3-1-2019

Contributions of VPS35 Mutations to Parkinson's Disease

Abir A. Rahman
Boise State University

Brad E. Morrison
Boise State University

Publication Information

Rahman, Abir A. and Morrison, Brad E. (2019). "Contributions of VPS35 Mutations to Parkinson's Disease". *Neuroscience, 401*, 1-10. http://dx.doi.org/10.1016/j.neuroscience.2019.01.006

NEUROSCIENCE

REVIEW

A. A. Rahman, B. E. Morrison / Neuroscience 401 (2019) 1–10

Contributions of VPS35 Mutations to Parkinson's Disease

Abir A. Rahman [a,b] **and Brad E. Morrison** [a,b*]

[a] *Department of Biological Sciences, Boise State University, Boise, ID 83725, USA*

[b] *Biomolecular Sciences Ph.D. Program, Boise State University, Boise, ID 83725, USA*

Abstract—Parkinson's Disease (PD) is a multi-system neurodegenerative disease where approximately 90% of cases are idiopathic. The remaining 10% of the cases can be traced to a genetic origin and research has largely focused on these associated genes to gain a better understanding of the molecular and cellular pathogenesis for PD. The gene encoding vacuolar protein sorting protein 35 (VPS35) has been definitively linked to late onset familial PD following the identification of a point mutation (D620N) as the causal agent in a Swiss family. Since its discovery, numerous studies have been undertaken to characterize the role of VPS35 in cellular processes and efforts have been directed toward understanding the perturbations caused by the D620N mutation. In this review, we examine what is currently known about VPS35, which has pleiotropic effects, as well as proposed mechanisms of pathogenesis by the D620N mutation. A brief survey of other VPS35 polymorphisms is also provided. Lastly, model systems that are being utilized for these investigations and possible directions for future research are discussed.

Key words: retromer, neurodegeneration, animal models, cellular mechanisms.

INTRODUCTION

Parkinson's disease (PD) is a complex neurological disorder involving both motor and non-motor symptoms. Affecting 1% of the population over 60, it is the second most common neurodegenerative disorder (Lau and Breteler, 2006; Williams-Gray et al., 2013). The prevalence of the disease rises with age. According to a meta-analysis report by Pringsheim, Jette, Frolkis, & Steeves, 2014, the prevalence is 41 per 100,000 between ages 40 and 49, rising up to 428 between ages 60 and 69 and 1087 between 70 and 79. Another report states that there is a greater incidence in men compared to women, at a ratio of approximately 1.5:1 (Elbaz et al., 2002; Taylor et al., 2007; Wooten et al., 2004). The case burden in US alone is estimated to rise to more than one million by 2030 (Marras et al., 2018). The deterioration in motor function occurs primarily due to a loss of dopamine signaling in the basal ganglia. This loss of dopamine is due to the progressive loss of dopaminergic neurons in the substantia nigra. However, it is not only the basal ganglia that is affected in PD. Research suggests that PD involves multiple areas of the brain and results from a complex interplay between genetic and environmental factors. Clinically described motor symptoms include resting tremors, bradykinesia, rigidity of limbs and gait defects. Moreover, there are numerous non-motor symptoms such as cognitive defects and dementia, mood disorders, sleep disorders that add to the suffering of the patients (Pringsheim et al., 2014; Ascherio and Schwarzschild, 2016; Tysnes and Storstein, 2017). According to the centers for disease control and prevention (CDC), medical complications due to PD rank as the 14th leading cause of death in the United States (Beard et al., 2017). With no known cure for this disease, research has been focused on understanding the cellular and molecular processes that may be responsible for the neurodegeneration (Fig. 1).

Hallmark histopathological features of PD are the loss of dopamine-producing neurons in the substantia nigra and the formation of large protein aggregates in surviving neurons termed Lewy bodies. Lewy bodies are composed primarily of α-synuclein protein in these neurons. The pathology of the α-synuclein aggregates shares many features with that of prion disease thereby spurring investigation into that hypothesis (Brundin and Melki, 2017; Surmeier et al., 2017). Mitochondrial dysfunction is also a widely reported feature of PD (Goswami et al., 2017). Familial PD-linked mutations have been identified in a number of genes (SNCA, LRRK2, VPS35, CHCHD2, GBA, Parkin, PINK1, DJ-1, ATP13A2, FBXO7 and PLA2G6) that have been shown to participate in mitochondrial function and biogenesis which further underscores the association with mitochondrial defects as a potential driver of the disease (Helley et al., 2017). Protein homeostasis, particularly

*Correspondence to: B.E. Morrison, Department of Biological Sciences, Boise State University, Boise, ID 83725, USA.
E-mail address: bradmorrison@boisestate.edu (B. E. Morrison).

