Reply to Tzoulis et al.: Genetic and clinical heterogeneity of essential tremor

In addressing our recent report of HTRA2 p.G399S as the gene and mutation responsible for essential tremor and subsequent Parkinson disease in a large kindred (1), Tzoulis et al. (2) screened this mutation in patients with Parkinson disease, essential tremor, tremulous cervical dystonia, and nontremulous cervical dystonia patients, and did not find a significant difference in carrier frequency compared with the general population. Their observation replicates our experience, in that in the kindred of our study, HTRA2 p.G399S was responsible for essential tremor and, among homozygotes, for Parkinson disease, but as we reported, this allele was not responsible for essential tremor in other families from the same population.

Both these observations support the conclusion that essential tremor is a heterogeneous disease, both clinically and genetically (3). In addition to *HTRA2*, two other genes for essential tremor have been identified: *DNAJC13* and *FUS*, and still other responsible genes have been mapped to chromosomes 2p22-24, 3q13, and 6p23 (1, 4). In any one patient, mutation at only one of these genes is sufficient for development of essential tremor, but the responsible gene differs among patients. These two features—the severity of individual causal mutations and different responsible genes in different families—are characteristic of genetic heterogeneity of complex diseases generally (5).

Phenotypic features of a genetically heterogeneous disease may offer clues as to the responsible gene. In the family harboring mutation in *HTRA2*, Parkinson disease appeared after more than a decade of essential tremor. Also, cervical dystonia was not among the presenting signs in any of the family members. These clinical features differ from the series of patients screened by Tzoulis et al.

Some of the patients screened by Tzoulis et al. may harbor *HTRA2* mutations other than p.G399S that would be revealed by more complete sequencing; this would be interesting to learn. It is also possible that mutations in the other known genes for essential tremor may be present in these patients. If not, then these patients, like those from the other kindreds in our series, offer the opportunity to identify additional causal genes for essential tremor.

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The authors declare no conflict of interest.

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