LRRK2 exonic variants and risk of multiple system atrophy

Michael G. Heckman, MS
Lucia Schottlaender, MD
Alexandra I. Soto-Ortolaza, BS
Nancy N. Diehl, BS
Sruiti Rayaprolu, BS
Kotaro Ogaki, MD, PhD
Shinsuke Fujioka, MD
Melissa E. Murray, PhD
William P. Cheshire, MD
Ryan J. Uitti, MD
Zbigniew K. Wszolek, MD
Matthew J. Farrer, PhD
Anna Sailer, MD
Andrew B. Singleton, PhD
Patrick F. Chinnery, PhD
Michael J. Keogh, BMBS
Steve M. Gentleman, PhD
Janice L. Holton, PhD
Kiely Aoife, PhD
David M.A. Mann, PhD
Safa Al-Sarraj, PhD
Claire Troakes, PhD
Dennis W. Dickson, MD
Henry Houlden, PhD
Owen A. Ross, PhD

Correspondence to
Michael G. Heckman:
heckman.michael@mayo.edu

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ABSTRACT

Objective: The aim of this study was to evaluate the association between common exonic variants in the leucine-rich repeat kinase 2 (*LRRK2*) gene and risk of multiple system atrophy (MSA).

Methods: One series from the United States (92 patients with pathologically confirmed MSA, 416 controls) and a second series from the United Kingdom (85 patients with pathologically confirmed MSA, 352 controls) were included in this case-control study. We supplemented these data with those of 53 patients from the United States with clinically probable or possible MSA. Seventeen common *LRRK2* exonic variants were genotyped and assessed for association with MSA.

Results: In the combined series of 177 patients with pathologically confirmed MSA and 768 controls, there was a significant association between *LRRK2* p.M2397T and MSA (odds ratio [OR] = 0.60, $p = 0.002$). This protective effect was observed more strongly in the US series (OR = 0.46, $p = 0.0008$) than the UK series (OR = 0.82, $p = 0.41$). We observed other noteworthy associations with MSA for p.G1624G (OR = 0.63, $p = 0.006$) and p.N2081D (OR = 0.15, $p = 0.010$). The p.G1624G-M2397T haplotype was significantly associated with MSA in the US series ($p < 0.0001$) and combined series ($p = 0.003$) but not the UK series ($p = 0.67$). Results were consistent when additionally including the US patients with clinical MSA, where the strongest single-variant association was again observed for p.M2397T (OR = 0.59, $p = 0.0005$).

Conclusions: These findings provide evidence that *LRRK2* exonic variants may contribute to susceptibility to MSA. Validation in other series and meta-analytic studies will be important.

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GLOSSARY

GEO-PD = Genetic Epidemiology of Parkinson's Disease; **LRRK2** = leucine-rich repeat kinase 2; **MAPT** = microtubule-associated protein tau; **MSA** = multiple system atrophy; **OR** = odds ratio; **PD** = Parkinson disease; **SNCA** = α -synuclein.

Multiple system atrophy (MSA) is a rare, sporadic, rapidly progressing neurodegenerative disorder that shares clinical and pathologic features with Parkinson disease (PD).¹ Elucidating possible causes of MSA has proven difficult; however, a recent genetic breakthrough came in the form of an association with a variant (rs11931074) in α -synuclein (*SNCA*), a well-established susceptibility gene in both familial and sporadic PD.^{2–4} In addition, the microtubule-associated protein tau (*MAPT*) H1 haplotype, another well-replicated risk factor for PD,² has shown evidence of association with MSA.⁵ The identification of genetic risk factors for MSA that also affect susceptibility to PD, coupled with the common clinical and pathologic features between these 2 α -synucleinopathies, suggests that other genetic risk factors for PD should be studied in relation to MSA. The leucine-rich repeat kinase 2 (*LRRK2*) gene is recognized as the most common genetic cause of PD and, like *SNCA*, also harbors several risk-modifying susceptibility variants.² In a large study of *LRRK2* in PD, the Genetic Epidemiology of Parkinson's Disease

