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Parkinson and Gaucher's diseases: common risk factors and future therapeutic targets

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Introduction: Gaucher's disease is an autosomal recessive disorder due to glucocerebrosidase (*GBA*) gene mutations and it's the most common Lysosomal Storage disorder. Several genetic mutations have been described to cause inefficient production of the correctly folded glucocerebrosidase enzyme (GCcase). Many studies suggest an association between mutations in *GBA* gene and susceptibility to developing Parkinson's disease (PD), underlining lower activity of GCase in Parkinsonian patients with or without *GBA* variants.

Objective: The aim of the study is to evaluate the frequency of low GCase's activity and *GBA* mutations in a large cohort of PD patients.

Methods: A cohort of 252 PD patients was selected at the Parkinson unit of AOU Careggi in Florence. For each patient, clinical data were collected and GCase enzyme activity screen was performed through Dried Blood Spot (DBS). *GBA* gene sequencing analysis was performed on patients with low GCase activity (<5 μmol/h/L).

Results: We found 78 patients with low GCase's activity and among these 22 patients with *GBA* mutations. The most common *GBA* variants found were p.(Asn370Ser) in 32%, p.(Leu444Pro) in 9%, p.(Glu326Lys) in 9%, p.(Asp409His) in 9% and p.(Thr369Met) in 4%. In this group of patients the average age of symptoms onset was 57,9±9,3 years. The first symptom was tremor in 14 patients and rigidity in 4. Ten patients manifested cognitive impairment during follow-up visits. Forty percent (N=9) of subjects had a positive family history of PD.

Conclusions: In our cohort the proportion of PD patients with reduced GCase's activity and the one with *GBA* mutations are consistent with already published data (from 5 to 20%). *GBA* variants represent a risk factor for Parkinson's disease and particularly for the forms with dementia. The modulation of GCase activity represents a potential therapeutic target for PD in the near future.