

4. Ventriglia M, Bocchio Chiavetto L, et al. Association between the BDNF 196 A/G polymorphism and sporadic Alzheimer's disease. *Mol Psychiatry* 2002;7:136–137.
5. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;34:939–944.

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Progressive Supranuclear Palsy and Parkinson's Disease in a Family with a New Mutation in the tau Gene

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Mutations in the gene encoding for tau protein are associated with neurodegenerative disorders marked by the presence of abnormally aggregated tau protein, such as frontotemporal dementia with parkinsonism linked to chromosome 17, progressive supranuclear palsy (PSP), and corticobasal degeneration. PSP is clinically characterized by a variable combination of postural instability and falls, akinesia, rigidity, axial dystonia, supranuclear gaze palsy, and cognitive or behavioral changes.¹ Most cases appear to be sporadic, with a significant association with a common haplotype including the tau gene and the flanking regions.² Familial cases show an autosomal dominant pattern of transmission with incomplete penetrance; genetic analysis of a few cases showed the occurrence of tau mutations, including a deletion of codon 296.³

Here, we report the identification of a novel mutation in the tau gene, resulting in the deletion of the amino acid 296, in a patient affected by a PSP-like syndrome. The proband is a 39-year-old man who developed antecollis, dysarthria, postural instability with falls, slowing of ocular movements, and increased deep tendon reflexes at age 36 years. Family history showed that (1) a paternal uncle developed an atypical parkinsonism at age 51 years, characterized by resting tremor, rigidity, bradykinesia, pyramidal signs, cognitive impairment, and unresponsiveness to L-dopa, and died 9 years later; (2) a paternal aunt is currently affected by typical Parkinson's disease (PD) with onset at age 63 years, and good and sustained response to L-dopa; and (3) a paternal uncle was reported to have died of amyotrophic lateral sclerosis.

Sequencing of exons 9 to 13 of the tau gene in the proband showed a heterozygous deletion of the two last bases of codon 296 and the first base of codon 297, producing a new codon identical to codon 297 and having as a final result the deletion of the highly conserved asparagine 296. The same mutation was found in the aunt with PD, in two asymptomatic sisters of the proband, and in three asymptomatic daughters of the uncle with atypical parkinsonism.

The relevance of codon 296 mutations to the pathogenesis of tauopathies is supported by in vitro experiments,⁴ showing that splicing and/or protein function are affected by individual mutations, with decreased microtubule assembly and increased tau aggregation. Deletion of codon 296, due to a

distinct mutation, previously was reported in a family with atypical PSP, characterized clinically by cognitive and memory disturbances in addition to oculomotor and gait abnormalities, and pathologically by PSP-like changes.^{3,5} The homozygous state produced this severe phenotype, whereas heterozygosity resulted in a mild PD-like condition responsive to L-dopa, with reduced penetrance.³ Interestingly, the heterozygous mutation in our family was associated with either L-dopa-responsive PD (paternal aunt) or PSP-like syndrome (proband). Because the proband's father did not show neurological abnormalities until death at age 62 years, incomplete penetrance cannot be excluded. Follow-up of healthy relatives carrying the mutation will provide further information on this issue.

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References

1. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Neurology* 1996;47:1–9.
2. Pastor P, Ezquerro M, Tolosa E, et al. Further extension of the H1 haplotype associated with progressive supranuclear palsy. *Mov Dis* 2002;17:550–556.
3. Pastor P, Pastor E, Carnero C, et al. Familial atypical progressive supranuclear palsy associated with homozygosity for the delN296 mutation in the tau gene. *Ann Neurol* 2001;49:263–267.
4. Grover A, DeTure M, Yen SH, et al. Effects on splicing and protein function of three mutations in codon N296 of tau in vitro. *Neurosci Lett* 2002;323:33–36.
5. Ferrer I, Pastor P, Rey MJ, et al. Tau phosphorylation and kinase activation in familial tauopathy linked to delN296 mutation. *Neuropathol Appl Neurobiol* 2003;29:23–34.

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Tau Gene delN296 Mutation, Parkinson's Disease, and Atypical Supranuclear Palsy

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The letter by Rossi and colleagues¹ reports a mutation resulting in the deletion of asparagine 296 in the tau gene in affected members with parkinsonism from a family different to that previously reported.² Functional studies have shown that the delN296 change can decrease the ability of four-repeat tau to promote microtubules assembly and increase in the ability of recombinant tau protein to aggregate in vitro^{3,4} with a variable effect on tau exon 10 splicing.^{3,4}

This independent description supports the pathogenicity of this mutation, and therefore it is of outstanding clinical interest. The authors also claim a new mutation where the two last bases of codon 296 and the first base of codon 297 have been deleted, resulting in the deletion of the highly conserved asparagine 296. However, as compared with the previously reported mutation,² the final result is the same at the resulting amino acid sequence (deletion of asparagine