https://doi.org/10.1016/j.neuroscience.2019.01.006
0306-4522/

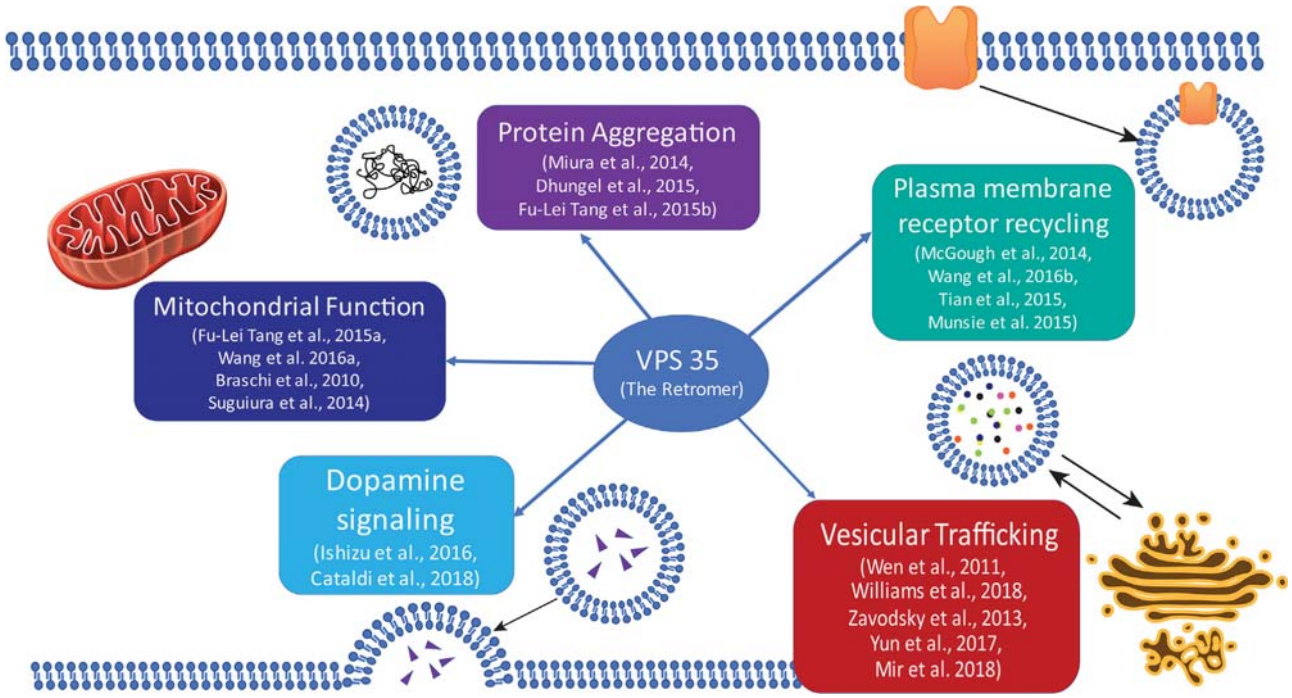

Fig. 1. Cellular processes affected by VPS35 mutation.

synucleinopathy, and mitochondrial health have therefore become major areas of focus for research into characterizing PD pathogenesis and developing therapeutics (Table 1).

IDENTIFIED VPS35 MUTATIONS

The VPS35 gene was identified by two independent studies in 2011 as linked to familial PD (Vilariño-Güell et al., 2011; Zimprich et al., 2011). These studies were conducted using exome sequencing technology on DNA obtained from families that exhibited evidence of hereditary PD. Subsequent studies have largely concluded that the D620N mutation is relatively rare, with a calculated prevalence of about 0.115%, from 15 reported case studies involving 21,824 PD patients worldwide (Ando et al., 2012; Guella et al., 2012; Guo et al., 2012; Kumar et al., 2012; Lesage et al., 2012; Sharma et al., 2012; Sheerin et al., 2012; Zhang et al., 2012; Chen et al., 2013; Sudhaman et al., 2013; Deng et al., 2013, 2012; Blanckenberg et al., 2014; Gagliardi et al., 2014; Koschmidder et al., 2014; Shannon et al., 2014; Gustavsson et al., 2015; Gambardella et al., 2016). Other polymorphisms in the VPS35 gene that were identified include L774M, P316S, R524W, I241M, M57I, G51S, R32S, I560T, H599R, M607V. However, all of these sequence variations, with the exception of D620N, have yet to be definitively linked to PD.

In 2005, a study identified VPS35 levels to be reduced in affected brain regions in Alzheimer's disease (Small et al., 2005). In addition, another study reported increased Amyloid β depositions in mice heterozygous for VPS35 knockout ($Vps35^{+/m}$) (Wen et al., 2011). Similarly, other work has linked abnormal microglial activity and abnormal hippocampal development, as observed in Alzheimer's Disease, to VPS35 depletion, but no polymorphisms in the VPS35 gene have been associated (Wang et al., 2012; Appel et al., 2018).

VPS35 AS PART OF THE RETROMER COMPLEX AND RELATED FUNCTIONS

VPS35 was originally identified in yeast as a member of the retromer complex. This complex is involved in the intracellular trafficking of proteins (Seaman et al., 1998). Its role in endosome to Golgi retrograde transport has been very well characterized (Seaman, 2012; Follett et al., 2014a; Trousdale and Kim, 2015). Retromer dysfunction has been implicated in Alzheimer's disease, Parkinson's disease and several other neurodegenerative diseases, along with various developmental processes, including wing and eye development in *Drosophila*, and bone development (Belenkaya et al., 2008; Zhang et al., 2011; Chan et al., 2016). In this context, the interaction of the retromer complex and the wnt signaling pathway has been extensively studied (Belenkaya et al., 2008; Zhang et al., 2011, 2018; Small and Petsko, 2015; Wang and Bellen, 2015; Chan et al., 2016). Structurally, VPS35 forms a trimer with VPS26 and VPS29, to form the cargo recognition complex (CRC). The CRC then associates with a dimer of sorting nexins, belonging to the SNX-BAR family of proteins. This association is further facilitated by RAB7. Together, the retromer complex plays important roles in vesicular sorting (Bonifacino and Hurley, 2008; Seaman et al., 2009; McGough and Cullen, 2011; Seaman, 2012; Lucas et al., 2016; Kovtun et al., 2018). Deficiency of either VPS35 or VPS29 leads to the degradation of the other two CRC components

