Our data necessitate a careful re-evaluation of the validity of the *SCA8* expansion as a cause for cerebellar ataxia. The large overlap between allele sizes found in control and affected individuals precludes the clear definition of normal and pathological ranges. Although none of our findings disproves functionality in the large family described by Koob *et al.*, in which the expansion segregates, we are concerned by the finding of five large, expanded alleles in our control population. One of these alleles (133) was of a similar size to, and another (174) was larger than, those found in the SCA8 family described by Koob *et al.*[1]. Although we cannot rule out the possibility that these two individuals would have gone on to develop cerebellar ataxia, this is unlikely. It is possible that the length of the CTA or interruptions in the CTG tract may influence penetrance of expanded *SCA8* alleles, but no alleles with more than 11 CTA or interruptions within the CTG tract were demonstrated in either ataxia patients or controls. It is also notable that a 92-year-old asymptomatic mother of an affected subject (patient 2) carries 127 CRs. Therefore, we speculate that partial penetrance of *SCA8*, as suggested by Koob *et al.*, may not be sufficient to explain our data. An alternative hypothesis is that *de novo* expansion in *SCA8* occurs frequently and these expanded alleles exist as polymorphisms in linkage disequilibrium with 'true' causative mutations in a gene for cerebellar ataxia on chromosome 13q21. We advise against any form of diagnostic or predictive testing for expansions in *SCA8* until a pathological mechanism, including an explanation for non-penetrance, has been established.

Acknowledgements

We thank the subjects for their participation. DNA from IPD brains and clinical information from IPD patients was provided by The Parkinson's Disease Society Brain Research Centre. DNA from brains of normal control subjects was provided by C. Morris of the Medical Research Council Neurochemical Pathology Unit. DNA from IPD and control brains was also provided by The Alzheimer's Brain Bank.

Paul F. Worth, Henry Houlden, Paola Giunti, Mary B. Davis & Nicholas W. Wood

Neurogenetics Section, Department of Clinical Neurology, Institute of Neurology, Queen Square, London, UK. Correspondence should be addressed to N.W.W. (e-mail: N.Wood@ion.ucl.ac.uk).

1. Koob, M.D. *et al. Nature Genet.* **21**, 379–384 (1999).
2. Harding, A.E., Diengdoh, J.V. & Lees, A.J. *J. Neurol. Neurosurg. Psychiatry* **47**, 853–856 (1984).

In reply—Stevanin *et al.*[1] and Worth *et al.*[2] suggest that the reduced penetrance of *SCA8* in ataxia families and the large alleles found in controls indicate that the CTG expansion may be a non-pathogenic polymorphism tightly linked to an ataxia locus. Because we isolated the CTG expansion from a single ataxia patient using RAPID cloning[3,4], the likelihood that the expansion would be tightly linked to an ataxia locus by chance can be conservatively estimated as 3×10^{-4} to 1.5×10^{-5}, the product of the frequency of alleles with more than 50 CTG repeats in the general population (1/100–1/500) multiplied by the portion of the human genome in a 10-cM interval (1/300, assuming 1 Mb=1 cM). To put these data[1,2] in perspective, it is important to realize that whereas all affected individuals in our large family had 107–127 CTG repeats, 20 asymptomatic family members had shorter alleles of 74–101 CTG repeats[3]. The only inconsistency between our data and that of Stevanin *et al.*[1] is that one of their control individuals had 107 CTG repeats. Worth *et al.*[2] found 2 alleles among their controls with more than 107 CTG repeats. Although we did not detect alleles in this size range among our control population, we reported two asymptomatic men with alleles (260 and 300 repeats) larger than those of their four ataxic offspring. This reduced penetrance causes small families to appear to have recessive or sporadic ataxia. The presence of the adjacent $(CTA)_{1-21}$ tract or sequence interruptions within the CTG tract may explain the reduced penetrance of *SCA8* (refs 1,3,5).

We presented[3] five lines of evidence supporting the hypothesis that the *SCA8* CTG expansion causes ataxia: (i) linkage data in a single family (lod=6.8, $\theta=0$) ; (ii) the biological relationship between repeat length and disease, with affected family members having longer CTG repeat tracts (mean=117) than asymptomatic carriers (mean=92, $P<10^{-6}$); (iii) the absence of alleles in the pathogenic range (107–127 CTG repeats) on 1,200 control chromosomes; (iv) a high frequency of expansions among apparently unrelated ataxia patients (8/102); and (v) the expression of *SCA8* transcripts mainly in central nervous system tissue[3]. We believe all available data support the hypothesis that this CTG expansion is directly associated with ataxia, but that a number of issues, including reduced penetrance, gender effects, and normal and pathogenic exapnsion ranges, will require further investigation.

Melinda L. Moseley[1,3], Lawrence J. Schut[2], Thomas D. Bird[4], John W. Day[2,3] & Laura P.W. Ranum[1,3]

Departments of [1]Genetics, Cell Biology and Development and [2]Neurology, and the [3]Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota, USA. [4]Department of Veterans' Affairs Medical Center, Seattle, Washington, USA. Correspondence should be addressed to L.P.W.R. (e-mail: laura@gene.med.umn.edu).

1. Stevanin, G. *et al. Nature Genet.* **24**, 213 (2000).
2. Worth, P.F. *et al. Nature Genet.* **24**, 214–215 (2000).
3. Koob, M.D. *et al. Nature Genet.* **21**, 379–384 (1999).
4. Koob, M.D. *et al. Nature Genet.* **18**, 72–75 (1998).
5. Moseley, M.L, Koob, M.D. & Ranum, L.P.W. *Am. J. Hum. Genet.* **65**, A462 (1999).