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Genetic landscape of early-onset Parkinson's disease in Italy: results of the PARKNET multicentric study

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Background: The advent of next-generation sequencing (NGS) unraveled the genetic landscape of Parkinson's disease (PD), with a particular attention on early-onset PD (EOPD). Few studies based on the genetic screening of genes associated with PD in specific populations have been conducted so far.

Objectives: To perform an integrated genetic analysis focused on EOPD from Italy. To assess the pathogenicity of identified variants for diagnostic purposes.

Methods: Eight Italian Movement Disorders Centers shared clinical and genetic data of EOPD patients (age at onset, AO<55y) that underwent genetic analysis for diagnostic purposes with NGS panel and MLPA. A minimum common gene set of 15 genes was assessed. Stratification of collected data according to an AO less than 40y was performed (vEOPD subgroup). The identified variants were classified according to the ACMG criteria.

Results: Genetic results of 650 EOPD patients were collected (160 vEOPD, 25%). A genetic diagnosis was possible in 97 of 650 patients (15%; 42 of 160 vEOPD, 26%), where *GBA* pathogenic/likely pathogenic variants (47 of 650, 7%; 13 of 160 vEOPD, 8%) and biallelic *PRKN* pathogenic/likely pathogenic SNVs/CNVs (15 of 650, 2%; 11 of 160 vEOPD, 7%) were the most common findings.

Conclusions: In this study, genetic results from the larger Italian EOPD cohort reported so far were collected. Our findings suggest that *GBA* variants are an important genetic factor in Italian EOPD patients. Biallelic *PRKN* and *PINK1* SNVs/CNVs are more represented in EOPD patients with younger clinical onset. Our results confirm that the screening of a small gene set, including *GBA*, *LRRK2*, *PRKN*, *PINK1*, and *SNCA*, seems to be sufficient for diagnostic purposes in EOPD patients without atypical features.