Clinical/Scientific Notes

C. Vilariño-Güell, PhD
A.I. Soto-Ortolaza, BSc
A. Rajput, MD
D.C. Mash, PhD
S. Papapetropoulos, MD, PhD
R. Pahwa, MD
K.E. Lyons, PhD
R.J. Uitti, MD
Z.K. Wszolek, MD
D.W. Dickson, MD
M.J. Farrer, PhD
O.A. Ross, PhD

MAPT H1 HAPLOTYPE IS A RISK FACTOR FOR ESSENTIAL TREMOR AND MULTIPLE SYSTEM ATROPHY

Mutations in the microtubule-associated protein tau gene (*MAPT*) cause frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).[1] In addition, the major common *MAPT*-containing H1 haplotype is associated with increased risk for 2 parkinsonian disorders: progressive supranuclear palsy (PSP) characterized by 4-repeat tau pathology and Parkinson disease (PD) with α-synuclein pathology.[2,3] However, the role of *MAPT* variation in other disorders with similar pathology or disease phenotype is unclear. We investigated the frequency of the *MAPT* H1 haplotype in both essential tremor (ET) and multiple system atrophy (MSA).

ET is the most common movement disorder, and prior evidence has indicated a common link between ET and PD from clinical, epidemiologic, and pathologic studies as well as some reports of brainstem Lewy bodies at autopsy in patients with ET.[4] MSA is a neurodegenerative disorder with α-synuclein pathology with a mixed clinical presentation combining autonomic dysfunction, parkinsonism, and cerebellar or pyramidal symptoms. The initial clinical signs of MSA with prominent parkinsonism can make it difficult to differentially diagnose it from early PD. In addition, up to 30% of patients with MSA with prominent parkinsonism may have a transient response to levodopa therapy.[5]

Methods. Genotyping of the *MAPT* H1 discriminating SNP (rs1052553) and H1c subhaplotype SNP (rs242557) was performed on a Sequenom MassArray iPLEX platform (San Diego, CA) (primer sequences are available on request) and analyzed with Typer 4.0 software. The rate of genotype calls was ≥95% in each population. The series contained 356 patients with clinical ET, 61 patients with pathologically confirmed MSA, and 409 US control subjects; all samples are North American Caucasians. Numerical variables were summarized with the sample mean, SD, and range (table e-1 on the *Neurology*® Web site at www.neurology.org). Associations between ET and MSA with *MAPT* rs1052553 and rs242557 were measured by χ^2 statistics with Pearson probability estimates and corresponding odds ratios (ORs) with confidence intervals (CIs).

Standard protocol approvals, registrations, and patient consents. The ethical review boards at each institution approved the study, and all participants provided informed consent.

Results. We observed an uncorrected association of *MAPT* H1 genotype with both ET ($p = 0.027$) and MSA ($p = 0.016$) when compared to the frequency in controls (table 1). No significant association was observed with SNP rs242557. The observed OR for ET [1.32 (1.03–1.67)] and MSA [1.91 (1.13–3.23)] are similar to those observed for PD in the same population [1.47 (1.15–1.89)].[6]

Discussion. Given the relatively small sample size for both the ET and MSA series, and the possible clinical overlap with PD in the ET series, these results must be treated with caution and require independent replication. However, it is intriguing that while the extended haplotype containing *MAPT* has now shown association with a number of parkinsonian disorders, there is no evidence of association with AD, which displays abundant tau pathology. Given the presence of α-synuclein pathology in PD, MSA, and ET, these findings indicate a possible interplay between these proteins. It has been previously suggested that α-synuclein induces fibrillization of tau and that coincubation of tau and α-synuclein synergistically promotes fibrillization of both proteins.[7]

