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Neurol Genet
2016;2:e85; doi: 10.1212/
NXG.0000000000000085

Supplemental data
at Neurology.org/ng

TREM2 p.R47H SUBSTITUTION IS NOT ASSOCIATED WITH DEMENTIA WITH LEWY BODIES

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Dementia with Lewy bodies (DLB) is the second leading cause of neurodegenerative dementia in the elderly and is clinically characterized by the presence of cognitive decline, parkinsonism, REM sleep behavior disorder, and visual hallucinations.^{1,2} At autopsy, α -synuclein-positive Lewy-related pathology is observed throughout the brain. Concomitant Alzheimer disease-related pathology including amyloid plaques and, to a lesser degree, neurofibrillary tangles are often present.² The clinical characteristics of DLB share overlapping features with Alzheimer disease dementia (AD) and Parkinson disease (PD). A recent genetic association study examining known hits from PD and AD identified variants at both the α -synuclein (*SNCA*) and *APOE* loci as influencing the individual risk to DLB.³ These findings would suggest that DLB may be a distinct disease with shared genetic risk factors with PD and AD.

The p.R47H substitution in the triggering receptor expressed on myeloid cells 2 (TREM2) protein is now a well-established risk factor for AD and has been suggested to play a more general role in other neurodegenerative disorders,^{4,5} although these latter findings were not confirmed in a large follow-up study.⁶ TREM2 p.R47H has not been evaluated in relation to risk of DLB to date. Therefore, we assessed the frequency of TREM2 p.R47H in a clinical series of patients with DLB and a pathologically defined series of Lewy body disease (LBD) cases defined by the McKeith criteria for likelihood of DLB.²

A total of 442 clinical DLB cases, 829 pathologically diagnosed LBD cases, and 1,154 clinical controls were included. Using the consensus criteria,⁷ pathologic samples were categorized as high (349), intermediate (254), and low clinical DLB likelihood (226). The clinical cases were enrolled as part of the Mayo Alzheimer's Disease Research Center and the Udall Center for Parkinson's Research, and pathologically diagnosed LBD cases included those from the brain bank for neurodegenerative disorders at Mayo Clinic Jacksonville. Seventy-three clinical DLB cases were also in the pathologic LBD group. Our controls were individuals free of dementia

or movement disorder at the time of examination and were included in our previous *TREM2* study.⁵ All patients were unrelated Caucasians. Median age at study in controls was 70 years (range: 45–95 years), and 44.6% were male. In patients with clinical DLB, median age at onset was 79 years (range: 49–100 years), and male sex was most common (74.4%). Median age at death in pathologic LBD cases was 80 years (range: 50–100 years), and 56.8% were male. The Mayo Clinic Institutional Review Board approved the study, and all patients or legal next of kin provided written informed consent. Screening of the *TREM2* c.140G>A (rs75932628; p.R47H) was performed using a custom Taqman genotyping assay (Life Technologies, Carlsbad, CA), with a call rate of 100%. Carrier status was confirmed using standard Sanger sequencing. There was no evidence of a departure from Hardy-Weinberg equilibrium in controls ($\chi^2 p \geq 0.99$).

Frequencies of TREM2 p.R47H were compared between controls and the different disease groups using unadjusted logistic regression models (unless no p.R47H carriers were observed in which case the Fisher exact test was used). We did not adjust logistic regression models for age or sex because this additional complexity would not be appropriate for this rare variant. The threshold for statistical significance was set at $p \leq 0.05$. PLINK (v1.07) (<http://pngu.mgh.harvard.edu/purcell/plink/>) was used to perform all statistical analyses.

The frequency of the p.R47H substitution was 0.17% in our controls, which is very similar to what is detected in the ExAC sample population (0.21%) (Cambridge, MA [<http://exac.broadinstitute.org/>]). The age range of the control carriers was 58–78 (table e-1 at Neurology.org/ng), and thus we cannot exclude that some will convert to AD later on. The variant was not observed in the clinical DLB series ($p = 0.58$ vs controls) and was only seen in 1 pathologic LBD case of high-likelihood DLB with a similar frequency (0.14%, $p = 0.86$) to that of healthy controls (table 1). We detected an increased frequency in the pathologically defined LBD cases with intermediate (0.78%, odds ratio [OR] = 4.6, $p = 0.032$) and low (0.88%, OR = 5.18, $p = 0.021$) likelihood DLB in comparison with controls (table 1).