From the Section of Biostatistics (M.G.H., N.N.D.) and Departments of Neuroscience (A.I.S.-O., S.R., K.O., M.E.M., D.W.D., O.A.R.) and Neurology (S.F., W.P.C., R.J.U., Z.K.W.), Mayo Clinic, Jacksonville, FL; Department of Molecular Neuroscience (L.S., A.S., H.H.), Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK; Department of Medical Genetics (M.J.F.), University of British Columbia, Vancouver, Canada; Laboratory of Neurogenetics (A.B.S.), National Institute on Aging, Bethesda, MD; Institute of Genetic Medicine (P.F.C., M.J.K.), Newcastle University, Central Parkway, Newcastle upon Tyne; Neuropathology Unit (S.M.G.), Department of Medicine, Imperial College London; Queen Square Brain Bank for Neurological Disorders (J.L.H., K.A.), Department of Molecular Neuroscience, UCL Institute of Neurology, University College London; Clinical and Cognitive Sciences Research Group (D.M.A.M.), Institute of Brain, Behavior and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Salford Royal Hospital, Salford; and MRC London Neurodegenerative Diseases Brain Bank (S.A.-S., C.T.), King's College London, UK.

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(GEO-PD) Consortium identified 17 common *LRRK2* exonic variants in a Caucasian series and observed several significant associations with PD.⁶ Herein, we utilize a large collection of data from patients with pathologically confirmed MSA and evaluate common *LRRK2* coding variants for association with MSA.

METHODS Subjects. We included one series from the United States (US) and a second series from the United Kingdom (UK) in our study. The US series consisted of data from all 92 patients with pathologically confirmed MSA obtained between 1998 and 2013 from the Mayo Clinic brain bank for neurodegenerative disorders in Jacksonville, FL, and 416 clinical controls from the Mayo Clinic in Jacksonville, FL, collected between 2001 and 2007. Controls were clinical individuals free of neurologic disease. We supplemented this series with 44 patients with clinically probable and 9 clinically possible MSA seen at the Mayo Clinic in Jacksonville, FL, between 2003 and 2011; diagnosis was made based on the Gilman criteria.⁷ The UK series involved data from all 85 patients from the UK with pathologically confirmed MSA obtained between 1987 and 2009 from the Queen Square

brain bank for neurologic disorders in London, UK, and 352 clinical controls. Controls were unrelated population controls who were randomly selected from the British 1958 Birth Cohort. Our primary analysis focused on the 2 pathologically confirmed patient-control series. None of the patients with MSA were carriers of an *LRRK2* pathogenic mutation. All individuals were non-Hispanic Caucasians and were unrelated within and between disease groups. Subject characteristics, including age, sex, MSA subtype, Lewy body disease pathology, and Braak stage for Alzheimer disease are displayed in table 1.

Genetic analysis. We selected all 17 *LRRK2* exonic variants that were observed with a minor allele frequency $\geq 0.5\%$ in the Caucasian series of the aforementioned large GEO-PD study (in which a total of 123 *LRRK2* exonic variants were evaluated) for inclusion in the current study.⁶ The 5 variants in exons 34 and 37 of *LRRK2* were genotyped using bidirectional Sanger sequencing on an ABI 3730XL DNA sequencer (Applied Biosystems, Foster City, CA). The other 12 *LRRK2* variants were genotyped using Sequenom MassARRAY iPLEX Gold chemistry and analyzed using Typer 4.0 (Sequenom, San Diego, CA) (primer sequences available on request) or the custom-built Illumina ImmunoChip (UK series). There was no evidence of departure from Hardy-Weinberg equilibrium in controls (all $\chi^2 p > 0.01$)

