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Dissecting the role of TWNK in Parkinson's disease: a comparative perspective between Movement Disorders and Neuromuscular Diseases Centers

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Introduction: Parkinsonian features have been described in patients with mutations in nuclear genes encoding for proteins involved in mtDNA metabolism, such as *POLG*, *TWNK*, *OPA1*, *SLC25A46* and *DGUOK*. However, the precise link between Parkinson's disease (PD) and dysfunction of these proteins is largely unknown.

Aim of the study: To look for the role of *TWNK* variants in a large cohort of PD patients and the presence of parkinsonism in a chronic progressive external ophtalmoplegia (cPEO) patients carrying *TWNK* mutations. To describe the clinical phenotypes, video-oculography, neuroimaging, and the effect of *TWNK* variants on mtDNA.

Methods: Genomic DNA was analyzed with a targeted customized gene panel for genes associated to PD and parkinsonism, including nuclear genes involved in mtDNA metabolism (i.e. *POLG*, *TWNK*, *OPA1*, *SLC25A46*). Genetic and clinical data of patients carrying TWNK mutations from a Neuromuscular Diseases Center were retrospectively analyzed.

Results: 317 patients with PD (196 males, 62%; 121 females, 38%) were consecutively analyzed. 6 patients (1.9%) with PD alone or in combination with bilateral palpebral ptosis carried a very rare heterozygotic mutation of *TWNK* (c.500T>C, p.L167P; c.1112G>A, p.R371Q; c.1381G>A, p.E461K; c.1618G>A, p.G540R; c.1966A>C, p.K656Q; c.2010G>C, p.Q670H). Considering cPEO patients with *TWNK* mutations (n=18), 5 had parkinsonism. Detailed phenotypic features were compared among all patients. The role of other genetic factors for the risk of PD was assessed.

Conclusions: TWNK variants seem to be a not so rare finding in patients with PD, even in absence of clinical evidence of cPEO. Identifying the genetic modifiers of PD risk in *TWNK* patients will shed a light on the link of PD pathogenesis and mitochondrial impairment.