Assessment of variation in α-synuclein seed amplification assay results in the PPMI cohort: Association with hyposmia

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1 INTRODUCTION

α-synuclein seed amplification assay (SAA) has emerged as a crucial biomarker for underlying Lewy pathology in patients with parkinsonian disorders.

Our previous report showed variations in the proportion of cases with positive α-synuclein SAA results depending on carrier status for genetic variants as well as clinical features of PD, particularly hyposmia.

The purpose of this presentation is to show additional data that addresses the heterogeneity among Parkinson's disease (PD) patients, including those with hyposmia, genetic variants, and controls based on α-synuclein seed amplification assay (SAA) results.

2 METHODS

α-synuclein-SAA analysis of cerebrospinal fluid (CSF) was performed using previously described methods.

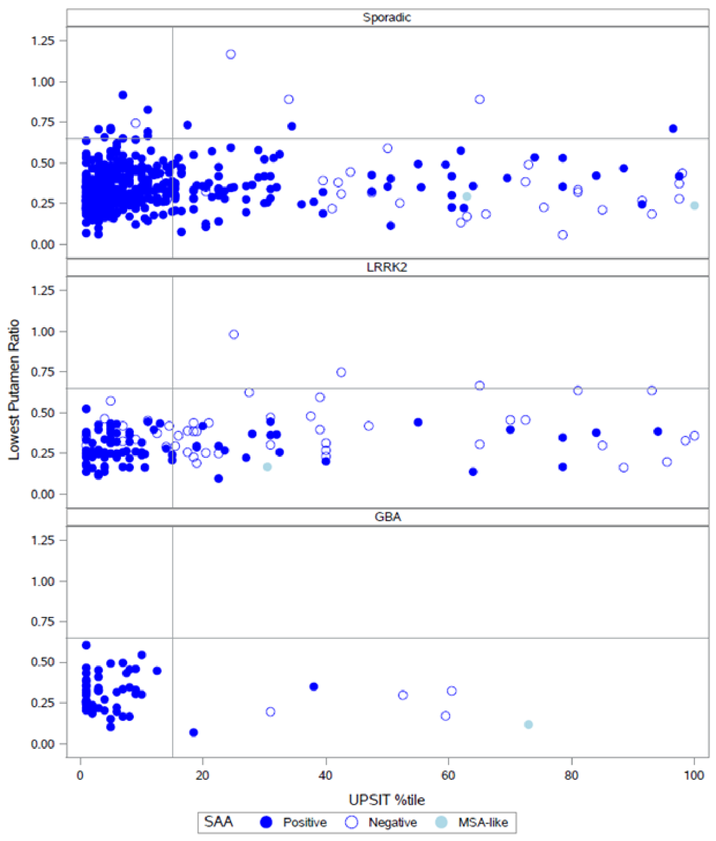
We assessed the frequency of positive α-synuclein SAA results in PD participants including those with genetic variants associated with PD: LRRK2, GBA and PRKN and SNCA.

We compared α-synuclein SAA results to olfactory testing across groups and assessed patterns of α-synuclein SAA results in PD patients with and without genetic variants associated with PD, healthy control (HC) and participants with clinical features of parkinsonism but with Scans Without Evidence of Dopaminergic Deficiency (SWEDDs).

