IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION OF VPS41 AS A POTENTIAL GENETIC MODIFIER OF PENETRANCE IN P.G2019S LRRK2-ASSOCIATED PARKINSON'S DISEASE

Jochen Ohnmacht (1,2), Dheeraj R. Bobbili (3), Max Meyrath (1,2), Dirk Remmers (2), Enrico Glaab (4), Stacia Wyman (5), Julia Kaye (6), Patrick May (3), Steven Finkbeiner (5,7,8), Rejko Krüger (1,2,9)

1) Translational Transversal Medicine, Luxembourg Institute of Health, Luxembourg;
2) Translational Neuroscience, LCSB, University of Luxembourg, Luxembourg;
3) Bioninformatics Group, LCSB, University of Luxembourg, Luxembourg;
4) Biomedical Data Science, LCSB, University of Luxembourg, Luxembourg;
5) Innovative Genomics Institute, University of California, Berkeley, USA;
6) Center for Systems and Therapeutics, Gladstone Institutes, San Francisco, USA;
7) Taube/Koret Center for Neurodegenerative Disease Research, Gladstone Institutes, San Francisco, USA;
8) Department of Neurology, University of California, San Francisco, USA;
9) Centre Hospitalier Luxembourg, Luxembourg

Abstract: Trait- or disease-associated genetic variants contribute to substantial variability and penetrance of complex traits and diseases in humans. While several causative genes and risk factors have been identified in familial forms of Parkinson's disease (PD), it remains unclear how patient's genomes shape the predisposition to develop PD. Mutations in LRRK2 are the most common autosomal dominantly inherited form of PD. The p.G2019S mutation displays incomplete penetrance and even within the group of affected individuals a broad range of age at disease onset (AAO) is observed. Through a whole genome sequencing approach in multiple families with p.G2019S LRRK2-associated PD, we have detected rare and common variants that might act as genetic modifiers of AAO. However, prioritizing disease-modifying variants and understanding their biological action remain a challenge.

Using a new scoring system, we prioritized coding variants acting as modifiers of AAO in these families for functional in vitro validation. Among these modifiers we find GO term enrichment for genes with association to "neuron projection" but also Golgi apparatus associated vesicle and transport. From the candidates we selected the missense variant p.E432K in VPS41 (a member of the HOPS complex essential in lysosome/endosome trafficking), predicted by segregation analysis to confer protective effect on AAO in one of the families analysed.

To this end, we assessed LRRK2 phenotypes in patient iPSC-derived dopaminergic neuron cultures. We found that VPS41 knockdown (KD) results in neurite outgrowth indistinguishable between p.G2019S and isogenic WT LRRK2 neurons. Lysosome and endosome morphology was altered upon VPS41 KD, but independent of LRRK2 status. The overexpression (OE) of WT and p.E432K VPS41 in HEK293T cells showed a differential starvation response, with increased localization of TFE3 to nuclei under baseline and starved conditions. In contrast, decreased TFE3 protein levels were previously reported in PD post-mortem substantia nigra compared to healthy controls. Through protein interaction assays we found that p.E432K VPS41 displays increased affinity to RAB7A indicating an increased interaction at the endosome/lysosome interface that is reported to be impaired in p.G2019S LRRK2 mutant neurons.

Our findings lend support the concept of disease modifying variants incrementally contributing to the differential risk to develop PD in the context of LRRK2 mutations. We are currently further investigating how p.E432K VPS41 affects neurite outgrowth, endosome/lysosome morphology and autophagy in patient derived neurons and their controls.