Table 1. Advantages and disadvantages of different model systems

Model System	Advantages	Disadvantages
Cell Culture	Ease of genetic manipulation via shRNA and siRNA, as well as lipofectamine and lentivirus. Homogeneous populations of cells can be obtained. Very close to human molecular physiology, especially when using human cell lines. Ideal for culturing in laboratory conditions.	Does not fully recapitulate the heterogeneous cell types and extracellular environment found in whole tissue samples. Immortalized cell lines are not like normal, healthy brain cells. Some exhibit chromosomal aberrations.
Rodent	Similar to human physiological conditions, in terms of in vivo experiments. Availability of isogenic animals, including Vps35 hemizygous deletion and conditional KO animals, as well as D620N mutant animals	Relatively difficult to perform genetic manipulations. Relatively long life cycles.
Fly	Relatively short life cycles. Libraries of flies with a wide range of polymorphisms available. Ease of genetic manipulations via RNAi, shRNA and siRNA. Well-characterized nervous system.	Fly neurons display some divergent characteristics compared to their human counterparts. Invertebrate model system. Significant evolutionary distance with humans. Short life spans make it difficult to study neurodegeneration that occurs due to long, progressive processes.
Worm	Fully mapped cell lineage and nervous system. Well-characterized metabolism and genetics, and a wide variety of transgenic nematodes available. Very easy to manipulate genetically by feeding bacteria expressing RNAi, and by EMS mutagenesis.	Invertebrate model system. Major evolutionary distance with humans. Neurons are physiologically and electrochemically distinct from mammalian neurons with respect to a number of parameters. Short life spans might not recapitulate human neurodegenerative disease conditions.
Yeast	Extremely short life span and extremely easy to grow and maintain in the laboratory. Very well-characterized metabolism and genetics. Ease of genetic manipulations and proteomic assays, including protein–protein and DNA–protein interaction assays. Single-celled eukaryote that shares many fundamental cellular processes with humans.	Not a neuronal model system. Intracellular and extracellular environment very different from that of a mammalian cell. Paracrine signaling very different from mammalian cells. Large evolutionary divergence from humans.

(Fuse et al., 2015). Transmembrane receptors such as the cation-independent mannose 6 phosphate receptor (CIMPR) and the membrane iron transporter DMT1 are well-characterized targets of retromer-mediated sorting (Arighi et al., 2004; Tabuchi et al., 2010; Lucas et al., 2016). In addition, there have been several studies on the role of the retromer in recycling of beta-2 adrenergic receptors (β2AR) in dendritic cells and trafficking of G protein-coupled receptors (Bunnett and Cottrell, 2010; Feinstein et al., 2011; Choy et al., 2014; Bowman et al., 2016; McGarvey et al., 2016; Pavlos and Friedman, 2017; Bahouth and Nooh, 2017; Sposini et al., 2017). The retromer is known to carry cargo from endosomes to the trans-Golgi network (TGN), performing retrograde transport, as well as carrying cargo from endosomes to the plasma membrane, allowing recycling of membrane bound receptors (Trousdale and Kim, 2015). Moreover, included in the list of retromer cargo, are degradative enzymes such as Cathepsin D, which are important for lysosomal function and could potentially influence autophagic flux. Furthermore, amyloid precursor protein (APP) and α-synuclein (SNCA) are also reported to be sorted by the retromer complex (Miura et al., 2014; Li et al., 2016; Gallon and Cullen, 2015; Aufschnaiter et al., 2017; Follett et al., 2017, 2014a; Reitz, 2018). These findings have sparked considerable interest in the contributions of the retromer to human diseases.

PROPOSED MECHANISMS OF VPS35 IN NEURONAL DYSFUNCTION

The importance of the roles played by the retromer complex in signal transduction and receptor trafficking points to the dysfunction of the retromer as the major potential mechanism of neuronal degeneration caused by the VPS35 D620N mutation (Follett et al., 2017, 2014a; Small and Petsko, 2015; Wang and Bellen, 2015; Reitz, 2018). Knockdown of VPS35 leads to the degradation of VPS29 and vice-versa (Fuse et al., 2015). Therefore, given that any free VPS35, existing outside the retromer complex, is rapidly degraded, the role of VPS35 D620N in PD is likely to involve altered retromer function. Trafficking defects of AMPA receptors was reported in a VPS35 heterozygote mouse model as well as cultured mouse hippocampal and cortical neurons treated with VPS35 shRNA (Munsie et al., 2015; Tian et al., 2015). Additionally, dopamine receptor D1 (DRD1) is also reported to be recycled with the involvement of VPS35 (Wang et al., 2016a).

Studies have reported reduced α-synuclein degradation in VPS35-deficient cells (Braschi et al., 2010; Miura et al., 2014; Sugiura et al., 2014; Tang et al., 2015a,b). Formation of toxic α-synuclein aggregates and fibril formation are hallmarks of PD (Patel and Witt, 2018). A study conducted by Menšíková et al.

