Correspondence

Reply to Correspondence From Inzelberg et al.—"Onset age of Parkinson disease"

To the Editor:

The association between Parkinson disease (PD) and apolipoprotein E (APOE) gene has been the subject of several studies. We first reported the observation that ε4 carriers had on average four years earlier age at onset than those without ε4 [Zareparsi et al., 1997]. We had estimated that a minimum sample of 400 patients was needed to detect earlier age at onset of PD in ε4 carriers. In a study of 521 unrelated Caucasian PD patients, we found that ε3ε4/ε4ε4 patients had significantly earlier onset than ε3ε3 patients [Zareparsi et al., 2002]. Inzelberg et al. [2002] have combined the samples from different studies and report that they do not detect a significant difference in onset among ε4 carriers and those without ε4.

One possible explanation is that the strength of the association between APOE and onset of PD may differ between samples collected at different sites. In our study, the difference in onset between ε3ε4/ε4ε4 versus ε3ε3 ranged from 2.2 to 8.5 years among patient samples collected in Oregon and Washington, respectively [Zareparsi et al., 2002]. Furthermore, the two samples displayed different trends for effect of ε2 on PD onset [Zareparsi et al., 2002]. Thus, it may not be suitable to combine samples from different centers without performing tests of heterogeneity. In fact, in two of the studies, ε4 carriers had slightly earlier onset [Inzelberg et al., 1998; Oliveri et al., 1999]. In addition, the combined sample is based on samples from different ethnic backgrounds. It is possible that the effect of APOE on PD onset differs between ethnic groups as mentioned by Inzelberg et al.

Inzelberg et al. [2002] confirm our finding of earlier onset in patients with positive family history. They further suggest that earlier onset in ε4 carriers may be due to family history and patients with *parkin* mutations. It should be noted that the earlier onset in ε3ε4/ε4ε4 patients was significant even after adjusting for the effect of family history on onset of PD. We agree that *parkin* mutations are reported in patients with an age at onset of greater than 30 years [Lucking et al., 2000]. Our recent studies indicate that five of our subjects had *parkin* mutations. Two were excluded from analysis because their age at onset was less than 30 years. For the remaining three, the APOE genotype, family history, and age at onset were as follows: 1) non-familial, ε2ε3, onset 37 years; 2) non-familial, ε3ε3, onset 39 years; and 3) familial, ε3ε3, onset 37 years. Thus, contrary to Inzelberg et al.'s [2002] suggestion, our findings could not have been due to the inadvertent inclusion of *parkin* mutation carriers. Exclusion of *parkin* mutation carriers strengthens our data in favor of earlier onset in ε3ε4/ε4ε4 versus ε3ε3, and in familial versus non-familial PD.

REFERENCES

Inzelberg R, Paleacu D, Chapman J, Korczyn AD. 1998. Apolipoprotein E and Parkinson's disease. Ann Neurol 44:294.

Inzelberg R, Schechtman E, Paleacu D. 2002. Onset age of Parkinson disease. Am J Med Genet.

Lucking C, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi B, Meco G, Denefle P, Wood N, Agid E, Brice A. 2000. Association between early-onset Parkinson's disease and mutations in the *parkin* gene. N Engl J Med 342:1560–1567.

Oliveri RL, Nicoletti G, Cittadella R, Manna I, Branca D, Zappia M, Gambardella A, Caracciolo M, Quattrone A. 1999. Apolipoprotein E polymorphisms and Parkinsons' disease. Neurosci Lett 277:83–86.

Zareparsi S, Kaye J, Camicioli R, Grimslid H, Oken B, Litt M, Nutt J, Bird T, Schellenberg G, Payami H. 1997. Modulation of the age at onset of Parkinson's disease by Apolipoprotein E genotypes. Ann Neurol 42:655–658.

Zareparsi S, Camicioli R, Sexton G, Bird T, Swanson P, Kaye J, Nutt J, Payami H. 2002. Age at onset of Parkinson disease and Apolipoprotein E genotypes. Am J Med Genet 107:156–161.

Sepideh Zareparsi*
Department of Opthalmology and Visual Sciences
University of Michigan
Ann Arbor, Michigan

Haydeh Payami
Department of Neurology
Oregon Health Sciences University
Portland, Oregon

*Correspondence to: Sepideh Zareparsi, Ph.D., Department of Ophthalmology and Visual Sciences, University of Michigan, 1000 Wall St., Room 510, Ann Arbor, MI 48105.
E-mail: zarepars@umich.edu

Received 12 April 2002; Accepted 15 April 2002
DOI 10.1002/ajmg.10581