SNCA Variants Are Associated with Increased Risk for Multiple System Atrophy

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To test whether the synucleinopathies Parkinson's disease and multiple system atrophy (MSA) share a common genetic etiology, we performed a candidate single nucleotide polymorphism (SNP) association study of the 384 most associated SNPs in a genome-wide association study of Parkinson's disease in 413 MSA cases and 3,974 control subjects. The 10 most significant SNPs were then replicated in additional 108 MSA cases and 537 controls. SNPs at the *SNCA* locus were significantly associated with risk for increased risk for the development of MSA (combined $p = 5.5 \times 10^{12}$; odds ratio 6.2).

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Multiple system atrophy (MSA) and Parkinson's disease (PD) are progressive neurodegenerative disorders characterized neuropathologically by deposition of abnormally phosphorylated α-synuclein. In PD, the aggregates are typically found in neurons as Lewy bodies, whereas in MSA, α-synuclein is deposited predominantly in the form of glial cytoplasmic inclusions.[1] These observations suggest that PD and MSA share a common pathogenic mechanism.

Although MSA appears to occur sporadically in the community, a number of recent observations have implicated genetic factors in the pathogenesis of the disease. First, neurological signs of parkinsonism are more common in relatives of MSA patients.[2,3] Second, affected members within families with *SNCA* duplication or triplication manifest clinical and pathological features similar to MSA.[4–6] Lastly, there are reports of MSA occurring within families, typically with an autosomal recessive inheritance pattern.[7,8]

We recently completed a genome-wide association study of 1,713 white PD cases and 3,974 white control subjects. Based on this initial cohort, 384 single nucleotide polymorphisms (SNPs) that were most associated with increased risk for development of PD were selected for further testing in an additional cohort of PD cases and control subjects, and we have presented these findings separately.[9] To test the hypothesis that MSA and PD share a common genetic causative factor, we tested the same 384 SNPs identified by our PD genome-wide association study in 413 MSA cases and 3,974 healthy control subjects. To confirm our findings, we then replicated the 10 most significant SNPs from this initial screening of MSA cases in an additional cohort of 108 MSA cases and 537 healthy control subjects. Our analysis demonstrated that genetic variants at the *SNCA* locus coding for α-synuclein were highly significantly associated with increased risk for development of MSA.

Subjects and Methods

Samples

The initial screening cohort consisted of 413 white MSA cases and 3,974 white healthy control subjects. The cases were a mixture of pathologically certain MSA patients (n = 99) and clinically probable or possible cases (n = 314). A total of 283 of 413 MSA cases were included from collaborating centers of the European MSA study group (www.emsa-sg.

org). The replication stage was composed of an independent cohort of 108 clinically probable white MSA cases and 537 white healthy control subjects. Diagnosis of patients was based on consensus criteria that Gilman and colleagues[10] established. Clinical features and collection sites of cases and control subjects are described in Supplemental Tables 1 and 2. The study was approved by each respective institutional review board, and written informed consent was obtained for each participant.

Genotyping

Genotyping of the 384 SNPs selected for the initial screening stage was performed using custom-made GoldenGate assays on a Veracode platform as per the manufacturer's instructions (Illumina, San Diego, CA). Raw genotype data were analyzed using Beadstudio software (version 3.1.0; Illumina).

For the replication stage, genotyping was performed by polymerase chain reaction followed by direct sequencing on an ABI 3730 DNA Analyzer (Applied Biosystems, Foster City, CA) (primer sequences listed in Supplemental Table 3). Genotype information for the control cohort used in the replication stage was extracted from publicly available data of 537 British healthy control subjects who had been previously genotyped on Illumina 610Y SNP chips.

Statistical Analysis

Statistical analysis was performed using PLINK software (v1.04).[11] For the screening stage, samples with a call rate less than 90% were excluded from analysis (n = 13 cases and 83 control subjects). SNPs with a minor allele frequency less than 0.01 (n = 3), SNPs with significant departure from Hardy–Weinberg equilibrium ($p < 0.001$; n = 29), SNPs with a missingness rate greater than 5% (n = 26), or SNPs with inaccurate clustering (n = 2) were excluded from analysis (15 SNPs failed more than one quality-control criterion). Each of the remaining 339 SNPs was then tested for association under allelic, genotypic, dominant, recessive, and trend models, and the lowest p value was calculated for each SNP (p_{min}). Applying the Bonferroni method to correct for multiple testing, the threshold p value for significance was 2.6×10^{-5} (two-sided α of 0.05 divided by [384 SNPs multiplied by 5 models]).