(2018) identified a VPS35 mutation and a FBXO7 mutation in a patient that displayed profuse Lewy body pathology in various brain regions, including the substantia nigra and other midbrain regions (Menšíková et al., 2018). This accumulation has classically been attributed to abnormal sorting of degradative enzymes that are normally targeted to the lysosome. However, this accumulation could also be partially explained by autophagy defects, similar to what has been reported in HeLa cells expressing the VPS35 D620N mutation (Mcgough et al., 2014; Zavodszky et al., 2014). The mechanism proposed in this study, for the autophagy disruption, was impaired WASH (Wiskott–Aldrich syndrome protein and SCAR homolog) complex association. Given that autophagy is a major process responsible for removing proteins, macromolecules and organelles (Gatica et al., 2018), this is another potential mechanism for the neurodegeneration caused by VPS35 (Barth et al., 2010; Lynch-Day et al., 2012; Tofaris, 2012).

Furthermore, defects in mitochondrial fusion and function have also been reported in some studies (Tang et al., 2015a,b; Wang et al., 2016b). Mitochondrial dysfunction has been shown to affect neuronal function severely and is believed to be a driving force of neurodegeneration (Hauser and Hastings, 2013; Mullin and Schapira, 2013; Subramaniam and Chesselet, 2013; Haelterman et al., 2014; Winklhofer, 2014). Also, it is noteworthy that autophagy is the only means by which damaged mitochondria are turned over (Ashrafi and Schwarz, 2013). Therefore, disruption in autophagy due to VPS35 D620N mutation may also result in, if not exacerbate, any mitochondrial dysfunction that may be directed by the VPS35 D620N mutation.

CURRENT MODEL ORGANISMS AND SYSTEMS FOR STUDYING VPS35

Cell Culture

A variety of tissue culture model systems are available for studying the structure and function of VPS35, and the pathogenic effects of its mutations. SH-SY5Y neuroblastoma cells can easily be induced to adopt a dopaminergic state by treatment with retinoic acid (Korecka et al., 2013; Krishna et al., 2014; Shipley et al., 2016). This system was used by Tang et al. (2015a,b) to demonstrate mitochondrial impairment due to VPS35 deficiency as well as due to the D620N mutation (Tang et al., 2015a,b). This system was also used to characterize the role of VPS35 in lysosomal clearance of AIMP2, which is a substrate of the PD associated gene, Parkin (Yun et al., 2017). Microglial BV2 cells have been used to understand the role of VPS35 in Alzheimer's Disease, and microglial physiology (Lucin et al., 2013; Yin et al., 2016). In addition, HEK 293T cells also present a popular choice for understanding cellular pathways affected by VPS35 and retromer function due to their high plasmid transfection efficiency (Yang et al., 2008; Follett et al., 2014b; Williams et al., 2018). McGough et al. (2014) used HeLa and RPE-1 cell lines to establish the interaction of VPS35 and FAM21 of the WASH complex (Mcgough et al., 2014). Cell lines can readily be transfected or virally transduced with an siRNA, shRNA or overexpression vectors to modulate the expression of VPS35 and other genes of interest (Nayerossadat et al., 2012). Korolchuk et al. (2007) knocked down VPS35 in Drosophila S2 cells using an RNAi approach, in order to identify novel proteins important for endocytosis, where candidate proteins were selected based on binding predictions to either α adaptin or clathrin heavy chain, or on having a predicted membrane bending domain (such as the BAR domain). These candidate proteins were then knocked down to screen for subsequent endocytosis defects. VPS35 was among the short list of proteins that were identified as exhibiting a significant reduction in endocytosis, where the effect due to VPS35 was the most severe (Korolchuk et al., 2007).

In addition to immortalized cell lines, primary neuronal and glial cultures have also been used to investigate VPS35 functions and mutations (Wen et al., 2011; Tsika et al., 2014; Tang et al., 2015a,b; Williams et al., 2018). Tang et al. (2015a,b) isolated and cultured dopaminergic neurons from brains of mice expressing microRNA directed against VPS35 (Tang et al., 2015a,b). These cells were found to have a reduced expression of MFN-2 or Mitofusin, and exhibited mitochondrial fragmentation, as well as impaired mitochondrial function. Similar results were obtained using SH-SY5Y and NLT neuroblastoma cultures (Tang et al., 2015a,b). In the study conducted by Tsika et al. (2014), rat primary cortical cultures were used to show that overexpression of human VPS35 resulted in neuronal cell death and higher sensitivity to cellular stress factors associated with PD (Tsika et al., 2014). Wen et al. (2011) demonstrated using mouse hippocampal slice cultures that VPS35 haploinsufficiency exacerbates long-term potentiation impairment already present in mice expressing Swedish mutant form of the amyloid precursor protein (Wen et al., 2011). Williams et al. (2018) discovered a novel link between the PD gene, Parkin, and VPS35, wherein Parkin mediates ubiquitination of VPS35, which does not affect VPS35 turnover, but may have a role to play in the retromer-mediated endosomal sorting (Williams et al., 2018). Using primary cortical neurons, they identified ATG9A, a WASH-dependent retromer cargo, to be missorted upon silencing of the Parkin gene. Using cell lines and primary cultures can therefore be very powerful tools for deciphering molecular mechanisms under precisely controlled conditions.

