

# Tau Pathology Associated With Parkinsonism and Mutation of Mitochondrial DNA Helicase Gene *TWNK*

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The *TWNK* gene encodes Twinkle, the mitochondrial DNA helicase that cooperates with the mitochondrial DNA polymerase (POLG) to maintain mitochondrial DNA integrity. Heterozygous *TWNK* mutations cause autosomal dominant progressive external ophthalmoplegia (PEO). Some patients with *TWNK*-linked PEO additionally develop late-onset neurodegenerative parkinsonism.<sup>1</sup> However, little is known about the neuropathology of *TWNK*-linked parkinsonism. In this study, we describe neuropathologic findings in a patient with PEO and parkinsonism and a heterozygous *TWNK* mutation.

The proband, a 76-year-old Flemish woman, presented with a 1-year history of gait difficulties and reduced facial expression. She reported no tremor, diplopia, autonomic symptoms, cognitive complaints, hallucinations, or nightmares. She had undergone bilateral corrective upper eyelid surgery because of ptosis at the age of 66 years and again at the age of 73 years. Clinical examination showed limitation of eye movements in all directions, which could not be overcome by oculocephalic maneuvers. Pupillary responses were normal. Speech was hypophonic, and there was mild hypomimia. Finger tapping showed mild decrement on the right side. There was mild rigidity in the right arm. She had no tremor. Gait was slow with reduced stride length and reduced right arm swing. Posture was stooped. Postural reflexes were normal. The Mini-Mental State Examination (MMSE) score was 29/30. Proprioception was reduced in the distal legs. Muscle strength, tendon reflexes, plantar reflexes, and coordination were normal. There was no muscle atrophy.

According to the patient, her mother, maternal aunt, and 2 of her 5 siblings also had bilateral ptosis (eFigure 1A, [links.lww.com/NXG/A447](https://links.lww.com/NXG/A447)). An MRI examination of the brain showed mild atrophy and white matter lesions, presumably due to small vessel disease (eFigure 1B), without disproportionate midbrain atrophy. The <sup>123</sup>I-FP-CIT SPECT revealed severely reduced putaminal binding bilaterally (eFigure 1C). EMG showed mild myopathic changes in proximal muscles. *TWNK* sequencing showed a heterozygous c.1120C>T (p.R374W) mutation, previously reported as pathogenic.<sup>2</sup> There were no mutations in *POLG*.

Levodopa had a favorable effect. Disease progression was slow. She developed freezing of gait but no dyskinesias or dementia. The MMSE score at the age of 82 years was still 27/30. She died of pyelonephritis with sepsis at the age of 84 years.

Brain autopsy revealed obvious neuron loss in the substantia nigra, dentate nucleus, and cerebellar Purkinje cell layer (Figure 1A and B, eFigure 2, [links.lww.com/NXG/A447](https://links.lww.com/NXG/A447)) and a tauopathy with predominantly four-repeat tau lesions (Figure 1C–K, eFigures 2 and 3). These lesions included threads, neuronal lesions in the form of neurofibrillary tangles (NFTs), pre-tangles, and single ballooned neurons, and astroglial lesions with features of tufted astrocytes and

