

# HTRA2 p.G399S in Parkinson disease, essential tremor, and tremulous cervical dystonia

Unal Gulsuner et al. (1) report that a variant in the HtrA serine peptidase 2 (*HTRA2*) gene [c.1195G > A (p.G399S); rs72470545] caused essential tremor in a large consanguineous Turkish family. The p.G399S substitution was found in both heterozygous and homozygous states, and the number of copies correlated with earlier age of onset and more severe tremor in homozygous individuals. Additionally, parkinsonism developed in five affected family members, after age 70 in heterozygotes and in middle age in homozygotes. The p.G399S substitution was not found in further Parkinson disease or essential tremor patients. Two heterozygous carriers were found among 364 Turkish controls. The p.G399S substitution has not been found more frequent in Parkinson disease patients than in control individuals (1–3). The authors discuss whether this discrepancy may be explained if the p.G399S substitution had a causal role in essential tremor and in the subset of Parkinson disease preceded by essential tremor.

To address the questions raised by Unal Gulsuner et al., we investigated the role of the p.G399S substitution in 204 Parkinson disease and 103 essential tremor patients from Western Norway, including a population-based incident cohort of Parkinson disease patients and controls (the ParkWest study) (4). Furthermore, we genotyped 72 probands with tremulous cervical dystonia and 29 probands with nontremulous cervical dystonia. Tremulous cervical dystonia is defined by the presence of head tremor, and this cervical dystonia subtype has been associated with a positive family history and arm tremor (5). Population frequency for the p.G399S substitution were generated from Norwegian attention deficit hyperactivity disorder patients ( $n = 589$ ) and healthy controls

( $n = 640$ ). Our studies were approved by the Regional Committee for Medical and Health Research Ethics, Western Norway (IRB00001872). Samples were genotyped using the HumanCoreExome 12v1-1 bead chip (Illumina). Genotypes were called with Illumina GenomeStudio V2011.1 and zCall softwares according to established criteria. Genotype quality control was performed using a standard protocol implemented in PLINK. Allele frequencies for the p.G399S substitution were considered for this study. Two of 204 Parkinson disease patients were heterozygous for the p.G399S substitution, one of them had tremor-dominant Parkinson disease and one had the akinetic-rigid subtype with no tremor. The substitution was found in a 76-y-old neurologically normal control individual ( $n = 204$  disease-free controls) and in 4 of 1,025 Norwegian subjects (suggesting a population carrier frequency of 0.4%). Importantly, the substitution was not observed in patients with essential tremor ( $n = 103$ ) or cervical dystonia ( $n = 101$ ). There were no homozygous carriers in our population. A previous screening of the p.G399S substitution in Norwegian Parkinson disease patients and control individuals identified one heterozygous patient ( $n = 391$ ) and nine heterozygous controls ( $n = 958$ ) (3). The minor allele frequency (MAF) was not significantly different between our tremor patients (MAF = 0.0025) and population controls (MAF = 0.0020) (Fisher's exact test  $P = 0.69$ ). A similar allele frequency has been reported in Europeans (MAF = 0.0040) by the Exome Aggregation Consortium.\* Overall, our results do not support an association between the HTRA2 p.G399S substitution and tremor.

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**1** Unal Gulsuner H, et al. (2014) Mitochondrial serine protease HTRA2 p.G399S in a kindred with essential tremor and Parkinson disease. *Proc Natl Acad Sci USA* 111(51):18285–18290.

**2** Simón-Sánchez J, Singleton AB (2008) Sequencing analysis of OMI/HTRA2 shows previously reported pathogenic mutations in neurologically normal controls. *Hum Mol Genet* 17(13):1988–1993.

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**4** Alves G, et al.; Norwegian ParkWest study group (2009) Incidence of Parkinson's disease in Norway: The Norwegian ParkWest study. *J Neurol Neurosurg Psychiatry* 80(8):851–857.

**5** Rubio-Agusti I, et al. (2013) Tremulous cervical dystonia is likely to be familial: Clinical characteristics of a large cohort. *Parkinsonism Relat Disord* 19(6):634–638.

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The authors declare no conflict of interest.

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\*See [exac.broadinstitute.org/](http://exac.broadinstitute.org/). Accessed March 19, 2015.