Table 1 Association analysis of TREM2 variant p.R47H in dementia with Lewy bodies and Lewy body disease

Disease group	N	Minor allele frequency, n (%)	OR (95% CI)	p Value
Controls	1,154	4 (0.17)	1.00 (reference)	NA
Clinical DLB	442	0	NA	0.58
Pathologic LBD ²	829	9 (0.54)	3.16 (0.97–10.31)	0.056
High CDLB likelihood	349	1 (0.14)	0.83 (0.09–7.41)	0.86
Intermediate CDLB likelihood	254	4 (0.78)	4.60 (1.14–18.52)	0.032
Low CDLB likelihood	226	4 (0.88)	5.18 (1.29–20.87)	0.021

Abbreviations: OR = odds ratio; CI = confidence interval; DLB = dementia with Lewy bodies; LBD = Lewy body disease; CDLB = based on McKeith criteria for likelihood of clinical DLB.²

ORs, 95% CIs, and p values result from unadjusted logistic regression models. For the clinical DLB vs controls comparison, logistic regression analysis was not possible owing to the lack of patients with clinical DLB who were p.R47H carriers. Therefore, an OR and 95% CI were not given for this comparison and the p value results from the Fisher exact test.

Power to detect associations with p.R47H for each disease group is displayed in table e-2.

We identified only 1 carrier of TREM2 p.R47H in our pathologic high-likelihood DLB series and none in our clinical DLB series. The increased frequency in the cases of intermediate and low likelihood of DLB may well reflect the fact that 5 of these cases are clinical AD for which TREM2 p.R47H is an established risk.⁶ In addition, 7 of 9 carriers have predominant AD pathology that categorizes them as having low or intermediate likelihood of clinical DLB. The other 2 carriers have brainstem LBD and diffuse LBD (table e-1). The findings of this study would suggest that the TREM2 p.R47H substitution is not a risk for DLB, leaving AD as currently the only neurodegenerative condition showing association with this TREM2 variant.

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

Study funding: The Mayo Clinic is a Morris K. Udall Parkinson's Disease Research Center of Excellence (National Institute of Neurological Disorders and Stroke P50 NS072187), an Alzheimer's disease Research Center (NIA P50 AG16574) and is supported by The Little Family Foundation and the Mangurian Foundation for Lewy body research and Mayo Clinic AD and related dementias genetics program. This work is also supported by National Institute of Neurological Disorders and Stroke R01 NS078086 (O.A.R.), R01 NS080820 (N.E.-T.), NIA R01 AG015866 (T.J.F.), U01 AG006786 (Mayo Clinic Study of Aging), RF AG51504 (N.E.-T.), U01 AG046139 (N.E.-T.), and a gift from Carl Edward Bolch, Jr., and Susan Bass Bolch. C.L. is the recipient of an FRSQ postdoctoral fellowship and is a 2015 Younkin Scholar supported by the Mayo Clinic Alzheimer's Disease and Related Dementias Genetics program.

Disclosure: Mr. Walton and Ms. Soto-Ortolaza report no disclosures. Dr. Murray has served on the editorial board of BMC Neurology. Dr. Lorenzo-Betancor and Dr. Ogaki report no disclosures. Mr. Heckman has served on the editorial board of Parkinsonism and Related Disorders. Ms. Rayaprolu reports no disclosures. Dr. Rademakers holds patents for Detecting and Treating Dementia, 12/302,691 (2008) and Methods and Materials for Detecting and Treating Dementia 12/413,869 (2009); and has received research support from NIH, the Mayo Clinic Udall Center of Excellence, the ALS Therapy Alliance, the Consortium for Frontotemporal Dementia, and the Florida State Alzheimer's Disease Research grant. Dr. Ertekin-Taner has served on the editorial board of the American Journal of Neurodegenerative Disease; holds a patent for Human Monoclonal Antibodies Against Amyloid Beta Protein, and Their Use as Therapeutic Agents Application (pending); and has received research support from NIH, CurePSP, Bright Focus, and Florida Health Ed and Ethel Moore Alzheimer's Disease Research Program Grant. Dr. Uitti serves on the editorial board of Neurology; holds a patent for LRRK2 (Mayo Clinic); and has received research support from ANS/St. Jude Medical, National Institute of Neurological Disorders and Stroke, and PARFF. Dr. van Gerpen receives research support from NIH. Dr. Wszolek has served on the scientific advisory boards of Mayo Clinic and Mayo Foundation; has served on the editorial boards of Parkinsonism and Related Disorders, the European Journal of Neurology, Neurologia i Neurochirurgia Polska, Medical Journal of the Rzeszow University and the National Medicines Institute, Clinical and Experimental Medical Letters, Translational Neuroscience, and Medycyna Praktyczna; holds the following patents: Mayo file #2004-185: Identification of mutations in PARK8, a locus for familial Parkinson's disease, Disclosure date: July 28, 2004; Mayo file #2004-291: Identification of a novel LRRK2 mutation, 6055G>A (G2019S), linked to autosomal dominant parkinsonism in families from several European populations, Disclosure date: October 12, 2004; has received publishing royalties from Wiley-Blackwell; and