Mice

Homozygous knockout of VPS35 is embryonically lethal in mice. To overcome this challenge several mice models have been developed, including a hemizygous deletion mutant (Wen et al., 2011). This mutant was used to demonstrate that VPS35 interacts with the protease BACE-1, predominantly responsible for Amyloid beta production, and that VPS35 reduction increases BACE-1 activity in the mouse hippocampus. In addition, A VPS35 D620N knock-in strain of mice has been developed recently by Cataldi et al. (2018), in collaboration with Jackson Laboratories, to further characterize dopamine release and monoamine transporters in a VPS35 D620N

mutant background (Cataldi et al., 2018). These mice were generated by Cre-recombinase-mediated recombination of the VPS35 exon 15, on chromosome 8. Subsequent assessment revealed no detectable movement disorder in these transgenic mice compared with non-transgenic controls. However, the dopamine turnover was reported to be increased. Dopamine transporter levels were reported to have been reduced while vesicular monoamine transporter levels were increased (Cataldi et al., 2018). Mir and colleagues (2018) used these same mice to study the interaction between LRRK2 and VPS35 (Mir et al., 2018). Using this model, they were able to demonstrate that the VPS35 D620N mutation increases LRRK2-catalyzed phosphorylation of three different RAB proteins, RAB 8a, 10 and 12. They concluded that the VPS35 D620N mutation causes a gain of function with respect to the kinase activity of LRRK2 and is an upstream regulator (Mir et al., 2018). A similar mouse model, generated using a CRISPR/Cas-9-mediated knock-in strategy, was used previously by Ishizu et al. (2016) to characterize reduced dopamine release in the striatum of heterozygous mice with one gene copy of VPS35 D620N knocked in ($VPS35^{D620N\ KI}$), while the other copy had one base pair deleted in exon 15, creating a premature stop codon, referred to as $VPS35^{Del1}$ (Ishizu et al., 2016). These $VPS35^{D620NKI}$/$VPS35^{Del1}$ heterozygous mice also displayed premature death and significant neurodegeneration throughout life, indicating that this model could be of considerable value for Parkinson's Disease research.

Rat

A transgenic rat model generated via lentivirus-mediated gene transfer has been described and utilized by Tsika et al. (2014). These rats overexpressed one of two human VPS35 constructs, one of wild-type and the other containing the D620N mutation. However, the researchers concluded that the human D620N construct did not alter vesicular sorting of retromer cargo proteins in primary cortical neurons from these animals. They went on to confirm this finding in yeast and human (patient donated) fibroblasts. Contrary to this finding, the human VPS35 D620N overexpression was found to induce neurodegeneration in the substantia nigra of these rats suggesting that, in this model, VPS35 D620N might be primarily causing neuronal loss without altering retromer function (Tsika et al., 2014).

Drosophila melanogaster. MacLeod et al. (2013) used an overexpression vector to demonstrate that overexpression of wild-type VPS35 reduced the defects caused by LRRK2 G2019S mutation, and those caused by RAB7L1 knockdown. This was shown in LRRK2 mutant flies and primary rat neuronal cultures (MacLeod et al., 2013). Similarly, a VPS35 overexpressing strain of flies was used by Linhart et al. in 2014, to demonstrate the rescue of LRRK mutation derived eye defects, by eye specific VPS35 overexpression in Drosophila (Linhart et al., 2014). In another study, flies with the Drosophila VPS35 (dVps35) knocked out, were shown to be embryonically lethal (Inoshita et al., 2017). This lethality could not be rescued by knock-in of human VPS35 wild-type or human VPS35 D620N. However, it was rescued by knock-in of dVps35 WT and by knocking in dVps35 D647N (the Drosophila analog of the D620N mutation in humans). Using transgenic flies expressing wild-type dVps35 or dVps35 D647N, in all three possible dVps35 heterozygote and homozygote backgrounds (+/+, +/−, −/−), they were then able to demonstrate that Drosophila LRRK (dLRRK) and dVps35 affect synaptic architecture and endocytosis via the same pathways (Inoshita et al., 2017).

Yeast and *Caenorhabditis elegans*

In 2006, Prasad and Clark identified the retromer as an important component in Wnt signaling-mediated neuronal polarity in *Caenorhabditis elegans*. In a mutagenesis screen, they identified a *vps-35* deletion mutant that resulted in reversed polarity of the mechanosensory neurons ALM and PLM. This defect was rescued by overexpressing *vps-35* specifically in Wnt-expressing muscle and epidermal cells, but not in the neurons themselves (Prasad and Clark, 2006). This presents an important mechanistic role of VPS35, because the role of Wnt signaling in PD has been described in literature (Berwick and Harvey, 2012; Salašová et al., 2017). Dhungel et al. (2015) discovered that in VPS35-deficient yeast cells, EIF4G1 upregulation was highly toxic, but the two mutations by themselves were not lethal (Dhungel et al., 2015). EIF4G1 is a translation initiation factor scaffold protein, responsible for the translation initiation complex formation (Villa et al., 2013). While they could not establish a direct interaction between the two proteins, a few common pathways were identified leading to the hypothesis that they were functionally related. The authors also noted that in a VPS35 null background, overexpression of EIF4G1 resulted in fewer but larger synaptic boutons. This group then investigated proteotoxic stress in yeast cells and activation of the unfolded protein response (UPR). It was seen that there was increased proteotoxic stress and UPR activation in VPS35 deletion mutants, only upon overexpressing EIF4G1. This led to the conclusion that the EIF4G1 upregulation combined with retromer dysfunction was causing toxic protein aggregation. In addition, this group demonstrated that Sortillin functions downstream of VPS35 or in parallel and is able to suppress the EIF4G1 overexpression toxicity in VPS35 deletion mutants. Lastly, this group showed, using yeast, *C. elegans* and transgenic mice that VPS35 deletion increases alpha synuclein-driven toxicity. In transgenic mice, increased toxicity was also seen after overexpression of VPS35 D620N and VPS35 P316S (Dhungel et al., 2015). Therefore, altered VPS35 function can facilitate protein aggregation, a hallmark of PD. Furthermore, Zhang et al. (2018) demonstrated using a *vps35* deletion mutant strain of *C. elegans* that VPS35 is required for propagating the mitochondrial unfolded protein response (UPR^{mt}) from cells undergoing mitochondrial stress to surrounding cells. Here, VPS35 and the retromer was proposed to be involved in the retrieval of a Wnt secretion factor, MIG-14, which in turn, played a role in secretion of the Wnt protein EGL-20. This led to the conclusion that