Table 1 Characteristics of patients with MSA and controls

Variable	US series			UK series	
	Patients with pathologically confirmed MSA (n = 92)	Patients with clinically diagnosed MSA (n = 53)	Controls (n = 416)	Patients with pathologically confirmed MSA (n = 85)	Controls (n = 352)
Age, y ^a	67.3 $\pm$ 8.6 (47-86)	69.4 $\pm$ 9.1 (49-88)	68.7 $\pm$ 10.7 (29-88)	66.0 $\pm$ 8.2 (50-86)	All either 44 or 45 ^b
Age at onset, y	NA	67.4 $\pm$ 8.8 (49-85)	NA	NA	NA
Sex, n (%)					
Male	56 (60.9)	30 (56.6)	221 (53.1)	44 (51.8)	NA
Female	36 (39.1)	23 (43.4)	195 (46.9)	41 (48.2)	NA
MSA subtype, n (%)					
MSA-P	35 (38.4)	39 (73.6)	NA	31 (36.5)	NA
MSA-C	12 (13.2)	5 (9.4)	NA	24 (28.2)	NA
Mixed	44 (48.3)	9 (17.0)	NA	30 (35.3)	NA
Lewy body disease pathology, n (%)	5 (5.4)	NA	NA	7 (8.2)	NA
Braak stage, n (%)					
0	18 (20.9)	NA	NA	38 (51.4)	NA
I	37 (43.0)	NA	NA	29 (39.2)	NA
II	20 (23.3)	NA	NA	7 (9.5)	NA
III	7 (8.1)	NA	NA	0 (0.0)	NA
IV	4 (4.7)	NA	NA	0 (0.0)	NA

Abbreviations: MSA = multiple system atrophy; MSA-C = cerebellar subtype of MSA; MSA-P = parkinsonian subtype of MSA; NA = not applicable. The sample mean $\pm$ SD (minimum-maximum) is given for age and age at onset.

^aFor the US series, the age provided is the age at death for patients with pathologically confirmed MSA and age at blood draw for the patients with clinically diagnosed MSA and controls. For the UK series, the age provided is the age at death for patients with MSA (all of whom were pathologically confirmed) and the age at blood draw for controls.

^bAll of the UK controls were either 44 or 45 years of age at the time of blood draw; only this general information was available for the UK controls—subject-specific age information was not available. Age at onset information was available only for the 53 US patients with clinically diagnosed MSA. Information was unavailable regarding MSA subtype (one US patient with pathologically confirmed MSA), Lewy body disease pathology (5 UK patients with pathologically confirmed MSA), and Braak stage (6 US patients with pathologically confirmed MSA, 11 UK patients with pathologically confirmed MSA). For the US patients with clinically diagnosed MSA, the 39 MSA-P were 30 probable and 9 possible MSA, the 5 MSA-C were all probable MSA, and the 9 mixed were all probable MSA.

and all genotype call rates were $\geq 99\%$. Linkage-disequilibrium between variants in controls is summarized in tables e-1A through e-1D on the *Neurology*[®] Web site at Neurology.org.

Statistical analysis. We evaluated associations between *LRRK2* variants and MSA using odds ratios (ORs) and 95% confidence intervals from logistic regression models. Models in the US series were adjusted for age and sex, no adjustment was made for models in the UK series, and models in the combined US-UK series were adjusted for series. Dominant models (i.e., presence vs absence of the minor allele) were utilized because of the small number of homozygotes of the minor allele for the majority of variants. We examined associations between *LRRK2* variants and MSA subtypes in the combined US-UK series of pathologically confirmed patients and controls using logistic regression models adjusted for series. Haplotype analysis was performed using score tests for association with the aforementioned model adjustments, and where haplotypes with a frequency of $<1\%$ were not considered.⁸ To account for multiple testing in the primary logistic regression analysis examining associations between *LRRK2* variants and overall risk of MSA, we used a single-step minP permutation adjustment,⁹ after which p values ≤ 0.0044 (US series), ≤ 0.0054 (UK series), and ≤ 0.0047 (combined series) were considered as statistically significant. Statistical analyses were performed using R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

Standard protocol approvals, registrations, and patient consents. The ethical review board at each institution approved the study. All subjects provided informed consent.

