Letters

In Reply We thank Dr Macerollo for the interesting commentary on our article.1 Mutations in the glucocerebrosidase (GBA) gene are widely recognized to be an important and common genetic risk factor for Parkinson disease (PD),2 and they are found in British patients with PD at a higher frequency than any other known PD-associated gene.3

In 2012, we continued the clinical evaluation of a unique cohort of GBA mutation–positive individuals for the early prodromal features of PD.1 What was perhaps surprising about this nonparkinsonian GBA–positive cohort at the initial assessment in 2010 was a significant difference from control individuals even at the baseline evaluation.4 At baseline, GBA mutation–positive individuals demonstrated hyposmia and cognitive impairment.4 Importantly, we found that olfaction and cognition remained significantly lower in GBA mutation–positive individuals compared with control individuals at 2 years’ follow-up.4 We further identified a significant deterioration across clinical markers in GBA mutation–positive individuals, consistent with the prodrome of PD. Within this group, 10% appeared to be progressing at a more rapid rate. It is interesting to compare our results, which identified 10% of GBA mutation–positive individuals developing parkinsonian motor features, with the reported estimate that 10% of patients with PD carry a mutation in GBA.2

Improved insight into possible disease mechanisms lays the basis for the development of new therapies to slow the rate of progression or stop the disease process.5 Thus, it is imperative to develop an early biomarker set to identify individuals at greatest risk for the development of PD. In this study, we attempted to identify patients likely to develop PD through the use of early clinical markers.1 This study cohort would be an ideal population to study a neuroprotective strategy or disease-modifying therapy.

As observed by Dr Macerollo, our data favor a link between the GBA mutation and a higher frequency of nonmotor symptoms and rate of clinical progression. Our work1 and those of others6,7 may suggest that the GBA mutation represents a poor prognostic marker for an individual who develops PD. The evidence from longitudinal studies demonstrates that patients with GBA–associated PD show a more rapid disease progression dominated by accelerated motor impairment with greater risk for progression to Hoehn and Yahr Scale stage 3+ and a greater preponderance to dementia or cognitive decline.6

Dr Macerollo asks about the specific alterations that lead to developing PD in a group of GBA mutation–positive individuals. We can only hypothesize that other genetic or possibly environmental factors may be of relevance here. Study of GBA mutation–positive individuals who do not go on to develop PD could provide insight into factors that may afford protection from PD.

Michelle Beavan, MRCP(UK)
Anthony H. V. Schapira, DSc, MD, FRCP, FMedSci


Corresponding Author: Anthony H. V. Schapira, DSc, MD, FRCP, FMedSci, Department of Clinical Neurosciences, UCL Institute of Neurology, University College London, Rowland Hill Street, London NW3 2PF, England (a.schapira@ucl.ac.uk).

Conflict of Interest Disclosures: None reported.