Objective: We aim to use Caenorhabditis elegans (C. elegans) as the simplest possible model to discover new gene(s) involved in dopaminergic neuroprotection.

Introduction: Parkinson's disease (PD) is associated with a specific dopaminergic neurodegeneration. This phenotype can be recapitulated in many models, including C.elegans (Nass et al. PNAS, 2002), using 6-hydroxy-dopamine (6OHDA). This neurotoxin is an oxidized derivative of dopamine.

Research on familial PD identified causative mutations in six major genes, but those are linked to a relatively low percentage of PD patients. The use of a powerful model organism might reveal more genes involved in PD.

Methods: Using forward genetics in C.elegans we identified four mutants hypersensitive to 6OHDA-induced neurodegeneration.

Results: The most hypersensitive mutant was mapped to chromosome X using SNP. This region was narrowed to 2Mbp using classical 3-point fine-mapping. The region was further reduced to 70Kbp by combining visible markers and SNP mapping. Using both Comparative Genomic Hybridization and deep sequencing we identified a mutation that causes the hypersensitivity. The mutation is in an integral membrane protein belonging to tetraspanin protein family. The 30 members of human tetraspanin protein family have been described to be potentially involved in cell adhesion, motility and tumour metastasis. The hypersensitivity of this mutant is also rescued with injection of fosmid containing wild type allele of tetraspanin.

Conclusion: We want to characterize this gene, and determine its epistatic relationship with genes involved in the dopamine biosynthesis. Additionally we will screen for mutations in the orthologue of this gene in PD patients.