RESULTS Associations between the 17 *LRRK2* variants and MSA are displayed in table 2, where only patients with pathologically confirmed MSA were considered. In the US series, there was an association between p.M2397T and MSA that was significant after adjustment for multiple testing (OR = 0.46, $p = 0.0008$). Nonsignificant trends toward association were observed for p.G1624G, p.M1646T, and p.N2081D. In the UK series, associations with MSA that were significant before multiple testing adjustment occurred for p.N551K and p.R1398H. When combining these 2 series, *LRRK2* p.M2397T showed a significant protective association with MSA (OR = 0.60, $p = 0.002$), while nonsignificant but noteworthy associations were observed for p.G1624G (OR = 0.63, $p = 0.006$) and p.N2081D (OR = 0.15, $p = 0.010$). Results of association analysis were similar when additionally including the 53 US patients with clinical MSA, where the strongest association with MSA was again observed for p.M2397T (OR = 0.59, $p = 0.0005$) (table e-2). Genotype frequencies are provided in tables e-3A through e-3C.

In an exploratory analysis, we also evaluated associations between *LRRK2* variants and MSA subtypes in the combined series of patients with pathologically confirmed MSA (66 MSA-P [parkinsonian subtype], 36 MSA-C [cerebellar subtype], 74 mixed) and controls (table e-4). Briefly, the protective direction of the association for p.M2397T was observed across

subtypes although was stronger for MSA-P (OR = 0.63, $p = 0.075$) and MSA-mixed (OR = 0.46, $p = 0.002$) than MSA-C (OR = 0.87, $p = 0.70$), with similar findings for p.G1624G and a consistent nonsignificant protective effect observed for p.N2081D.

Of note, although the p.N551K-R1398H-K1423K haplotype that is protective for PD⁶ was observed at a lower frequency in patients with MSA compared to controls in the combined series (5.4% vs 7.2%, OR = 0.78), this did not approach significance ($p = 0.37$, table e-5). Given that p.G1624G and p.M2397T were in moderately strong linkage disequilibrium ($r^2 > 0.75$), we examined a haplotype for these 2 variants in relation to risk of MSA and observed a significant association in the combined series ($p = 0.003$, table e-6). These results were consistent when additionally including the US patients with clinical MSA (data not shown).

DISCUSSION In this investigation, we provide evidence that common *LRRK2* exonic variants may be associated with risk of MSA. More specifically, we identified a significant protective association for p.M2397T in the combined series, and other weaker potential findings of interest were noted for p.G1624G and p.N2081D. Of note, unlike *SNCA* rs11931074 and the *MAPT* H1 haplotype, none of these variants have previously been associated with PD. The 2 PD risk factors identified in the aforementioned GEO-PD study,⁶ *LRRK2* p.M1646T and the p.N551K-R1398H-K1423K haplotype, were not consistently associated with MSA. The association between the *LRRK2* p.M1646T substitution and MSA in our combined series (OR = 1.64) is similar to what we previously reported for PD (OR = 1.43)⁶; however, this risk association was observed only in the US series and was reversed in the UK series. Similarly, the magnitude of the association between the protective haplotype and risk of MSA in the combined series (OR = 0.78) is comparable to that seen in our previous GEO-PD study (OR = 0.86),⁶ but this protective effect was seen only in the UK series.

It is worth addressing some of the discrepant findings between the US and UK series. First, because of the small number of patients with MSA in the individual series, estimated associations with MSA are imprecise, and some between-series variability is to be expected. For p.M2397T, p.G1624G, and p.N2081D, although these associations were all observed more strongly in the US series, the protective direction of the effects was also observed in the UK series. Regarding p.M1646T and the p.N551K-R1398H-K1423K haplotype where associations varied more dramatically between series, both of these occurred relatively rarely, and therefore associations

