Precision medicine in Parkinson's disease: an integrated multidisciplinary approach to develop innovative protocols for early diagnosis and disease progression

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Background
Parkinson’s disease (PD) is the second most common neurodegenerative disorder (1-5% of the general population) for which neither effective cure nor early diagnostic tools are available that could tackle the pathology in the early phase. The disease is characterized by the loss of mesencephalic-diencephalic dopaminergic (mdDA) neurons of the substantia nigra (SN) in association with the presence of Lewy bodies in some surviving neurons [1].

To date, the diagnosis of PD is mainly clinical based on the identification of the characteristic signs and symptoms of the disease due to the massive degeneration of mdDA neurons (over 60% at onset movement symptoms) of the SN. Structural and functional diagnostic imaging techniques are able to detect the qualitative and quantitative neurological alterations only when the symptoms of the disease are already evident and therefore brain degeneration is already massive. To date the genetic diagnosis of PD is only effective in an extremely small percentage of cases carrying known mutations in a small number of genes, while for the rest of the patients (> 90%) there is no genetic diagnosis. The approach we propose based on the joint contribution of a number variants in appropriate genes, will permit to design diagnostic protocols for early prediction of PD which can meet the needs of a wider range of patients.

Results
We performed a multi-stage study to identify candidate genes, likely involved in the etiopathogenesis of the late onset Parkinson’s disease (LOPD). The study included a discovery stage based on the analysis of whole exome data from 26 dominant LOPD families, a validation stage performed on 1,542 independent PD patients and 706 controls from different cohorts and the assessment of polygenic variants load in the Italian cohort (394 unrelated patients and 203 controls).

This analysis identified 169 disrupting variants in 26 candidate genes for LOPD. Interestingly, 16 out of these 26 genes have not been associated to the disease before, were expressed in midbrain and were involved in pathways potentially deregulated in PD, including mitochondrial metabolism, vesicular trafficking and autophagy. Moreover, we demonstrated for the first time that the co-inheritance of multiple rare variants (≥ 2) in the 26 genes may predict PD occurrence in about 20% of patients, both familial and sporadic cases, with high specificity (> 93%; p = 4.4x10^{-5}). Furthermore, patients carrying multiple rare variants showed higher risk of manifesting dyskinesia induced by levodopa treatment [2-4].

Ongoing studies
Realization of diagnostic tools for PD
We intend to improve the predictive/diagnostic power of the LOPD protocol by including Mendelian and susceptibility PD genes. The presence of one or more variants will be tested for association with phenotypic manifestation of PD (motor, non-motor, and cognitive signs, as well as age at onset, LID and neuroimaging changes) to assess the variant burden effect on progression, and prognosis of the disease (Granted by Ricerca Finalizzata Ministry of Health 2020-2023).

Identification of novel biomarkers for early prediction and progression
The project intends to identify novel biomarkers for PD and clinical parameters related to the PD etiology by jointing ‘omics’ approaches (whole exome sequencing, serum miRNome and metabolomics) with bioinformatics and bio-statistical methods to discover important biomarkers present in complex biological samples (Granted by PON-MISE Neurotechno, 2020-2023).

**Generation of humanized mouse models for PD**

To study the pathogenic effect of single and multiple mutations we have already generated mouse models carrying single mutations identified in PD patients, which have never been generated so far. We also intend to generate mouse models carrying multiple mutation in different genes to recapitulate the genetic complexity observed in PD patients. Phenotypic analysis will include: i) identity, natural survival and vulnerability to parkinsonian drug (MPTP); ii) behavioral and locomotor activity analysis; iii) in vivo imaging through preclinical digital small animal system PET/CT; correlation with human phenotype (Granted by PON-MISE iPLAT, 2020-2023 and Ricerca Finalizzata Ministry of Health 2020-2023).

**References:**


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