For the replication stage, one SNP was excluded because of departure from Hardy–Weinberg equilibrium in control subjects ($p < 0.01$). The remaining SNPs were tested for association under a recessive model, because this model was the best fit in the screening stage. Based on Bonferroni correction for multiple testing, a p value less than 0.005 was considered significant (two-sided α of 0.05 divided by 10 SNPs tested). The power of this cohort to replicate loci at this significance level with the odds ratios observed in the screening stage is shown in Supplemental Figure 2.

Results

Screening Stage

A total of 384 SNPs were genotyped in a cohort of 413 MSA cases and 3,974 control subjects. After quality-control filters were applied, 339 SNPs were tested for association with disease in a final dataset of 400 cases and 3,891 control subjects under allelic, genotypic, dominant, recessive, and trend models (results of the screening stage are shown in the Table and in Supplemental Figure 1).

Replication Stage

To replicate these findings, we genotyped the 10 most significantly associated SNPs identified in the screening stage in an independent, additional cohort of 108 MSA samples and 537 control samples (see the Table). Sequence analysis demonstrated a likely genotyping error for rs10515822; reexamination of cluster plots confirmed this error, and this SNP was removed from further analysis. Applying a recessive model, we observed highly significant associations exceeding the Bonferroni threshold for two of these SNPs, namely, rs11931074 ($p = 1.6 \times 10^{-4}$) and rs3857059 ($p = 1.3 \times 10^{-6}$). When data from the replication stage were combined

Table. **Nine Most Significantly Associated Single Nucleotide Polymorphisms**

SNP ID	Chromosome	Gene	Risk Allele	Screening Stage		Replication Stage		Combined	
				p_{min} (test model)	OR (95% CI) [RR vs (RP + PP)]	$p_{recessive}$	OR (95% CI) [RR vs (RP + PP)]	$p_{recessive}$	OR (95% CI) [RR vs (RP + PP)]
rs11931074	4q22.1	Downstream of SNCA	T	1.7E–07(recessive)[b]	5.4 (2.7–11.1)	1.6E–04[a]	6.6 (2.15–19.93)	5.5E–12	6.2 (3.4–11.2)
rs3857059	4q22.1	SNCA	G	6.9E–04(recessive)	3.8 (1.7–8.5)	1.3E–06[a]	9.8 (3.20–29.78)	2.1E–10	5.9 (3.2–10.9)
rs9480154	6q25.1	Downstream of PPP1R14C	A	1.6E–05(recessive)[b]	5.0 (2.2–11.2)	0.99	1.0 (0.12–8.81)	1.3E–04	3.9 (1.8–8.2)
rs2794256	6q22.31	LOC728727	T	1.7E–03(recessive)	1.7 (1.2–2.5)	0.17	1.6 (0.81–3.19)	4.0E–04	1.7 (1.3–2.4)
rs2042079	2p24.2	Intergenic	A	2.7E–03(recessive)	1.7 (1.2–2.5)	0.21	1.6 (0.77–3.18)	8.0E–04	1.7 (1.3–2.4)
rs13139027	4p16.2	Upstream of MSX1	A	2.5E–03(recessive)	3.9 (1.5–10.1)	0.53	1.5 (0.41–5.63)	1.8E–03	3.2 (1.5–6.9)
rs2515501	8p23.2	MCPH1	T	6.5E–04(recessive)	2.4 (1.4–4.1)	0.45	0.6 (0.13–2.52)	7.0E–03	1.9 (1.2–3.2)
rs2896159	7q31.2	Intergenic	T	3.0E–03(recessive)	0.7 (0.5–1.1)	0.38	1.3 (0.73–2.26)	0.43	1.3 (1.1–1.6)
rs2856336	12p13.2	ETV6	C	1.6E–08(recessive)[b]	4.6 (2.6–8.3)	0.12	—[c]	2.4E–05	3.1 (1.8–5.5)

[a]Exceeded Bonferroni significance threshold in the replication stage (i.e., $\alpha' = 0.05/10 = 0.005$). [b]Exceeded Bonferroni significance threshold for multiple testing in the screening stage (i.e., $\alpha' = 0.05/[384*5] = 2.6E\text{-}05$). [c]Unable to calculate odds ratio (OR) because of low allele frequency in cases. SNP = single nucleotide polymorphism; CI = confidence interval; R = risk allele; P = protective allele; HWE = Hardy–Weinberg equilibrium.

with data from the screening stage, the p value for rs11931074 was 5.5×10^{-12} (odds ratio for homozygous risk allele carriers = 6.2 [95% confidence interval [CI]: 3.4–11.2]), and for rs3857059 was 2.1×10^{-10} (odds ratio for homozygous risk allele carriers = 5.9 [95% CI: 3.2–10.9]) (see Supplemental Table 4 for details). These two SNPs are in complete linkage disequilibrium ($r^2 = 1.0$ in the Centre d'Etude du Polymorphisme Humain HapMap population from Utah), and lie in intron 4 of *SNCA* (rs3857059) and downstream of *SNCA* (rs11931074) (Fig). None of the remaining eight SNPs reached significance in the replication stage or in the combined analysis.

