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Reply to: SNCA Variants Are Associated With Increased Risk of Multiple System Atrophy

Owen A. Ross, PhD[1], **Carles Vilariño-Güell, PhD**[1], **Zbigniew K. Wszolek, MD**[2], **Matthew J. Farrer, PhD**[1], and **Dennis W. Dickson, MD**[1]

[1]Department of Neuroscience, Mayo Clinic, Jacksonville, FL

[2]Department of Neurology, Mayo Clinic, Jacksonville, FL

Parkinson disease (PD) and multiple system atrophy (MSA) are disorders distinguished by pathologic accumulation of α-synuclein in neurons and glia. A common variation in the gene for α-synuclein (*SNCA*) is known to be associated with PD, but its role in MSA is unclear. Recently, Scholz et al reported a single-nucleotide polymorphism (SNP) (rs111931074) in the 3′ region of *SNCA* , originally identified in a genome-wide association study in PD, that increased the risk for MSA by nearly 6-fold in a subset of pathologically confirmed cases.[1] Our studies assessing the influence of *SNCA* variation in PD have examined the frequency of this SNP in a PD patient-control series from Ireland, Serbia, and Germany.[2,3] Although significant association was observed across the *SNCA* locus, rs111931074 was not associated with increased risk of PD, with a very low frequency (<1%) of minor allele homozygotes found in both patients and controls.

The association observed by Scholz et al of *SNCA* rs111931074 with MSA was most pronounced under a recessive model, especially in pathologically confirmed MSA. A frequency of the TT minor allele homozygote was 2% in a clinical series (n = 308) and 6% in a pathological series (n = 92) of MSA patients, compared with 0.6% in controls (n = 3,889). The effect of this variant appears to be most pronounced in pathologically confirmed MSA, with a dilution of the signal in clinical samples. The high diagnostic error in MSA may be the reason for the weaker association, and studies in our brain bank series suggest that as many as 25% of clinically diagnosed MSA patients do not have MSA at autopsy (unpublished findings). Therefore, we set out to replicate the finding in our pathologically confirmed MSA cases (n = 58). We identified a similar increased frequency of the TT homozygotes (n = 3; 5%; Table). In a combined analysis for the Mayo and Scholz series, the association of rs111931074 with pathologically confirmed MSA was examined using logistic regression under a recessive model, adjusting for series, resulting in an odds ratio of 9.32 (Table).

A role for *SNCA* variants in MSA is not surprising, given α-synuclein pathology, and suggests a common disease mechanism for PD and MSA. Recently, an individual with *SNCA* multiplication mutation was reported with a clinical syndrome reminiscent of MSA[4]; there was no evidence of *SNCA* multiplication in our MSA cases.[5] With the advent of next generation DNA sequencing, a research priority is to sequence *SNCA* and the surrounding region to identify the functional variation responsible for risk of disease.

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TABLE

SNCA rs111931074 in MSA and Controls

Series	Affection Status	Samples, No.	GG, No. (%)	GT, No. (%)	TT, No. (%)	T allele, No. (%)	Odds Ratio (95% CI)	*p* Value
Mayo	MSA	58	46 (79)	9 (16)	3 (5)	15 (13)	4.71 (1.03–21.65)	0.06
	Control	350	304 (87)	42 (12)	4 (1)	50 (7)		
Scholz et al[1]	MSA	92	66 (71)	20 (22)	6 (7)	32 (17)	12.26 (4.85–31.01)	<0.00001
	Control	3889	3303 (85)	564 (15)	22 (1)	608 (8)		
Combined	MSA	150	112 (75)	29 (19)	9 (6)	47 (16)	9.32 (4.03–21.55)	<0.00001
	Control	4239	3607 (85)	606 (14)	26 (1)	658 (8)		

MSA = multiple system atrophy; CI = confidence interval.