Table 2 Associations between *LRRK2* exonic variants and MSA

Variant	Amino acid	Position	MA	US series (92 patients with pathologically confirmed MSA, 416 controls)				UK series (85 patients with pathologically confirmed MSA, 352 controls)				Combined series (177 patients with pathologically confirmed MSA, 768 controls)	
				MA count and frequency (%)		Association with MSA		MA count and frequency (%)		Association with MSA		Association with MSA	
				Patients (n = 92)	Controls (n = 416)	OR (95% CI)	p Value	Patients (n = 85)	Controls (n = 352)	OR (95% CI)	p Value	OR (95% CI)	p Value
rs10878245	L153L	38918058	T	75 (40.8)	300 (36.1)	1.17 (0.73, 1.87)	0.50	68 (40.0)	299 (42.7)	0.80 (0.49, 1.31)	0.37	0.99 (0.71, 1.39)	0.95
rs7308720	N551K	38943967	G	18 (10.0)	60 (7.2)	1.44 (0.80, 2.60)	0.22	5 (2.9)	56 (8.1)	0.35 (0.13, 0.90)	0.029	0.88 (0.54, 1.42)	0.59
rs10878307	I723V	38958256	G	12 (6.5)	60 (7.2)	0.81 (0.40, 1.60)	0.54	13 (7.6)	41 (5.9)	1.40 (0.71, 2.75)	0.33	1.05 (0.65, 1.69)	0.85
rs7966550	L953L	38974962	C	20 (10.9)	99 (11.9)	0.79 (0.45, 1.41)	0.43	19 (11.2)	109 (15.6)	0.60 (0.34, 1.07)	0.08	0.68 (0.45, 1.02)	0.064
rs7133914	R1398H	38989178	A	16 (8.7)	58 (7.0)	1.27 (0.69, 2.34)	0.44	6 (3.5)	57 (8.2)	0.41 (0.17, 1.00)	0.049	0.83 (0.51, 1.35)	0.45
rs11175964	K1423K	38989254	A	17 (9.2)	57 (6.9)	1.44 (0.79, 2.62)	0.23	6 (3.5)	57 (8.1)	0.42 (0.17, 1.00)	0.051	0.89 (0.55, 1.45)	0.64
rs35507033	R1514Q	38994045	A	0 (0.0)	5 (0.6)	NA ^a	0.59	0 (0.0)	4 (0.6)	NA ^a	1.00	NA ^a	1.00
rs33958906	P1542S	38994128	T	5 (2.7)	23 (2.8)	0.98 (0.36, 2.67)	0.97	4 (2.4)	22 (3.1)	0.74 (0.25, 2.20)	0.58	0.88 (0.42, 1.83)	0.72
rs1427263	G1624G	39000101	C	55 (29.9)	272 (32.9)	0.57 (0.36, 0.91)	0.017	57 (33.5)	266 (37.9)	0.71 (0.44, 1.15)	0.16	0.63 (0.45, 0.88)	0.006
rs11176013	K1637K	39000140	A	78 (42.4)	355 (42.8)	0.87 (0.54, 1.39)	0.55	79 (46.5)	342 (48.7)	0.74 (0.44, 1.24)	0.25	0.80 (0.57, 1.14)	0.22
rs35303786	M1646T	39000166	C	5 (2.7)	5 (0.6)	4.61 (1.30, 16.38)	0.018	1 (0.6)	11 (1.6)	0.37 (0.05, 2.89)	0.34	1.64 (0.63, 4.24)	0.31
rs11564148	S1647T	39000168	A	53 (28.8)	254 (30.7)	0.72 (0.46, 1.15)	0.17	48 (28.2)	190 (27.1)	0.96 (0.59, 1.54)	0.85	0.83 (0.59, 1.15)	0.25
rs10878371	G1819G	39002527	T	79 (42.9)	353 (42.8)	0.91 (0.56, 1.46)	0.68	80 (47.1)	343 (48.7)	0.78 (0.46, 1.31)	0.35	0.84 (0.60, 1.20)	0.34
rs33995883	N2081D	39026953	G	0 (0.0)	20 (2.4)	NA ^a	0.033	1 (0.6)	9 (1.3)	0.45 (0.06, 3.60)	0.45	0.15 (0.02, 1.08)	0.010
rs10878405	E2108E	39028521	A	58 (31.5)	251 (30.2)	0.89 (0.56, 1.40)	0.61	51 (30.0)	204 (29.1)	1.09 (0.68, 1.74)	0.73	0.97 (0.70, 1.35)	0.87
rs33962975	G2385G	39043597	G	27 (14.7)	114 (13.7)	1.17 (0.70, 1.94)	0.55	31 (18.2)	95 (13.6)	1.64 (0.98, 2.73)	0.058	1.36 (0.95, 1.94)	0.096
rs3761863	M2397T	39044919	T	50 (27.2)	288 (34.6)	0.46 (0.29, 0.73)	0.0008	55 (32.4)	247 (35.4)	0.82 (0.51, 1.32)	0.41	0.60 (0.43, 0.84)	0.002