3 RESULTS

Samples per cohort

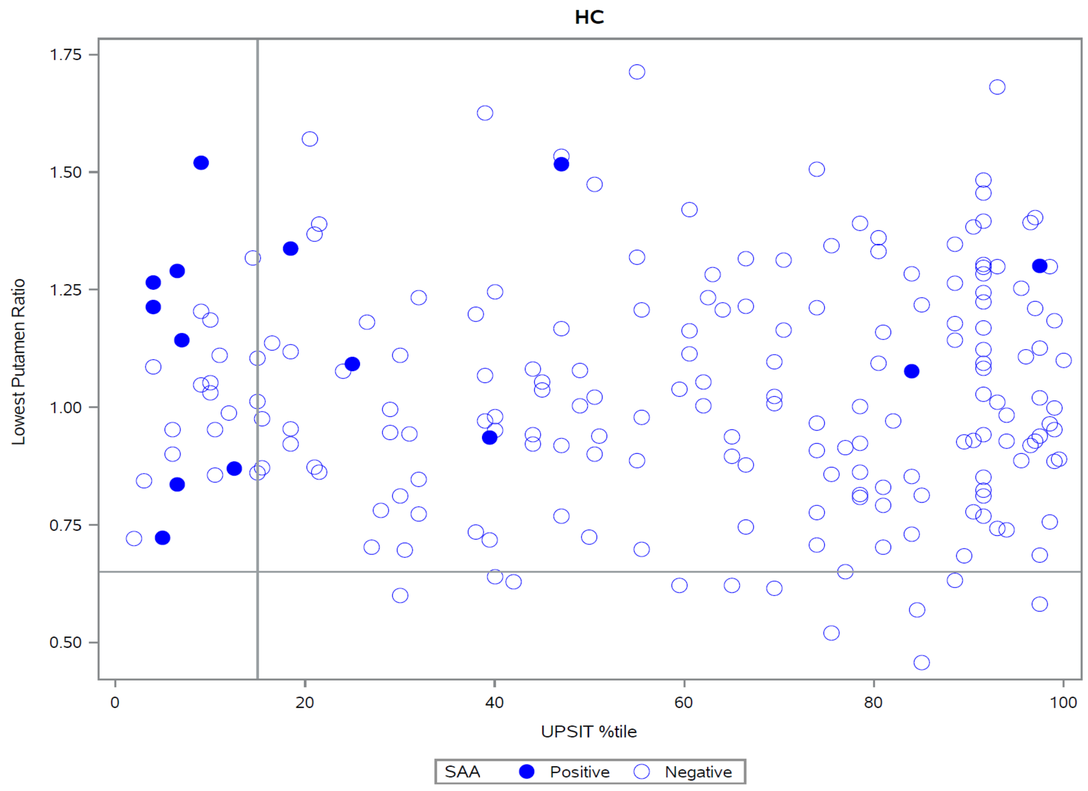
	PD	HC	SWEDD
Original	552	166	57
New	783	212	59



- 97% (548/567) of all PD with UPSIT <= 15th %ile are SAA positive
- 59% (114/193) of all PD with UPSIT > 15th %ile are SAA positive
- 85% (70/82) of LRRK2 PD with UPSIT <= 15th %ile are SAA positive
- 34% (21/62) of LRRK2 PD with UPSIT > 15th %ile are SAA positive
- 88% (629/713) of all PD with DAT < 65% are SAA positive
- 63% (12/19) of all PD with DAT >= 65% are SAA positive
- 66% (84/128) of LRRK2 PD with DAT < 65% are SAA positive
- 0% (0/3) of LRRK2 PD with DAT >= 65% are SAA positive

3 RESULTS, cont.

SAA status for HC subjects depending on DAT and hyposmia



SAA status for SWEDDs depending on UPSIT group

SAA	Total	UPSIT %tile <= 15	UPSIT %tile > 15
Positive	10 (16.9%)	3 (30.0%)	7 (14.3%)
Negative	49 (83.1%)	7 (70.0%)	42 (85.7%)

SAA status for individual LRRK2 and GBA variants

Group	SAA	Total	UPSIT %tile <= 15	UPSIT %tile > 15
LRRK2				
G2019S	Positive MSA-like	1 (0.8%)		1 (1.9%)
	Positive	84 (67.7%)	65 (90.3%)	19 (36.5%)
	Negative	39 (31.5%)	7 (9.7%)	32 (61.5%)
R1441G	Positive	4 (26.7%)	3 (33.3%)	1 (16.7%)
	Negative	11 (73.3%)	6 (66.7%)	5 (83.3%)
Other LRRK2	Positive	2 (100.0%)	1 (100.0%)	1 (100.0%)
GBA				
N409S Heterozygous	Positive MSA-like	1 (1.9%)		1 (16.7%)
	Positive	49 (92.5%)	47 (100.0%)	2 (33.3%)
	Negative	3 (5.7%)		3 (50.0%)
N409S Homozygous	Positive	4 (100.0%)	4 (100.0%)	
Severe GBA	Positive	6 (85.7%)	6 (100.0%)	
	Negative	1 (14.3%)		1 (100.0%)
Other GBA	Positive	1 (100.0%)	1 (100.0%)	
G2019S-N409S Heterozygous	Positive	2 (66.7%)	2 (100.0%)	
	Negative	1 (33.3%)		1 (100.0%)
G2019S-Severe GBA	Positive	1 (100.0%)		1 (100.0%)
G2019S-Other GBA	Positive	1 (100.0%)	1 (100.0%)	

Severe GBA include IVS2+1G>A, L29Afs*18, L483P, R159W variants; Other LRRK2 include N1437H, R1441C variants; Other GBA include R502C, R535H variants.

4 CONCLUSION

There is substantial variability in α-synuclein SAA across PD groups defined by genetic variant carrier status.

While the frequency of positive α-synuclein SAA results differs across subgroups, the co-occurrence of positive α-synuclein SAA and hyposmia is a consistent clinical-biomarker phenotype in all PD subgroups and extends into groups without clinical or physiological evidence of parkinsonism.

5 ACKNOWLEDGMENT

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