While we observed an association between the *MAPT* H1 haplotype and both ET and MSA, the functional variant remains to be identified. The expanded H1 haplotype contains *MAPT*, which is the best candidate gene to explain the observed association; however, other genes are present in this haplotype that cannot be excluded. It is postulated that the alternate *MAPT* haplotypes affect a differential expression of 3-repeat and 4-repeat tau protein in FTDP-17.[2] The SNP displaying the strongest association with risk of the tauopathy PSP (rs242557) does not show the same association with PD, MSA, or

Supplemental data at www.neurology.org

Table 1 Allele and genotype frequencies for *MAPT* rs1052553 and rs242557[a]

		Genotype, n (%)			Allele, n (%)			
SNP	Group	AA	AG	GG	A	G	Odds ratio (95% CI)	*p* Value
rs1052553	Control	231 (57)	148 (36)	27 (7)	610 (75)	202 (25)		
	ET	221 (65)	100 (30)	18 (5)	542 (80)	136 (20)	1.32 (1.03–1.67)	0.027[b]
	MSA	46 (75)	12 (20)	3 (5)	104 (85)	18 (15)	1.91 (1.13–3.23)	0.016[b]
rs242557	Control	52 (13)	185 (45)	172 (42)	289 (35)	529 (65)		
	ET	54 (16)	149 (44)	135 (40)	257 (38)	419 (62)	1.12 (0.91–1.39)	0.284
	MSA	13 (22)	25 (42)	21 (36)	51 (43)	67 (57)	1.39 (0.94–2.06)	0.095

Abbreviations: CI = confidence interval; ET = essential tremor; MSA = multiple system atrophy; SNP = single nucleotide polymorphism.
[a] For rs1052553 allele A corresponds to the H1 haplotype, and for rs242557 allele A corresponds to the H1c haplotype.
[b] Significant.

ET, suggesting different pathomechanisms for disease risk.[2,6]

It is now crucial to determine the functional risk variants that are located on the backbone of the extended H1 haplotype containing *MAPT*. With the established genomic capture and next-generation sequencing approaches, this goal is within reach. Sequencing of the entire extended haplotype will identify the variants influencing risk of PSP, PD, MSA, or ET, and help elucidate the disease pathways involved.

From the Division of Neuropathology (D.W.D.), Department of Neuroscience (C.V.-G., A.I.S.-O., M.J.F., O.A.R.), and Department of Neurology (R.J.U., Z.K.W.), Mayo Clinic College of Medicine, Jacksonville, FL; Division of Neurology (A.R.), Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; Department of Neurology (D.C.M., S.P.), School of Medicine, University of Miami, Miami, FL; and Department of Neurology (R.P., K.E.L.), University of Kansas Medical Center, Kansas City.

Study funding: Supported by NIH/NINDS P50 NS40256 and P01AG017216, the family of Carl and Susan Bolch, and a Mayo Clinic Florida Research Committee Essential Tremor grant.