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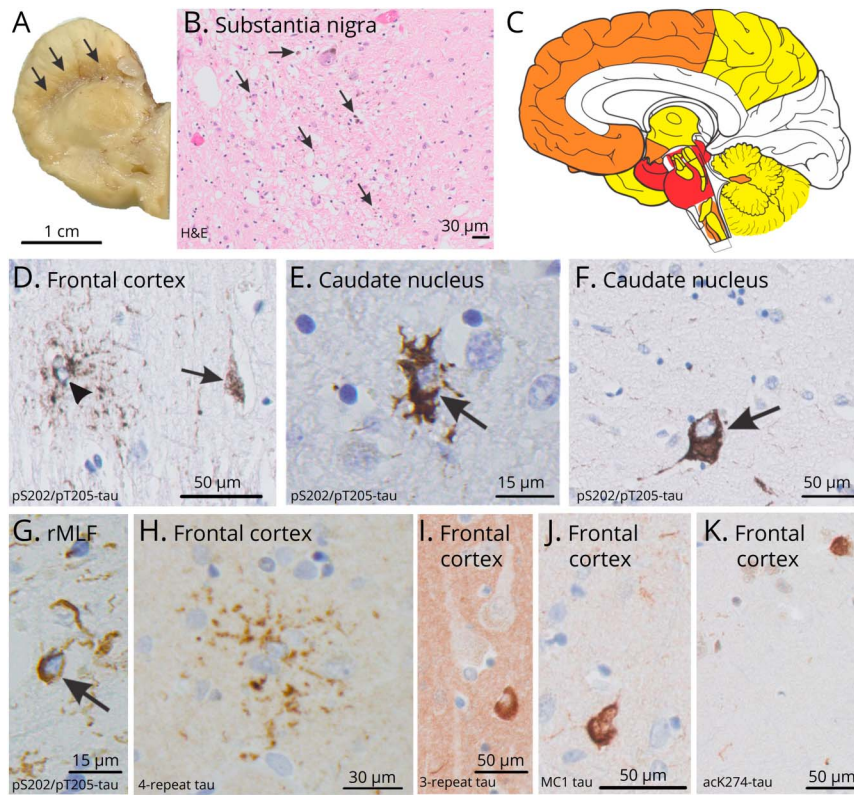
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**Figure 1** Neuropathologic Findings in the *TWINK* Mutation Carrier



(A) Reduced pigmentation of the substantia nigra (arrows). (B) Loss of melanin-containing neurons in the substantia nigra and detection of extraneuronal melanin (arrows), indicative of degeneration of melanin-containing neurons. (C) Schematic distribution of tau pathology in the brain. Yellow indicates areas with mild tauopathy manifestation, orange indicates those with moderate, and red indicates those with severe tau pathology. (D-G) Examples of different types of tau lesions, as demonstrated with an antibody against pSer202/pT205-tau: pretangles (arrow in D), astrocytic tau lesions best fitting with the criteria for astrocytic plaques (arrowhead in D), tufted astrocytes (E), ballooned neurons (F), and coiled bodies in the reticular part of the medial longitudinal fascicle (G). (H-K) Molecular pattern of tau pathology (see also eTable 2, [links.lww.com/NXG/A447](https://www.links.lww.com/NXG/A447)): 4-repeat tau was observed in the astrocytic plaque-like lesions (H), whereas 3-repeat tau was observed only in neurofibrillary tangles (I). Neurofibrillary tangles and threads also exhibited the MC1-conformational epitope (J) and acetylated acK274-tau (K).

subpial and perivascular thorn-shaped astrocytes. A few three-repeat tau-positive threads and NFTs were also observed (Figure 1I). The tau lesions were found in all brain regions investigated except the occipital cortex (eTable 1) and were positive for pS202/pT205-tau, pT231-tau, pS396/pS404-tau, and, to a smaller extent, acetylated ac-K274-tau and tau with the MC1 configuration previously proposed to be Alzheimer disease (AD)-specific (Figure 1D-K, eTable 2). Most severe tau pathology was found in the substantia nigra and other midbrain nuclei, whereas the putamen and globus pallidus were only mildly affected (eTable 1, eFigures 2 and 3). In the pons, tau lesions were also positive for ubiquitin and phosphoubiquitin (eFigure 4). TDP43 was seen in a few inclusions in subiculum/CA1. Neuritic plaques or  $\alpha$ -synuclein pathology were not observed. Alzheimer-related pathology (Braak NFT stage II and Thal amyloid phase 4) was prevalent. There was moderate cerebral amyloid angiopathy of the noncapillary type, moderate atherosclerosis of the circle of Willis, and severe small vessel disease. The psoas muscle showed mild neurogenic changes without obvious signs of a mitochondriopathy.