has received research support from NIH/National Institute of Neurological Disorders and Stroke, NIH/NIA, the Mayo Clinic Center for Regenerative Medicine, Mayo Clinic Center for Individualized Medicine, Mayo Clinic Florida Neuroscience Focused Research Team grants, Carl Edward Bolch, Jr., Susan Bass Bolch, and the Sol Goldman Charitable Trust. Dr. Smith has served on the scientific advisory board of the University of Wisconsin Alzheimer's Disease Center; has received travel funding/speaker honoraria from the International Congress on Alzheimer Disease, the American Academy of Clinical Neuropsychology, the American Board of Professional Psychology, and the National Academy of Neuropsychology; has served on the editorial board of *The Clinical Neuropsychologist* and the *Journal of International Neuropsychological Society*; receives royalties from Oxford University Press and the American Psychological Association (forthcoming); has been a consultant for Homeinstead Senior Living Inc.; has received research support from the National Center for Research Resources Rizza, the Mayo Clinic Center for Clinical and Translational Research; the National Institute on Aging, Information Transfer Core, Mayo Clinic Alzheimer's Disease Research Center, the National Institute on Neurological Disease & Stroke, and the Patient Centered Outcomes Research Institute. Dr. Kantarci has served on the data safety monitoring board for Takeda Global Research & Development Center Inc., Pfizer Inc., and Janssen Alzheimer Immunotherapy; and has received research support from R01 AG040042, P50AG044170/P2, and the Minnesota Partnership for Biotechnology and Medical Genomics. Dr. Lowe serves on scientific advisory boards for Bayer Schering Pharma and Piramal Life Sciences, receives research support from GE Healthcare, AVID Radiopharmaceuticals, NIA, NCI, the Minnesota Partnership for Biotechnology and Medical Genomics, the Elsie and Marvin Dekelboum Family Foundation, the Leukemia & Lymphoma Society, the Liston Family Foundation, and Siemens Molecular Imaging. Dr. Parisi has served on the Defense Health Board Healthcare Delivery Subcommittee; has received publishing royalties from Oxford; and has received research support from NIH. Dr. Jones, Dr. Savica, and Dr. J. Graff-Radford report no disclosures. Dr. Knopman has served on the scientific advisory boards of the Bluefield project, Lundbeck Pharmaceuticals, and DIAN study DSMB; has received travel funding/speaker honoraria from the Alzheimer Conference (Seoul Korea) and the Behavioral Neurology Conference (Hyderabad, India); has served on the editorial board of *Neurology*; and has received research support from TAURX, Lilly, Biogen, NIH, the Mayo Alzheimer's Disease Research Center, the Mayo Alzheimer Disease Patient Registry, and the ARIC Dementia Study. Dr. Petersen has served on the scientific advisory boards of Pfizer and Janssen Alzheimer Immunotherapy; has received publishing royalties from Oxford University Press; has been a consultant for Roche Incorporated, Merck, Genetech, Biogen, and Eli Lilly; has received research support from the National Institute on Aging; and has served on the National Advisory Council on Aging (NIA). Dr. N.R. Graff-Radford has served on the editorial board of *Alzheimer Disease and Therapy*; has received publishing royalties from UpToDate; and has received research support from TauRx, Lilly, Biogen, and NIA. Dr. Ferman has received research support from NIH/NIA. Dr. Dickson has served on the editorial boards of *Acta Neuropathologica*, *Brain*, *Brain Pathology*, *Neurobiology of Aging*, *Annals of Neurology*, *Neuropathology*, the *International Journal of Clinical and Experimental Pathology*, and the *American Journal*

of Neurodegenerative Disease; and has received research support from P50AG016574, P50NS072187, P01NS084974, P01AG003949, the Society for PSP: Foundation for PSP/CBD and Related Disorders, and the Mangurian Foundation. Dr. Boeve has served as an investigator for clinical trials sponsored by GE Healthcare and FORUM Pharmaceuticals; receives royalties from the publication of a book entitled *Behavioral Neurology of Dementia* (Cambridge Medicine, 2009); serves on the Scientific Advisory Board of the Tau Consortium; has consulted for Isis Pharmaceuticals and Ionis Pharmaceuticals; and receives research support from the NIH (U01 AG045390, U54 NS092089, P50 AG016574, U01 AG006786, R01 AG015866, R01 AG032306, R01 AG041797), GE Healthcare, FORUM Pharmaceuticals, C2N Diagnostics, the Little Family Foundation, and the Mangurian Foundation. Dr. Ross serves on the editorial boards of PLoS ONE, *American Journal of Neurodegenerative Disease*, *Molecular Neurodegeneration*, and *Parkinsonism and Related Disorders*, and he is funded by NIH grants NS078086 and NS072187 and the Michael J. Fox Foundation. Dr. Labbé reports no disclosures. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.

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Received February 18, 2016. Accepted in final form June 15, 2016.

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Neurol Genet 2016;2;

DOI 10.1212/NXG.0000000000000085

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