Abbreviations: CI = confidence interval; MA = minor allele; MSA = multiple system atrophy; NA = not applicable; OR = odds ratio.

The ORs, 95% CIs, and p values result from logistic regression models. Models in the US series were adjusted for age (age at death for patients with pathologically confirmed MSA and age at blood draw for controls) and sex, no adjustment was made for models in the UK series, and models in the combined series were adjusted for series (US or UK). Each *LRRK2* variant was considered under a dominant model, and therefore ORs correspond to presence of the MA.

^a For rs35507033 and rs33995883, because none of the patients with MSA had a copy of the MA, logistic regression analysis and OR estimation were not possible, and p values result from Fisher exact test. After applying a single-step minP permutation adjustment for multiple testing, p values ≤0.0044 (US series), ≤0.0054 (UK series), and ≤0.0047 (combined series) were considered as statistically significant.

with MSA are especially imprecise. Most characteristics were generally similar between the 2 pathologically confirmed MSA series, although MSA subtype was moderately different between the US and UK series and this could have contributed to some of the between-series variation. It is also possible that genetic or other disease modifiers are responsible for these differing associations. Larger studies are needed to validate our findings and to better understand the relationship between these *LRRK2* exonic variants and risk of MSA, but regarding the results of our study, emphasis is best placed on the combined series, which contains the most information.

Most of the previous studies of *LRRK2* in MSA have focused on *LRRK2* p.G2019S, which is the most common cause of familial PD but appears to be absent in patients with MSA.¹⁰ The only study of a potential *LRRK2* risk-modifying susceptibility variant in MSA of notable sample size was performed by Lu et al.,¹¹ where in a series of 57 Taiwanese patients with MSA, p.G2385R, a well-replicated risk factor for PD in Asians, was found to occur at a similar frequency as in controls. In contrast to these reports, our results suggest that *LRRK2* variation may be associated with susceptibility to MSA.

A great strength of this study is the large number of patients with pathologically confirmed MSA. However, although our MSA series is larger than those of many previous MSA genetic studies, it is important to point out that this sample size is still small for a genetic association study, and therefore our findings require validation. Related to this, the possibility of type II error (i.e., a false-negative association) is important to consider, and emphasis is best placed on 95% confidence limits when interpreting the results of association analysis. In addition, without available genome-wide population control markers, population stratification could have affected our results. Finally, caution is warranted when interpreting findings of rare variants such as p.M1646T and p.N2081D and also in MSA-subtype analysis, where estimates are imprecise. Nonetheless, acknowledging these limitations, our results suggest that further study of *LRRK2* exonic variants in MSA is warranted.

AUTHOR CONTRIBUTIONS

Michael G. Heckman: drafting/revising the manuscript, analysis and interpretation of data. Lucia Schottlaender: revising the manuscript, analysis and interpretation of data. Alexandra I. Soto-Ortolaza: revising the manuscript, analysis and interpretation of data. Nancy N. Diehl: revising the manuscript, analysis and interpretation of data. Sruti Rayaprolu: revising the manuscript, analysis and interpretation of data. Kotaro Ogaki: revising the manuscript, analysis and interpretation of data. Shinsuke Fujioka: revising the manuscript and interpretation of data. Melissa E. Murray: revising the manuscript, interpretation of data. William P. Cheshire: revising the manuscript, contribution of patients. Ryan J. Uitti: revising the manuscript, contribution of patients. Zbigniew K. Wszolek: revising the manuscript, contribution of patients. Matthew J. Farrer:

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