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Genetic variation of the retromer subunits VPS26A/B-VPS29 in Parkinson's disease

Barbara Shannon, BSc[1,†], **Alexandra Soto-Ortolaza, BSc**[1,†], **Sruti Rayaprolu, BSc**[1], **Heather D Cannon, AS**[1], **Catherine Labbé, PhD**[1], **Bruno. A Benitez, PhD**[2,3], **Jiyoon Choi, PhD**[2,3], **Timothy Lynch, FRCPI**[4], **Magdalena Boczarska-Jedynak, MD PhD**[5], **Grzegorz Opala, MD**[5], **Anna Krygowska-Wajs, MD**[6], **Maria Barcikowska, MD**[7], **Jay A. Van Gerpen, MD**[8], **Ryan J. Uitti, MD**[8], **Wolfdieter Springer, PhD**[1,9], **Carlos Cruchaga, PhD**[2,3], **Zbigniew K. Wszolek, MD**[8], and **Owen A. Ross, PhD**[1,9,*]

[1]Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA [2]Hope Center for Neurological Disorders, Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA [3]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA [4]Dublin Neurological Institute at the Mater Misericordiae University Hospital, Conway Institute of Biomolecular & Biomedical Research, University College Dublin, Ireland [5]Department of Neurology, Medical University of Silesia, Katowice, Poland [6]Department of Neurology, Jagiellonian University, Krakow, Poland [7]Department of Neurodegenerative Disorders, Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland [8]Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA [9]Neurobiology of Disease Track, Mayo Graduate School, Mayo Clinic, Rochester, Minnesota, USA

Abstract

We recently showed that mutation of the *VPS35* gene can cause late-onset Parkinson's disease. In the present study we sequenced 702 affected subjects from the Mayo Clinic Parkinson's disease patient-control series for the *VPS29* and *VPS26A/B* genes. We identified only two rare non-synonymous variants in the VPS26A p.K93E and VPS29 p.N72H. The results show that mutations in the genes composing the retromer cargo recognition subunit are not a common cause of Parkinson's disease.

Keywords

Genetics; Parkinson's disease/Parkinsonism; Retromer; VPS35

[*]**Corresponding author's contact information:** Owen A. Ross PhD, Department of Neuroscience, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224, Tel: (904)-953-6280, Fax: (904)-953-7370, ross.owen@mayo.edu.
[†]These authors contributed equally

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1. Introduction

Recent studies have demonstrated that mutation of the Vacuolar Protein Sorting 35 Homolog gene (*VPS35*; VPS35 p.D620N) is a rare cause of autosomal dominant Parkinson's disease (PD) (Vilarino-Guell, et al., 2011,Zimprich, et al., 2011). Subsequently, several independent studies have detected the mutation in PD patients and not in controls (see supplemental table 1). The VPS35 protein is a component of the cargo recognition subunit of the retromer, a highly conserved protein complex that plays a critical role in transmembrane receptor recycling and protein transport between the endoplasmic reticulum and the trans Golgi network (Bonifacino and Rojas, 2006). The cargo binding trimeric subcomplex of the retromer is composed of VPS35, VPS26, and VPS29. VPS35 binds independently to both VPS26 and VPS29, and VPS35 also binds in a VPS29-dependent manner to a membrane associated sorting nexin dimer. Mammals have two paralogues of the VPS26 subunit that share 70% amino acid identity; VPS26A and VPS26B. VPS26A and VPS26B compete for a single-binding site on VPS35 to define distinct retromer complexes that are not functionally equivalent (Bugarcic, et al., 2011). Given the pathogenic mutation in *VPS35*, we set out to establish if genetic variants within the *VPS26A, VPS26B* and *VPS29* genes may also contain variation, which may be relevant to PD pathogenesis.

2 Methods

The Mayo Clinic discovery patient-control series contained 702 patients with clinical diagnoses of PD, and 752 age-matched unaffected and unrelated control subjects. All subjects are unrelated, non-Hispanic Caucasians of mixed European ancestry, recruited at Mayo Clinic Florida. Bi-directional DNA sequencing was performed on all coding exons of *VPS26A* (n=9), *VPS26B* (n=6) and *VPS29* (n=4) in the Mayo Clinic Florida PD patient series (n=702). Identified variants were screened through our control series and three further patient-control series from the US, Ireland and Poland (1204 cases and 1301controls). Key demographic and clinical data are summarized in Supplemental Table 2. The ethical review boards at each institution approved the study, and all participants provided informed consent.

3. Results

Sequencing identified 14 variants: 11 exonic variants and 3 in the untranslated regions (UTR) (Supplemental Table 3). Ten variants detected were novel rare variants not present in the public Exome Variant Server, two result in nonsynonymous changes, in exon 4 of *VPS26A* (NM_004896) c.277 A>G (p.K93E) and in exon 4 of *VPS29* (NM_057180) c.216 A>C (p.N72H). These variants were detected in two patients with familial PD and were not observed in 752 control subjects from the Mayo Clinic Florida series (Supplemental Figure 1). Further screening of three additional patient-control series identified VPS29 p.N72H in one Polish control and VPS26A p.K93E was not observed; using *in silico* prediction software both mutations are predicted to be benign.

4. Discussion

We recently reported a mutation in the *VPS35* gene (VPS35 p.D620N) as a cause of autosomal dominant PD. Our results demonstrate that mutations within the *VPS26A*, *VPS26B* and *VPS29* genes are rare and do not play a major role for PD risk in our population. This work is supported by a recent study on *VPS29A* variation in a German PD patient-control series (Koschmidder, et al., 2013). The results of our sequencing study and previous work on *VPS35* has highlighted the highly conserved nature of the protein components of the cargo recognition subunit.

While the identification of mutations in *VPS35* might suggest dysfunctions in the retromer complex as a contributor to PD, the molecular and cellular mechanisms remain unclear. A recent study now implicates the interaction of *VPS35* with *LRRK2*, and with the locus *PARK16* gene *RAB7L1* and thus might strengthen the role of defective protein sorting within vesicular compartments in the pathogenesis of PD (MacLeod, et al., 2013). Another report recently suggested that enhanced levels of VPS35 could also protect from mitochondrial insults resulting from MPP+ treatment (Bi, et al., 2013). Taken together the results of these studies suggest that mutations in the *VPS26A*, *VPS26B* and *VPS29* genes that encode other protein subunits of the retromer cargo recognition complex are not a common cause of PD. This finding may support the hypothesis that the VPS35 p.D620N substitution affects the binding of a specific cargo, rather than a generalized dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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