Analysis of Pathology-Proved Multiple System Atrophy Cases
To exclude the possibility that PD cases mistakenly clinically diagnosed as MSA might be falsely driving the association with *SNCA*, we analyzed the SNPs rs11931074 and rs3857059 in pathology-proven MSA cases and healthy control subjects (n = 92 cases and 3,891 control subjects after quality-control filtering). Both SNPs remained significantly associated with increased risk for development of MSA (recessive model

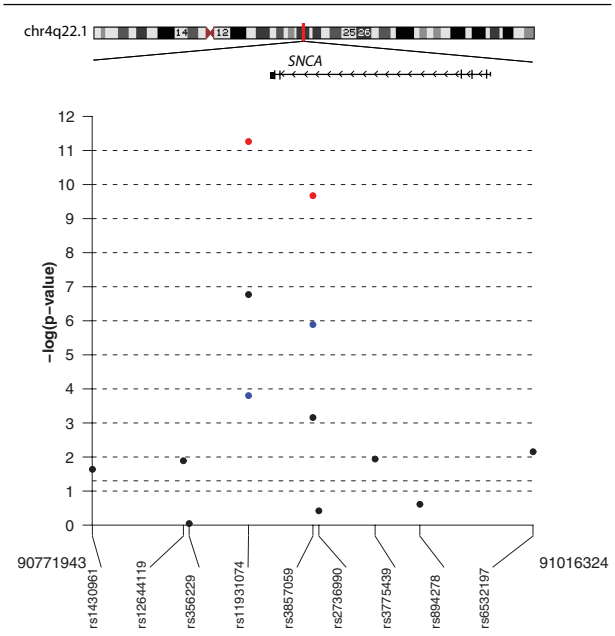

Fig. Location of the association signal at the SNCA locus on chromosome 4q22.1. Association signals are shown for all single nucleotide polymorphisms (SNPs) genotyped in (A) screening-stage samples (black circles), *(B) replication-stage samples* (blue circles), *and (C) for combined screening- and replication-stage samples* (red circles). *The most associated SNPs, rs11931074 and rs3857059, lie in or near the SNCA gene, and are in complete linkage disequilibrium. The plot were generated using the SNP.plotter package within R version 2.6.1.*

p value for rs11931074 = 1.4×10^{-11}; p value for rs3857059 = 4.9×10^{-6}; see Supplemental Table 5).

Analysis of Clinical Multiple System Atrophy Subtypes
From available records, 136 patients could be unequivocally assigned to the MSA-P subtype, and 75 patients were MSA-C cases (see Supplemental Table 2 for further details on these cohorts). An analysis in these subgroups could not detect the association between *SNCA* variants and increased risk for development of MSA (MSA-P: rs11931074, $p = 0.194$; rs3857059, $p = 0.183$; MSA-C: rs11931074, $p = 0.075$; rs3857059, $p = 0.069$; recessive model using Fisher's exact test), probably because of lack of power in the relatively small subgroups. However, this result also suggests that the association is not driven just by one MSA subphenotype.

Discussion

In this study, we have demonstrated that genetic variants within the *SNCA* locus are associated with increased risk for development of MSA. These data represent the first genetic variants convincingly identified for patients with MSA. This study is important in that genetic factors play a greater role in the pathogenesis of MSA, which entity primarily suggests thought of as sporadic in occurrence. The veracity of our findings is underscored by the strength of the association that clearly exceeded the conservative Bonferroni threshold for statistical significance, by the successful replication of our findings in an independent cohort, and by the role that *SNCA* is already known to play in the disease process based on neuropathological findings.[4–6]