EGL-20 was acting as a ‘‘mitokine” signal that induced UPRmt in a cell-non-autonomous manner in the surrounding cells and required functional retromer activity (Zhang et al., 2018).

FUTURE RESEARCH DIRECTIONS

With the advent of CRISPR/Cas-9-mediated genome editing technology, therapeutic applications targeting the VPS35 gene can now be conceived (Calatayud et al., 2017). This could potentially be done in inducible pluripotent stem cells, obtained from a patient, genetically modified and transplanted into the affected individual’s brain. This technique has recently been described and is awaiting U.S Food and Drug Administration approval (Loring, 2018). A major obstacle in such an approach is the prion like properties of α-synuclein aggregates (Brundin and Melki, 2017). The pre-existing toxic α-synuclein aggregates in the patient’s existing brain environment may induce the formation of α-synuclein fibrils in the transplanted cells, thus negating any genetic corrections made in the transplanted cells. Supporting this concern, previous clinical trials involving the transplantation of embryonically derived grafts have shown synucleinopathy in the transplanted cells upon autopsy (Kordower et al., 2008; Li et al., 2008).

In addition, further characterization of the VPS35 D620N knock-in mice is now required to properly investigate the cellular pathways that are perturbed. This *in vivo* model system will allow for a more direct comparison of a mouse model system and human disease without the artifacts association with overexpression and/or random integration of a transgene using virus conventional transgenic mouse generation. The creation of a PD-relevant cell line containing the D620N mutation in the endogenous VPS35 gene would add validity to findings already reported using cells that have a VPS35 D620N construct stably overexpressed. Finally, characterization of the pathways perturbed by mutations in VPS35, is far from complete. A better understanding of the interplay of VPS35 and these pathways is required, so that therapeutic interventions can be crafted.

ACKNOWLEDGEMENTS

This work was supported by the Institutional Development Awards (IDeA) from the National Institute of General Medical Sciences (grants P20GM103408 and P20GM109095) and the National Institute of Neurological Disorders and Stroke (grant R15NS096702) of the National Institutes of Health. Additional support was provided by The Biomolecular Research Center at Boise State University.

REFERENCES

Ando M, Funayama M, Li Y, Kashihara K, Murakami Y, Ishizu N, Toyoda C, Noguchi K, Hashimoto T, Nakano N, Sasaki R, Kokubo Y, Kuzuhara S, Ogaki K, Yamashita C, Yoshino H, Hatano T, Tomiyama H, Hattori N (2012) *VPS35* mutation in Japanese patients with typical Parkinson’s disease. Mov Disord 27:1413–1417. https://doi.org/10.1002/mds.25145.

Appel JR, Ye S, Tang F, Sun D, Zhang H, Mei L, Xiong W-C (2018) Increased microglial activity, impaired adult hippocampal neurogenesis, and depressive-like behavior in microglial VPS35-depleted mice. J Neurosci 38:5949–5968. https://doi.org/10.1523/JNEUROSCI.3621-17.2018.

Arighi CN, Hartnell LM, Aguilar RC, Haft CR, Bonifacino JS (2004) Role of the mammalian retromer in sorting of the cation-independent mannose 6-phosphate receptor. J Cell Biol 165:123–133. https://doi.org/10.1083/jcb.200312055.

Ascherio A, Schwarzschild MA (2016) The epidemiology of Parkinson’s disease: risk factors and prevention. Lancet Neurol 15:1257–1272. https://doi.org/10.1016/S1474-4422(16)30230-7.

Ashrafi G, Schwarz TL (2013) The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ 20:31–42. https://doi.org/10.1038/cdd.2012.81.

Aufschnaiter A, Kohler V, Büttner S (2017) Taking out the garbage: cathepsin D and calcineurin in neurodegeneration. Neural Regen Res 12:1776. https://doi.org/10.4103/1673-5374.219031.

Bahouth SW, Nooh MM (2017) Barcoding of GPCR trafficking and signaling through the various trafficking roadmaps by compartmentalized signaling networks. Cell Signal 36:42–55. https://doi.org/10.1016/j.cellsig.2017.04.015.

Barth S, Glick D, Macleod KF (2010) Autophagy: Assays and artifacts. J Pathol 221:117–124. https://doi.org/10.1002/path.2694.

Beard JD, Steege AL, Ju J, Lu J, Luckhaupt SE, Schubauer-Berigan MK (2017) Mortality from amyotrophic lateral sclerosis and Parkinson’s disease among different occupation groups – United States, 1985–2011. MMWR Morb Mortal Wkly Rep 66:718–722. https://doi.org/10.15585/mmwr.mm6627a2.

