risk including patients with prodromal features including hyposmia and REM sleep behavior disorder (RBD), non-manifesting carriers (NMC) of PD genes (eg. LRRK2, GBA) and healthy controls. Participants have regular clinical evaluations, dopamine imaging and biofluid collection. SAA analysis was performed using reported methods (Amprion, Inc.) on previously collected samples. We assessed sensitivity and specificity in PD patients and healthy controls, including PD subgroups (men vs. women, genetic variant carriers, subjects with and without olfactory deficits). We determined the frequency of positive CSF SAA results in prodromal subjects (RBD and hyposmia) and NMCs.

Results: 1,139 participants were included in this analysis including 557 patients with PD, 163 HCs, 55 SWEDDs, 51 prodromal subjects and 313 NMCs. Sensitivity and specificity in PD patients and HCs were 88% and 96% respectively. Sensitivity in PD with typical olfactory deficit was 98%. Sensitivity was lower in certain subgroups including LRRK2 carriers (67%) and PD patients without olfactory deficit (71%). The subgroup with the lowest sensitivity was female LRRK2 carriers without olfactory deficit (23%). Among prodromal and at-risk groups, 86% of RBD and hyposmic cases has positive SAA. 8% of NMC (LRRK2 and GBA) were positive.

Conclusions: Our results confirm the diagnostic accuracy for PD of a-syn SAA from CSF in typical PD and demonstrate that SAA is positive in a majority of prodromal cases and a smaller fraction of at-risk NMCs. These findings along with the variability among subgroups indicate that SAA may be a crucial biomarker to establish homogeneous at risk cohorts for observational and interventional studies.

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-dataspecimens/download-data).

For up-to-date information on the study, visit ppmi-info.org. PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including 4D Pharma, AbbVie Inc., AcureX Therapeutics, Allergan, Amathus Therapeutics, Aligning Science Across Parkinson's (ASAP), Avid Radiopharmaceuticals, Bial Biotech, Biogen, BioLegend, Bristol Myers Squibb, Calico Life Sciences LLC, Celgene Corporation, DaCapo Brainscience, Denali Therapeutics, The Edmond J. Safra Foundation, Eli Lilly and Company, GE Healthcare, GlaxoSmithKline, Golub Capital, Handl Therapeutics, Insitro, Janssen Pharmaceuticals, Lundbeck, Merck & Co., Inc., Meso Scale Diagnostics, LLC, Neurocrine Biosciences, Pfizer Inc., Piramal Imaging, Prevail Therapeutics, F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc., Sanofi Genzyme, Servier, Takeda Pharmaceutical Company, Teva Neuroscience, Inc., UCB, Vanqua Bio, Verily Life Sciences, Voyager Therapeutics, Inc., Yumanity Therapeutics, Inc.

Results

Table: Overall and subgroup accuracy

	N	Specificity (95% CI)	Sensitivity (95% CI)
HC	163	96.3% (93.4, 99.2)	
SWEDD	55	89.1% (80.9, 97.3)	
All PD cases	557		87.8% (85.1, 90.5)
All HC/PD cases*	566	94.6% (91.1, 98.0)	86.4% (83.6, 89.2)
Sporadic PD	374		93.3% (90.8, 95.8)
LRRK2 PD	122		67.2% (58.9, 75.5)
GBA PD	49		95.9% (90.4, 100.0)
LRRK2 PD			
Males	65		78.5% (68.5, 88.5)
Females	57		54.4% (41.5, 67.3)
Hyposmics	65		89.2% (81.7, 96.8)
Normosmics	52		38.5% (25.2, 51.7)

*Inconclusive participants are included in this calculation and are treated as false negative for PD and false positive for HC

Figure: Positive SAA results are less likely in PD LRRK2 carriers and PD patients without severe olfactory loss

