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A new pathogenic variant in GBA gene in a man with Parkinson's disease

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Introduction: GBA gene mutations are the most significant genetic risk factor for developing Parkinson's disease (PD) and a known cause of dementia with Lewy bodies (LBD). GBA-PD clinical features are earlier onset, more rapid progression and higher frequency and severity of non-motor symptoms.

Objective: We describe the clinical case of a 65-years-old PD patient heterozygous for two GBA mutations, enrolled in the MuTaParGa2018.0942 project.

Methods: The subject was selected from patients referred to the Parkinson Unit at AOU Careggi and screened for β-glucocerebrosidase (GBA) enzymatic activity on Dried Blood Spot using tandem mass spectrometry (LC-MS/MS). GBA gene analysis was performed using AmpliSeq for Illumina Custom DNA panel and identified variants were confirmed using Sanger sequencing.

Results: The disease was clinically diagnosed, supported by SPECT-Brain-DaTscan test, at the age of 60. Symptoms started 2 years earlier with bradykinesia and resting tremor (affecting the left side mostly) gait disturbance and postural instability. A prodromal phase with vivid dreams and sleeptalking was also reported. Levodopa and dopamine-agonist therapies improved the symptoms. The patient had a positive family history of PD (maternal uncle) and dementia (mother) and suffered from monoclonal gammopathy, maculopathy and allergic asthma. After 3 years the clinical course worsened both for motor and non-motor symptoms; particularly balance impairment increased. Brain FDG-PET tomography revealed a pattern compatible with LBD. Brain MRI highlighted calcium salts deposits in the basal nuclei. GBA enzymatic activity resulted reduced and compatible with carrier status. GBA gene analysis identified the presence of the common mutation c.1448T>C p.(Leu483Pro) and the new missense variant c.631G>A p.(Val211Ile). Unfortunately, CIS or TRANS allelic segregation analysis is not available.

Conclusions: The reported case confirms the known data relating to the clinical phenotype of patients with PD and GBA mutations and increases knowledge about the genotype of this category of patients.