After the neuropathologic finding of a tauopathy, genetic analysis of *MAPT*, *GRN*, *C9ORF72*, *LRRK2*, *VPS35*, *PRKN*, *PINK1*, and *PARK7* was performed, but no mutations were found.

The absence of Lewy pathology confirmed that the patient's parkinsonism did not represent coincidental idiopathic

Parkinson disease (PD) but was likely caused by the *TWINK* mutation. Brain autopsy findings have previously been reported in only 3 heterozygous *TWINK* mutation carriers. Two of these 3 cases did not have parkinsonism but, nevertheless, showed loss of substantia nigra dopaminergic neurons, albeit without Lewy or tau pathology.<sup>3</sup> A very recent report described a *TWINK* mutation carrier with PEO and parkinsonism who had dopaminergic cell loss with Lewy pathology and no tau deposition,<sup>1</sup> in contrast with our case. Taken together, these cases suggest that heterozygous *TWINK* mutations can cause dopaminergic cell death with either Lewy pathology or tau pathology or with neither of these. Similar pathologic heterogeneity has been observed in PD patients with *LRRK2* mutations.<sup>4</sup>

The presence of mitochondrial dysfunction in this patient was supported by detection of phosphoubiquitin, a marker of PINK1-mediated mitophagy activation.<sup>5</sup> Tau pathology was previously also observed in a patient with a mutation in the gene for the mitochondrial metalloprotease paraplegin (SPG7).<sup>6</sup> We cannot exclude the possibility that the unusual pattern of tau pathology and neuron loss in our case was unrelated to the *TWINK* mutation and resulted from coincidental parallel presence of multiple tauopathies such as progressive supranuclear palsy (PSP), AD, and age-related tau astroglialopathy. However, the tau pathology pattern was not typical of PSP because of the only mild involvement of globus pallidus and putamen<sup>7</sup> and the multiple phenotypes of tau-

exhibiting astrocytes. Future work will need to elucidate the role of mitochondrial failure in the etiology of tauopathies.

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Name	Location	Contribution
<b>Wim Vandenberghe, MD, PhD</b>	Department of Neurology, University Hospitals Leuven, Laboratory for Parkinson Research, Department of Neurosciences, KU Leuven, Leuven Brain Institute, Belgium	Study concept, data collection, analysis and interpretation of data, and drafting and revision of the article for content
<b>Dorien Imberechts, MSc</b>	Laboratory for Parkinson Research, Department of Neurosciences, KU Leuven, Leuven Brain Institute, Belgium	Data collection, analysis and interpretation of data, and revision of the article for content

## Appendix (continued)

Name	Location	Contribution
<b>Koen Van Laere, MD, PhD, DSc</b>	Division of Nuclear Medicine, University Hospitals Leuven, Nuclear Medicine and Molecular Imaging, Department of Imaging and Pathology, KU Leuven, Belgium	Data collection, analysis and interpretation of data, and revision of the article for content
<b>Levi Jannis, MD</b>	Department of Pathology, University Hospitals Leuven, Belgium	Data collection, analysis and interpretation of data, and revision of the article for content
<b>Gert De Hertogh, MD, PhD</b>	Department of Pathology, University Hospitals Leuven, Belgium	Data collection, analysis and interpretation of data, and revision of the article for content
<b>Alicja Ronisz, MSc</b>	Laboratory for Neuropathology, Department of Imaging and Pathology, KU Leuven, Leuven Brain Institute, Belgium	Data collection, analysis and interpretation of data, and revision of the article for content
<b>Dietmar Rudolf Thal, MD, PhD</b>	Department of Pathology, University Hospitals Leuven, Laboratory for Neuropathology, Department of Imaging and Pathology, KU Leuven, Leuven Brain Institute, Belgium	Neuropathologic examination, analysis, diagnosis, and interpretation of data; drafting of figures and tables; and revision of the article for content

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