typical AD groups. Biparietal patients were younger at symptom onset (mean ± SD age, 56.1 ± 4.1 vs 65.6 ± 6.9 years; P < .001), scored higher on the Mini-Mental State Examination (mean ± SD score, 23.1 ± 2.8 vs 19.2 ± 4.3; P = .01) and were less likely to be APOE ε4–positive (2/10 vs 25/29, P < .001).

Comment. Possessing an APOE ε4 allele is the most important genetic risk factor yet identified for sporadic AD and also significantly lowers onset age. It is therefore striking that despite their young age at onset, only 2 of our 10 biparietal patients were ε4-positive. While we believe that a lack of association between biparietal AD (or posterior cortical atrophy AD) and APOE ε4 genotype has not previously been reported, this observation is supported by supplementary online data from 1 study where only 1 of 6 patients with posterior cortical atrophy (mean age at onset, 58.5 years) with pathologically confirmed AD possessed an ε4 allele.

We suggest that in biparietal AD, at least in part mediated by lack of APOE ε4, the pathological process is directed away from medial temporal structures and toward the parietal lobes. In support of this, decreased hippocampal pathologic abnormality has been reported in posterior cortical atrophy compared with typical AD and increased hippocampal atrophy in AD has been shown to be related to APOE ε4 dose. Other, as yet undetermined factors are likely to be responsible for early initiation of the pathological cascade in this distinctive phenotypic variant. This finding, if replicated in larger studies, may have implications for our understanding of the pathogenesis of AD and factors influencing the regional predilection of this and other neurodegenerative diseases. It may be important to consider biparietal and other AD variants separately in studies seeking genetic associations in AD.

Jonathan M. Schott, MD, MRCP
Basil H. Ridha, MRCP
Sebastian J. Crutch, PhD
Daniel G. Healy, MRCP
James B. Uphill, BSc
Elizabeth K. Warrington, FRS
Martin N. Rossor, MD, FRCP
Nick C. Fox, MD, FRCP

Correspondence: Dr Fox, Dementia Research Centre, Institute of Neurology, UCL, Queen Square, London WC1N 3BG, England (n.fox@dementia.ion.ucl.ac.uk).

Funding/Support: This study was funded by the Alzheimer’s Society, United Kingdom (Dr Schott), and the Medical Research Council, United Kingdom (Drs Rossor and Fox).

Acknowledgment: We are grateful to Merle James-Gallon and Jason Warren for help with this study. We particularly thank the patients and their caregivers who participated in this study.

Comment. Our data suggest that G2019S, which occurs at a frequency of approximately 1% in sporadic3 and 3% in familial1,2 PD, is not a common cause of AD. We had adequate power to detect G2019S in our sample, which predominantly comprised cases with a family history of dementia, even if the true frequency of the mutation in AD was nearly 10-fold less than that in PD. Our findings are consistent with recent studies6,7 and argue that the concomitant AD pathology observed in some mutation-positive patients1 might simply be a chance occurrence rather than a direct result of dysfunction of the LRRK2-encoded product (dardarin) itself.

This study did not assess the frequency of less common PD-related LRRK2 mutations in AD nor did it address the existence of pathogenic mutations specific to AD. Furthermore, the role of LRRK2 in determining susceptibility to disorders other than AD and PD is not yet clear. Comprehensive studies of the gene in large samples of patients with other parkinsonian disorders, motor neuron disease, and non-AD dementing illnesses will be necessary to determine whether LRRK2 truly represents a molecular link between neurodegenerative diseases.

Cyrus P. Zabetian, MD, MS
Chris J. Lauricella, BS
Debby W. Tsuang, MD, MSc
James B. Leverenz, MD
Gerard D. Schellenberg, PhD
Haydeh Payami, PhD

Correspondence: Dr Payami, Wadsworth Center, New York State Department of Health, PO Box 22002 Albany, NY 12201-2002 (hpayami@wadsworth.org).

Funding/Sponsor: This study was supported by grants P01 AG017586, K08 NS044138, P30 AG08017, P50 AG005136, R01 NS036960, R01 NS048595, and U24 AG021886 from the National Institutes of Health, Bethesda, Md; a Research Enhancement Award Program grant and the Veterans Integrated Service Network 20 (VISN 20) Geriatric and Mental Illness Research, Education, and Clinical Centers, Department of Veterans Affairs, Washington, DC; and the New York State Department of Health Wadsworth Center, Albany.

Acknowledgment: We thank the patients and their families for participating in the study and Dr William Lee, Stephen Ayres, Jason Isabelle, Erica Martinez, and Dora Yearout for technical support and assistance with data preparation.