Disclosure: Dr. Vilariño-Güell and Dr. Soto-Ortolaza report no disclosures. Dr. Rajput has served on scientific advisory boards for Novartis and UCB; has received funding for travel and speaker honoraria from Novartis; serves on the editorial board of the *Canadian Journal of Neurological Sciences*; and has received research support from Novartis, Allergan Inc., the NIH (NINDS U01 NS050324-01A1 [local PI]), CIHR, International Essential Tremor Foundation, Regina Curling Classic for Parkinson's Research, and Parkinson's disease and movement disorders endowment through RUH Foundation. Dr. Mash serves on scientific advisory boards for NIH PMDA, Boris Sokolov, and SRA; has received funding for travel or speaker honoraria from the Institute for the Prevention of In Custody Deaths; has patents pending re: Noribogaine and Biomarkers of Parkinson disease; is employed as Chief Scientific Officer for DEMERx Inc., and serves as a consultant for Phylogeny, Inc. Dr. Papapetropoulos serves as Associate Editor for *Yearbook of Neurology* and on the editorial boards of *Open Journal of Neurology* and *Open Journal of Neurosurgery*; has a patent pending re: MRPS6 Gene in PD; is employed as Senior Medical Director, Medical Affairs for Allergan, Inc.; and owns stock in Allergan, Inc. and Biogen Idec. Dr. Pahwa has served on scientific advisory boards and as a consultant for Teva Pharmaceutical Industries Ltd., Merck Serono, Schering-Plough Corp., Novartis, Medtronic, Inc., GE Healthcare, Biogen Idec, Boehringer Ingelheim, IMPAX Laboratories, Inc., and Ceregene; serves as Co-Editor in Chief of the *International Journal of Neuroscience*; receives publishing royalties for *Pocket Note Series* (Oxford University Press, 2009, 2010); serves on speakers' bureaus for Teva Pharmaceutical Industries Ltd., Medtronic, Inc., GlaxoSmithKline, and Novartis; receives research support from GlaxoSmithKline, Novartis, IMPAX Laboratories, Inc., Merck Serono, Boehringer Ingelheim, Schering-Plough Corp., the NIH/NINDS, and the National Parkinson Foundation; and served as an expert witness in a welding-related legal case. Dr. Lyons serves on a scientific advisory board for St. Jude Medical; serves as Co-Editor in Chief for the *International Journal of Neuroscience*; and serves as a consultant for Teva Pharmaceutical Industries Ltd. and Novartis. Dr. Uitti serves as an Associate Editor of *Neurology*®; has received research support from Advanced Neuromodulations Systems and from the NIH; and his institution receives annual royalties from Lundbeck Inc. from the licensing of the technology related to PARK8/LRRK2. Dr. Wszolek serves as Co-Editor-in-Chief of *Parkinsonism and Related Disorders*, Regional Editor of the *European Journal of Neurology*, and on the editorial boards of *Neurologia i Neurochirurgia Polska*, *Advances in Rehabilitation*, the *Medical Journal of the Rzeszow Univ*ersity, and *Clinical and Experimental Medical Letters*; holds and has contractual rights for receipt of future royalty payments from patents re: A novel polynucleotide involved in heritable Parkinson's disease; receives royalties from publishing *Parkinsonism and Related Disorders* (Elsevier, 2007, 2008, 2009), and the *European Journal of Neurology* (Wiley-Blackwell, 2007, 2008, 2009); and receives research support from Allergan, Inc., the NIH, the Pacific Alzheimer Research Foundation (Canada), the CIHR, the Mayo Clinic Florida Research Committee CR program, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch. Dr. Dickson serves on the editorial boards of the *American Journal of Pathology*, *Journal of Neuropathology and Experimental Neurology*, *Brain Pathology*, *Neurobiology of Aging*, *Journal of Neurology Neurosurgery and Psychiatry*, *Annals of Neurology*, and *Neuropathology*; and receives research support from the NIH. Dr. Farrer serves on a scientific advisory board for the Michael J. Fox Foundation; serves/has served on the editorial boards of *Neurobiology of Disease* and *Parkinsonism and Related Disorders*; is co-inventor on patents re: LRRK2 gene and mutations; receives institutional research support from Lundbeck Inc.; has received research support from the NIH (NS40256 [Project and Core PI]), the Pacific Alzheimer Research Foundation, and the Michael J Fox Foundation; and his institution receives annual royalties from Lundbeck Inc. from the licensing of the technology related to PARK8/

LRRK2. Dr. Ross serves on the editorial board of *Open Longevity Science*.

Received June 24, 2010. Accepted in final form August 30, 2010.

Address correspondence and reprint requests to Dr. Owen A. Ross, Mayo Clinic, Department of Neuroscience, 4500 San Pablo Road, Jacksonville, FL 32224; ross.owen@mayo.edu

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Carles Vilariño-Güell.

ACKNOWLEDGMENT

The authors thank all those who have contributed to their research, particularly the patients and families who donated DNA samples for this work.

1. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998;393:702–705.
2. Rademakers R, Melquist S, Cruts M, et al. High-density SNP haplotyping suggests altered regulation of tau gene expression in progressive supranuclear palsy. Hum Mol Genet 2005;14:3281–3292.
3. Simon-Sanchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet 2009;41:1308–1312.
4. Louis ED, Faust PL, Vonsattel JP, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007;130:3297–3307.
5. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670–676.
6. Wider C, Vilarino-Guell C, Jasinska-Myga B, et al. Association of the MAPT locus with Parkinson's disease. Eur J Neurol 2010;17:483–486.
7. Giasson BI, Forman MS, Higuchi M, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. Science 2003;300:636–640.

S.H. Kim, MD
W. Kim, MD, PhD
K.W. Lee, MD, PhD
E.K. Hong, MD, PhD
H.J. Kim, MD, PhD

TUMEFACTIVE DEMYELINATION, AN UNCOMMON FORM OF TACROLIMUS NEUROTOXICITY

The immunosuppressant tacrolimus (FK 506) is widely used in transplantation medicine, although it has neurotoxic side effects. The neurotoxicity of tacrolimus to the CNS consists mainly of leukoencephalopathy with clinical and radiologic features similar to posterior reversible encephalopathy syndrome (PRES).[1] The neurologic symptoms and signs of leukoencephalopathy usually develop within 3 months of commencing treatment with tacrolimus.[1] We describe a patient who developed tumefactive inflammatory demyelinating lesions as an atypical manifestation of tacrolimus neurotoxicity.

Case report. A 54-year-old woman with hepatocellular carcinoma underwent cadaver liver transplantation in May 2009. After transplantation, she was treated with tacrolimus 0.075 mg/kg and mycophenolate mofetil 250 mg BID. In September 2009, she developed slurred speech and right-side weakness 2 days before admission. Brain MRI scanned 2 days after symptoms onset showed 2 large mass-like lesions in the left corona radiata and frontal lobe. The lesions were hyperintense on T2-weighted images with an open ring pattern on gadolinium enhancement (figure, A). The serum tacrolimus level was 8.5 ng/mL (therapeutic range 5.0–15.0 ng/mL). The CSF analysis showed normal cell count, but elevated total protein level (103 mg/dL). Oligoclonal bands were absent and immunoglobulin G index was within normal range. The laboratory investigations for viruses including JC virus, Epstein-Barr virus, herpes simplex virus, cytomegalovirus, and other infections such as tuberculosis, mycoses, and parasites in the CSF and serum were all negative.

Her symptoms worsened over the next 3 days and she developed right hemiplegia, motor aphasia, and altered mental status. As we could not rule out the possibility of post-transplant malignancy or opportunistic infection such as progressive multifocal leukoencephalopathy (PML), though the mode of manifestation was not compatible, we performed an open craniotomy for excisional biopsy of the left frontal mass. Interestingly, the neuropathologic examination showed acute inflammatory demyelination with no evidence of tumor cells or PML (figure, C).

Hypothesizing that tacrolimus induced the demyelinating lesions, the tacrolimus was discontinued immediately and high-dose steroids were initiated. Over the following weeks, maintained on mycophenolate mofetil only, her symptoms gradually improved, although the hemiparesis remained. Follow-up MRI obtained 8 months later showed a marked reduction in the extent of the lesions and no new lesions were seen (figure, B).

Discussion. Our patient showed several characteristics distinct from reported CNS neurotoxicity caused by tacrolimus. First, she had focal mass-like lesions mimicking a brain tumor or abscess. Second, the pathology of brain biopsy revealed acute inflammatory demyelination. Finally, the symptoms occurred relatively late, nearly 5 months after starting the tacrolimus treatment. These findings suggested that the underlying pathomechanism of lesion formation in our patient differed from that of reported tacrolimus neurotoxicity.

The pathomechanism of tacrolimus-induced CNS neurotoxicity remains unclear. Some studies have suggested that extracellular edema with endothelial damage caused by tacrolimus explains the