Eur J Exp Bio, 7:5
DOI: 10.21767/2248-9215-C1-003

The contribution of mutant GBA alleles to the development of Parkinson's disease in carriers of Gaucher disease mutations

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Gaucher disease (GD) is an autosomal recessive disease resulting from mutations in the acid β-glucocerebrosidase (GCase) encoding gene, GBA, which leads to accumulation of glucosylceramide. GD patients and carriers of GD mutations have a significantly higher propensity to develop Parkinson's disease (PD) in comparison to the non-GD population. This implies that mutant GBA allele is a predisposing factor for development of PD in carriers of GD mutations. We have previously shown that in cells that derived from patients of GD and carriers of GD mutations, mutant GCase molecules undergo ER retention, which leads to lead to ER stress and to activation of the unfolded protein response (UPR). We used *Drosophila* melanogaster to confirm that development of PD in carriers of GD mutations results from the presence of mutant GBA alleles. *Drosophila* has two GBA orthologs and each one of them has a mutant allele. We generated two different *Drosophila* models for carriers of GD mutations: Flies double heterozygous for the two-endogenous mutant GBA orthologs and flies expressing the human N370S or the L444P GCase variants. All lines exhibited UPR, death of dopaminergic cells, shorter life span and had a decreased negative geotaxis. ER stress and Parkinsonian signs could be rescued by growing the double heterozygous flies or flies containing the N370S or the L444P mutant GCase variants in the presence of the pharmacological chaperone ambroxol. Our results 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's disease.

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