Orthostatic tremor (OT) is a high-frequency (13-18 Hz) leg tremor occurring in standing position. Orthostatic tremor has an unknown pathophysiologic mechanism. It is thought to be sporadic but siblings with OT from 3 unrelated families were reported. No mutations have been reported in OT. We describe a patient with OT carrying a C10orf2 TWINKLE mutation to highlight the possible association of OT with mitochondrial dysfunction and mutations in the mitochondrial replicative helicase Twinkle.

**OBSERVATIONS** A man in his late 60s had ptosis and tremor on standing for 30 years, followed by development of progressive external ophthalmoplegia. Polygraphic recordings revealed an orthostatic synchronic tremor with 17.5-Hz frequency. Electromyography/nerve conduction studies showed evidence for a mild myopathy and associated mild axonal sensorimotor peripheral neuropathy. Muscle biopsy revealed ragged red fibers; mild cerebral atrophy was evident by magnetic resonance imaging. Molecular analysis revealed a novel heterozygous missense mutation at an evolutionarily conserved residue of the C10orf2 TWINKLE gene.

**CONCLUSIONS AND RELEVANCE** Although the incidental association of OT and C10orf2 TWINKLE mutation is possible, the simultaneous onset of OT and eyelid ptosis at a much younger age than usually observed for OT raises the possibility of mitochondrial dysfunction and loss of mitochondrial DNA integrity in the pathogenesis of OT.
paresis, reduced Achilles reflexes, and bilateral leg tremor only on standing. He had no clinical evidence for parkinsonism or cerebellar dysfunction. The only medications he was taking were hydralazine, carvedilol, and candesartan cilexetil for hypertension; ezetimibe for hypercholesterolemia; and levothyroxine sodium for hypothyroidism. His family history was reportedly significant for bilateral eyelid ptosis and limited eye movements in an older sister and ptosis in a son in his early 40s. The patient's creatine kinase and blood lactate values were within normal limits. Thyrotropin, liver enzymes, ferritin, blood manganese and mercury, and serum copper and ceruloplasmin levels were also normal. One to 2 ragged red fibers per fascicle were present in many fascicles in the muscle biopsy specimen. Electromyography/nerve conduction studies showed evidence for a mild myopathy and a prominent upper extremity tremor of similarly high frequency emerges. B, The power spectra analyses confirm a frequency peak at around 17.5 Hz in all muscles.

Discussion
We identified a C10orf2 TWINKLE mutation in a patient with OT and progressive external ophthalmoplegia. This observation raises the question of a possible role of mitochondrial dysfunction in the genesis of OT, a disorder well characterized electrophysiologically but of obscure etiology and pathogenesis. Although considered sporadic, the few observed familial cases have suggested the possibility of a genetic etiology, but to our knowledge, no molecular defects have been reported in OT. The detection of a C10orf2 TWINKLE mutation in our patient might shed light on the pathogenesis of this form of tremor. We cannot prove that OT is the result of the mutated Twinkle and therefore cannot exclude the incidental coexistence of 2 independent neurological disorders, OT on one side and Twinkle-related progressive external ophthalmoplegia on the other side. However, the simultaneous manifestation of OT...
and bilateral ptosis in the late 30s and the onset of the OT at an age younger than commonly observed may favor a common pathogenesis. The lack of lactate peaks on brain magnetic resonance spectroscopy did not help in establishing or excluding the existence of a mitochondrial encephalopathy in our patient. Indeed, normal brain magnetic resonance spectroscopy has been observed in subjects with mitochondrial encephalopathy, including subjects with disorders of the mtDNA replication.11 The patient’s sister and son, who reportedly have ptosis and ophthalmoparesis, also carry p.M455T in C10orf2 TWINKLE, consistent with the autosomal dominant inheritance of the mutation. The affected family members reportedly have no tremor but have not undergone a neurological examination. In addition, the reported lack of OT in the affected family members could reflect the phenotypic variability of the C10orf2 TWINKLE-linked mitochondrial disorder, or it could signal a lower penetrance of OT compared with progressive external ophthalmoplegia, as previously observed for the parkinsonism in families with C10orf2 TWINKLE mutations.12-13 Variable penetrance and younger age could account for the lack of symptoms in the other son with the mutation.

Twinkle is a nuclear-encoded human mtDNA helicase. It has an essential role in mtDNA replication with its antagonistic unwinding and annealing activity of double- and single-stranded DNA, respectively. Mutant Twinkle results in loss of mtDNA integrity in the form of mtDNA multiple deletions or depletion. Dominant mutations in C10orf2 TWINKLE lead to autosomal dominant chronic progressive external ophthalmoplegia,14 while recessive mutations result in early-onset encephalopathy or multisystemic failure.15 Heterozygous C10orf2 TWINKLE mutations have been detected in few patients with parkinsonism and ophthalmoplegia, raising the question of a possible role of Twinkle in the dopaminergic circuits.15-17 Recent studies have shown an increase in dopaminergic neurodegeneration and mtDNA deletions in Twinkle mutant mice, underscoring the important role of Twinkle in maintaining mtDNA integrity in dopaminergic neurons.16 These findings could support the suggested role of striatal dopamine transporter deficit in the genesis of OT. This case expands the clinical spectrum of Twinkle-associated disorders and for the first time, to our knowledge, raises the possibility that loss of mtDNA integrity might play a role in the pathogenesis of OT, a disorder still poorly understood.

REFERENCES