Project Title: Exploring the genetic basis of Parkinson's Disease
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Background:
Glucosylceramidase Beta 1 (*GBA1*) is a gene located on chromosome 1 encoding for the lysosomal enzyme glucocerebrosidase (GCase), which hydrolyzes glucosylceramide and glucosylsphingosine. Biallelic pathogenic variants in *GBA1* cause Gaucher disease (GD). However, *GBA1* variants are also among one of the common genetic risk factors for Parkinson's Disease (PD). *GBA1* variants are classified into Severe, Mild, Risk and Variants of Unknown Significance (VUS) based on their GD causation.
Carriers of severe *GBA1* variants have a 9-10-fold increased risk of developing PD with an earlier age of onset and more rapid motor and cognitive decline , whereas carriers of mild variants show a 4-fold increased risk.
To date, more than 300 variants have been reported, with most of them being classified as Unknown as their contribution to PD risk has not been supported by case-control large scale studies. Consequently, Unknown variants are often excluded from genetic analysis, thus hampering their potential reclassification into risk or pathogenic PD-causing variants. In the latest years, a limited number of studies have been published attempting to reclassify these variants using different statistical methods. However, none of these studies functionally validated these findings to support their involvement in the disruption of the lysosomal function.
Aims:
By exploiting our large in-house cohort of PD patients that are routinely tested for *GBA1* variants using an ad-hoc sequencing workflow (LongNext) and followed up clinically in the Mondino Hospital, the aims of this project will be:

1) Identify and stratify *GBA1* variants into severe, mild, risk and unknown and create a database reporting for each patient the list of variants together with the main demographic, motor and cognitive information. Variants will be clustered based on clinical features and predictions made using in silico tools to highlight pattern similarities between unknown variants and the remaining classes.
2) Patients with a prioritized unknown variant and having available specimens will undergo biological testing, such as G-Case activity measured fusing fluorimetric assays to evaluate lysosomal enzymatic function, a-synuclein aggregation propensity will be examined through seeding assay with detection and characterisation performed using Western blotting, to functionally validate the variant pathogenicity.

Techniques:
The candidate PhD student will acquire knowledge on bioinformatics, specifically learning to work using a unix-based server and creating scripts for data extraction and NGS-based workflows. The candidate will work with R, python and bash languages and use genomic databases such as VEP, AlphaGenome, UCSC. Most analyses will require a strong statistical background as the main focus of this project will be to perform unsupervised clustering, modeling and correlation of outcomes.