The contribution of mutant GBA to the development of Parkinson's disease

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Gaucher disease (GD), an autosomal recessive disease, results from mutations in the acid β-glucocerebrosidase (GCase) encoding gene, GBA, which leads to accumulation of glucosylceramides. GD patients and carriers of GD mutations have a significantly higher propensity to develop Parkinson disease (PD) in comparison to the non-GD population. In my research proposal I have shown that in fibroblasts derived from patients of GD and carriers of GD mutations, mutant GCase variants retained in the ER and lead to ER stress and to activation of the ER stress response, known as the unfolded protein response (UPR).

We used the fruit fly *Drosophila melanogaster* as an animal model to further study the pathological effect of mutant GCase variants in cells and its contribution to the development of PD in carriers of GD mutations. *Drosophila* has two GBA orthologs (CG31148 and CG31414), each of which has a minos insertion, which creates C-terminal deletion in the encoded GCase. Flies double heterozygous for the two endogenous mutant GBA orthologs presented UPR and locomotor dysfunction as shown in my research proposal. These flies developed parkinsonian signs, manifested by death of dopaminergic cells, reduction in tyrosine hydroxylase production and a shorter life span. We also established transgenic flies carrying either the normal or the mutant human N370S, and L444P variants. UPR activation and development of parkinsonian signs could be recapitulated in flies expressing these three mutant versions of GBA alleles.
UPR and parkinsonian signs could be partially rescued by growing the double heterozygous flies, or flies expressing the N370S or the L444P human mutant GCase variants, in the presence of the pharmacological chaperone ambroxol, which binds and removes mutant GCase from the ER.

Our results are with biological significance because they strongly suggest that the presence of a mutant GBA allele in dopaminergic cells leads to ER stress and to their death, and contributes to development of Parkinson disease. Furthermore, our study suggest a potential pharmaceutical solution for the development of parkisonian signs seen in GD patients and carriers of GD mutations.