Previous studies (including sequencing of *SNCA* coding sequence, gene dosage measurements, microsatellite testing, and haplotype studies) have failed to identify significant association of *SNCA* variants with MSA.[12–16] These negative results can be explained by the smaller sample sizes of these studies, and by the fact that none of the *SNCA* risk variants identified in our study was tested. Our replication of the association between *SNCA* variants and MSA in an independent patient and control cohort indicates that population stratification was unlikely to be falsely driving the finding. The failure to replicate our findings in MSA-P and MSA-C clinical subgroups was likely due to small sample size and the diagnostic uncertainty inherent to clinical criteria.[17] A combination of these factors would negatively impact the power to detect association within these patient subsets, and studies of larger cohorts will be required to dissect the true pathogenic role of *SNCA* variants within each of these clinical categories. In contrast, analysis in the smaller, but diagnostically accurate, subset of pathology-proven MSA cases clearly demonstrates that *SNCA* variants are associated with increased risk for disease.

The significant associations with increased risk for MSA were most clearly observed under the recessive model. However, it is possible that the relatively small size of our case–control cohort was powered only to identify individuals carrying two risk alleles, but that an undetected additive risk at these loci exists. Additional studies involving larger patient cohorts are required to determine whether persons with a single copy of the risk allele are at increased risk for development of MSA.

How does genetic variation at the *SNCA* locus confer an increased risk for development of MSA? Previous sequence analysis of *SNCA* coding sequence failed to identify pathogenic mutations; thus, direct alteration of the amino acid sequence is considered an unlikely mechanism of disease.[12,16] The most plausible explanation, therefore, would be a change in gene expression regulation. This explanation is supported by the observation that duplication or triplication of *SNCA* leads to glial cytoplasmic inclusion formation in the brains of affected individuals, and that in some subjects, the clinical presentation resembles a MSA phenotype.[4–6] A modest alteration in gene expression levels, although pathogenic in a given individual, may have escaped detection in previous *SNCA* expression studies of small sample size.[18–20] The identified risk variants may also alter the splicing pattern of *SNCA* in a pathogenic manner, or alter *SNCA* messenger RNA processing, or additional genetic factors may be responsible for the different manners of synuclein accumulation in PD and MSA.

How do the results of our candidate SNP association study in MSA compare with our genome-wide association study in PD? We identified significant association with the *SNCA* locus in both diseases.[9] The odds ratio associated with carrying a single risk allele of the *SNCA* SNP rs3857059 was 1.3 in both diseases (95% CI in PD: 1.2–1.5; 95% CI in MSA: 1.1–1.6), whereas the odds ratio for homozygous carriers was 3.8 (95% CI: 2.4–5.9) in PD and 5.9 (95% CI: 3.2–10.9) in MSA.

In summary, our study has conclusively demonstrated that genetic variants in *SNCA* play a role in the pathogenesis of MSA, and that these genetic factors overlap with those found in PD. These data support the general notion that variability at the gene that encodes the major pathologically deposited species is a risk factor in neurological diseases involving protein deposition[21] but highlights that often large sample sizes are required to see such an effect. Additional genetic loci undoubtedly remain to be identified in the pathogenesis of this fatal neurodegenerative disease.

Appendix

European Multiple System Atrophy study group members include Wolfgang Oertel, Ullrich Wüllner, Stefano Goldwurm, Maria Teresa Pellecchia, Werner Poewe, Gregor K. Wenning, and Thomas Gasser.

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Decreased Ventilatory Response to Hypercapnia in Dementia with Lewy Bodies

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A systematic autonomic dysfunction observed among patients with dementia with Lewy bodies (DLB) has recently attracted close attention. Here, we compare cardiovascular and pulmonary autonomic functions among patients with DLB, patients with Alzheimer's disease, and healthy control subjects. All 15 DLB patients demonstrated severely low ventilatory response to hypercapnia, whereas none of the other subjects demonstrated abnormal results. The majority of the DLB patients showed impaired heart rate variability, low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, and orthostatic hypotension. Ventilatory response to hypercapnia as a marker of respiratory autonomic function is a promising diagnostic tool for DLB.

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Dementia with Lewy bodies (DLB) is regarded as the second-most common degenerative dementia after Alzheimer's disease (AD).[1] The clinical criteria for DLB alone can separate many patients with DLB from other related disorders including AD. However, despite high diagnostic specificity, such criteria have lower sensitivity, and improved methods of case detection are required.[2] Several articles have emphasized that patients with DLB have autonomic physical symptoms, such as syncope, orthostatic hypotension, urinary incontinence, and constipation.[3–5] These autonomic symptoms, as well as a low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy,[6,7] are included as a supportive feature of the criteria of the Consortium on DLB.[8] Accordingly, autonomic assessment may prove useful to

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