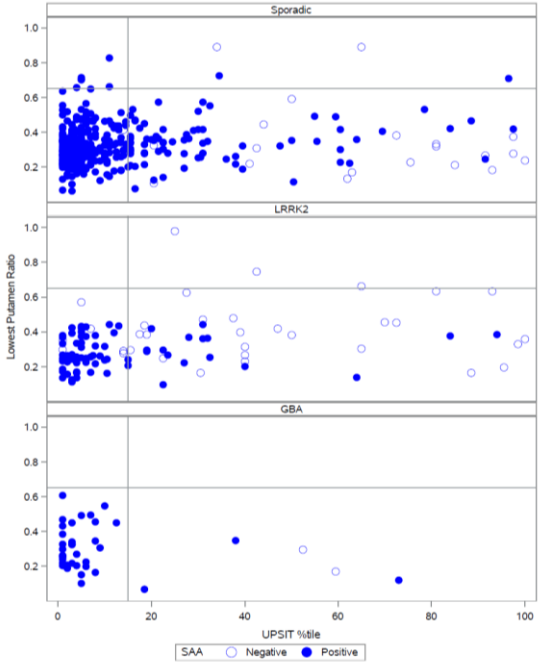


Table: Association with clinical features for sporadic and genetic PD groups

Variable	Sporadic SAA+ (N = 349)	Sporadic SAA- (N = 25)	LRRK2 SAA+ (N = 82)	LRRK2 SAA- (N = 40)	GBA SAA+ (N = 47)	GBA SAA- (N = 2)
Age (yrs)	61.9 (9.2)	64.6 (11.2)	60.8 (8.3)	68.9 (6.1)***	62.4 (9.5)	67.8 (10.4)
Male sex	228 (65%)	16 (64%)	51 (62%)	14 (35%)*	27 (57%)	2 (100%)
Disease duration (yrs since PD diagnosis)	0.6 (0.6)	0.5 (0.4)	3.2 (2.1)	2.9 (2.1)	3.5 (2.4)	1.0 (0.5)
MDS-UPDRS I	5 (4)	8 (6)*	8 (6)	8 (7)	8 (5)	4 (6)
MDS-UPDRS II	6 (4)	8 (5)	7 (5)	6 (5)*	9 (5)	8 (4)
MDS-UPDRS III	21 (9)	22 (7)	24 (11)	19 (9)*	29 (11)	25 ()
Total MDS-UPDRS	32 (13)	37 (13)	41 (17)	32 (15)*	46 (15)	44 ()
UPSIT percentile	12 (16)	56 (32)***	12 (17)	44 (30)***	6 (12)	56 (5)
Hyposmic (<=15%tile)	264 (76%)	4 (17%)***	58 (74%)	7 (18%)***	43 (93%)	0 (0%)
RBDSQ	4 (3)	4 (3)	4 (2)	3 (2)	6 (4)	3 (2)
SCOPA-AUT	9 (6)	10 (6)	13 (8)	13 (8)	13 (7)	8 (4)
GDS	2 (2)	3 (3)*	3 (3)	3 (3)	3 (3)	1 (1)

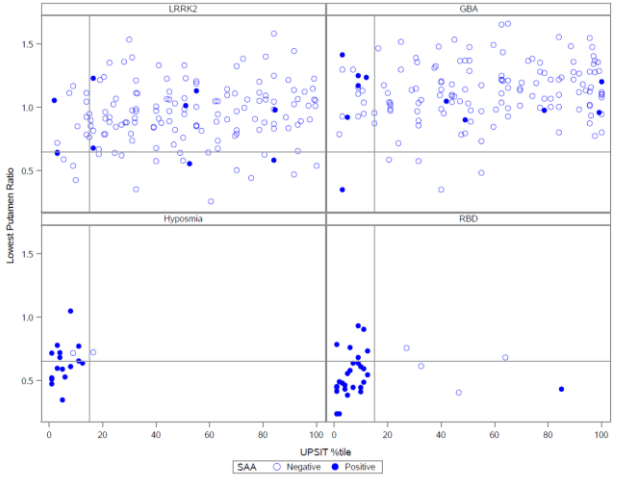
Wilcoxon rank sum tests p-values are used for continuous outcomes
Chi-square and Fisher's Exact tests are used for categorical outcomes.
* p<0.05; ** p<0.001; *** p<0.0001.
Comparisons for GBA were not performed due to low sample size.

Table: Association with biomarkers for sporadic and genetic PD groups

Variable	Sporadic SAA+ (N = 349)	Sporadic SAA- (N = 25)	LRRK2 SAA+ (N = 82)	LRRK2 SAA- (N = 40)	GBA SAA+ (N = 47)	GBA SAA- (N = 2)
Mean striatum SBR	1.40 (0.37)	1.35 (0.53)	1.24 (0.36)	1.38 (0.39)	1.25 (0.48)	0.80 (0.31)
CSF abeta < 683	104 (32%)	8 (35%)	27 (33%)	13 (34%)	23 (50%)	0 (0%)
CSF tau < 266	304 (93%)	22 (92%)	76 (93%)	32 (82%)	44 (96%)	2 (100%)
CSF asyn < 1000	71 (22%)	3 (13%)	11 (25%)	2 (10%)	4 (50%)	N/A
Serum NfL	13.07 (7.29)	15.01 (5.90)*	12.72 (8.44)	20.69 (11.39)**	16.14 (12.96)	26.70 ()
Total di-18:1 BMP	5.1 (4.8)	5.8 (7.7)	16.2 (15.3)	23.8 (32.2)	6.6 (4.9)	12.9 (3.3)

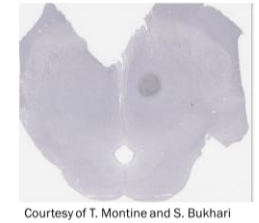
Wilcoxon rank sum tests p-values are used for continuous outcomes
Chi-square and Fisher's Exact tests are used for categorical outcomes.
* p<0.05; ** p<0.001; *** p<0.0001.
Comparisons for GBA were not performed due to low sample size.

Figure: Among prodromal and NMC cases: almost all NMC have negative SAA results, and normal olfaction and DAT binding; almost all prodromal cases are SAA positive and have hyposmia. Most, but not all, have abnormal DAT



•Conclusions

- A-syn SAA accurately distinguishes PD participants from controls and SWEDDS and could be incorporated into clinical trials to help stratify participants
- Subgroups of PD participants, based on genetics (LRRK2 carriers) or on clinical features (normal olfaction) are more likely to be SAA-. SAA-, LRRK2 variants with normal olfaction and might represent a different pathological phenotype



Courtesy of T. Montine and S. Bukhari

- Almost all LRRK2 and GBA NMC were SAA negative, suggesting that the presence of a-syn aggregates is not a life-long state.
- Almost all prodromal PPMI participant with either hyposmia or RBD, plus DAT deficit were SAA positive
- Some prodromal SAA+ cases had normal dopamine imaging suggesting a pattern of biomarker changes in which a-syn aggregation precedes deficits in DAT binding.