Belenkaya TY, Wu Y, Tang X, Zhou B, Cheng L, Sharma YV, Yan D, Selva EM, Lin X (2008) The retromer complex influences Wnt secretion by recycling Wntless from endosomes to the trans-golgi network. Dev Cell 14:120–131. https://doi.org/10.1016/j.devcel.2007.12.003.

Berwick DC, Harvey K (2012) The importance of Wnt signalling for neurodegeneration in Parkinson’s disease. Biochem Soc Trans 40:1123–1128. https://doi.org/10.1042/BST20120122.

Blanckenberg J, Ntsapi C, Carr JA, Bardien S (2014) EIF4G1 R1205H and VPS35 D620N mutations are rare in Parkinson’s disease from South Africa. Neurobiol Aging 35:445. https://doi.org/10.1016/j.neurobiolaging.2013.08.023. 445.e1-3.

Bonifacino JS, Hurley JH (2008). Retromer Curr Opin Cell Biol 20:427–436. https://doi.org/10.1016/j.ceb.2008.03.009.

Bowman SL, Shiwarski DJ, Puthenveedu MA (2016) Distinct G protein-coupled receptor recycling pathways allow spatial control of downstream G protein signaling. J Cell Biol 214:797–806. https://doi.org/10.1083/jcb.201512068.

Braschi E, Goyon V, Zunino R, Mohanty A, Xu L, McBride HM (2010) Vps35 mediates vesicle transport between the mitochondria and peroxisomes. Curr Biol 20:1310–1315. https://doi.org/10.1016/j.cub.2010.05.066.

Brundin P, Melki R (2017) Prying into the prion hypothesis for Parkinson’s disease. J Neurosci 37:9808–9818. https://doi.org/10.1523/JNEUROSCI.1788-16.2017.

Bunnett NW, Cottrell GS (2010) Trafficking and signaling of G protein-coupled receptors in the nervous system: implications for disease and therapy. CNS Neurol Disord Drug Targets 9:539–556.

Calatayud C, Carola G, Consiglio A, Raya A (2017) Modeling the genetic complexity of Parkinson’s disease by targeted genome edition in iPS cells. Curr Opin Genet Dev 46:123–131. https://doi.org/10.1016/j.gde.2017.06.002.

Cataldi S, Follett J, Fox JD, Tatarnikov I, Kadgien C, Gustavsson EK, Khinda J, Milnerwood AJ, Farrer MJ (2018) Altered dopamine release and monoamine transporters in Vps35 p.D620N knock-in mice. npj Park Dis 4:27. https://doi.org/10.1038/s41531-018-0063-3.

Chan ASM, Clairfeuille T, Landao-Bassonga E, Kinna G, Ng PY, Loo LS, Cheng TS, Zheng M, Hong W, Teasdale RD, Collins BM, Pavlos NJ (2016) Sorting nexin 27 couples PTHR trafficking to

retromer for signal regulation in osteoblasts during bone growth. Mol Biol Cell 27:1367–1382. https://doi.org/10.1091/mbc.E15-12-0851.

Chen Y, Chen K, Song W, Chen X, Cao B, Huang R, Zhao B, Guo X, Burgunder J, Li J, Shang H-F (2013) VPS35 Asp620Asn and EIF4G1 Arg1205His mutations are rare in Parkinson disease from Southwest China. Neurobiol Aging 34:1709.e7–1709.e8. https://doi.org/10.1016/j.neurobiolaging.2012.11.003.

Choy RW-Y, Park M, Temkin P, Herring BE, Marley A, Nicoll RA, von Zastrow M (2014) Retromer Mediates a Discrete Route of Local Membrane Delivery to Dendrites. Neuron 82:55–62. https://doi.org/10.1016/j.neuron.2014.02.018.

Deng H, Gao K, Jankovic J (2013) The *VPS35* gene and Parkinson's disease. Mov Disord 28:569–575. https://doi.org/10.1002/mds.25430.

Deng H, Xu H, Deng X, Song Z, Zheng W, Gao K, Fan X, Tang J (2012) VPS35 mutation in Chinese Han patients with late-onset Parkinson's disease. Eur J Neurol 19:e96–e97. https://doi.org/10.1111/j.1468-1331.2012.03800.x.

Dhungel N, Eleuteri S, Li L, Kramer NJ, Chartron JW, Spencer B, Kosberg K, Fields JA, Stafa K, Adame A, Lashuel H, Frydman J, Shen K, Masliah E, Gitler AD (2015) Parkinson's Disease Genes VPS35 and EIF4G1 Interact Genetically and Converge on α-Synuclein. Neuron 85:76–87. https://doi.org/10.1016/j.neuron.2014.11.027.

Elbaz A, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA (2002) Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol 55:25–31. https://doi.org/10.1016/S0895-4356(01)00425-5.

Feinstein TN, Wehbi VL, Ardura JA, Wheeler DS, Ferrandon S, Gardella TJ, Vilardaga J-P (2011) Retromer terminates the generation of cAMP by internalized PTH receptors. Nat Chem Biol 7:278–284. https://doi.org/10.1038/nchembio.545.

Follett J, Bugarcic A, Collins BM, Teasdale RD (2017) Retromer's role in endosomal trafficking and impaired function in neurodegenerative diseases. Curr Protein Pept Sci 18:687–701. https://doi.org/10.2174/1389203717666160311121246.

Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA, Collins BM, Bugarcic A, Teasdale RD (2014a) The Vps35 D620N mutation linked to Parkinson's disease disrupts the cargo sorting function of retromer. Traffic 15:230–244. https://doi.org/10.1111/tra.12136.

Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA, Collins BM, Bugarcic A, Teasdale RD (2014b) The Vps35 D620N Mutation Linked to Parkinson's Disease Disrupts the Cargo Sorting Function of Retromer. Traffic 15:230–244. https://doi.org/10.1111/tra.12136.

Fuse A, Furuya N, Kakuta S, Inose A, Sato M, Koike M, Saiki S, Hattori N (2015) VPS29-VPS35 intermediate of retromer is stable and may be involved in the retromer complex assembly process. FEBS Lett 589:1430–1436. https://doi.org/10.1016/j.febslet.2015.04.040.

Gagliardi M, Annesi G, Tarantino P, Nicoletti G, Quattrone A (2014) Frequency of the ASP620ASN mutation in VPS35 and Arg1205His mutation in EIF4G1 in familial Parkinson's disease from South Italy. Neurobiol Aging 35:2422.e1–2422.e2. https://doi.org/10.1016/j.neurobiolaging.2014.04.020.

Gallon M, Cullen PJ (2015) Retromer and sorting nexins in endosomal sorting. Biochem Soc Trans 43:33–47. https://doi.org/10.1042/BST20140290.

Gambardella S, Biagioni F, Ferese R, Busceti CL, Frati A, Novelli G, Ruggieri S, Fornai F (2016) Vacuolar protein sorting genes in Parkinson's disease: a re-appraisal of mutations detection rate and neurobiology of disease. Front Neurosci 10:532. https://doi.org/10.3389/fnins.2016.00532.

Gatica D, Lahiri V, Klionsky DJ (2018) Cargo recognition and degradation by selective autophagy. Nat Cell Biol 20:233–242. https://doi.org/10.1038/s41556-018-0037-z.

Goswami P, Joshi N, Singh S (2017) Neurodegenerative signaling factors and mechanisms in Parkinson's pathology. Toxicol Vitr 43:104–112. https://doi.org/10.1016/j.tiv.2017.06.008.

Guella I, Soldà G, Cilia R, Pezzoli G, Asselta R, Duga S, Goldwurm S (2012) The Asp620asn mutation in VPS35 is not a common cause of familial Parkinson's disease. Mov Disord 27:800–801. https://doi.org/10.1002/mds.24927.

Guo J, Sun Q, Lv Z, Yu R, Li K, Zhang Y, Tian J, Xia K, Yan X, Tang B (2012) VPS35 gene variants are not associated with Parkinson's disease in the mainland Chinese population. Parkinsonism Relat Disord 18:983–985. https://doi.org/10.1016/j.parkreldis.2012.05.002.

Gustavsson EK, Guella I, Trinh J, Szu-Tu C, Rajput A, Rajput AH, Steele JC, McKeown M, Jeon BS, Aasly JO, Farrer MJ (2015) Genetic variability of the retromer cargo recognition complex in parkinsonism. Mov Disord 30:580–584. https://doi.org/10.1002/mds.26104.

Haelterman NA, Yoon WH, Sandoval H, Jaiswal M, Shulman JM, Bellen HJ (2014) A mitocentric view of Parkinson's disease. Annu Rev Neurosci 37:137–159. https://doi.org/10.1146/annurev-neuro-071013-014317.

Hauser DN, Hastings TG (2013) Mitochondrial dysfunction and oxidative stress in Parkinson's disease and monogenic parkinsonism. Neurobiol Dis 51:35–42. https://doi.org/10.1016/j.nbd.2012.10.011.

Helley MP, Pinnell J, Sportelli C, Tieu K (2017) Mitochondria: a common target for genetic mutations and environmental toxicants in Parkinson's disease. Front Genet 8:177. https://doi.org/10.3389/fgene.2017.00177.

Inoshita T, Arano T, Hosaka Y, Meng H, Umezaki Y, Kosugi S, Morimoto T, Koike M, Chang H-Y, Imai Y, Hattori N (2017) Vps35 in cooperation with LRRK2 regulates synaptic vesicle endocytosis through the endosomal pathway in Drosophila. Hum Mol Genet 26:2933–2948. https://doi.org/10.1093/hmg/ddx179.

Ishizu N, Yui D, Hebisawa A, Aizawa H, Cui W, Fujita Y, Hashimoto K, Ajioka I, Mizusawa H, Yokota T, Watase K (2016) Impaired striatal dopamine release in homozygous Vps35 D620N knock-in mice. Hum Mol Genet 25:ddw279. https://doi.org/10.1093/hmg/ddw279.

Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW (2008) Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 14:504–506. https://doi.org/10.1038/nm1747.

Korecka JA, van Kesteren RE, Blaas E, Spitzer SO, Kamstra JH, Smit AB, Swaab DF, Verhaagen J, Bossers K (2013) Phenotypic characterization of retinoic acid differentiated SH-SY5Y cells by transcriptional profiling. PLoS One 8. https://doi.org/10.1371/journal.pone.0063862 e63862.

Korolchuk VI, Schutz MM, Gomez-Llorente C, Rocha J, Lansu NR, Collins SM, Wairkar YP, Robinson IM, O'Kane CJ (2007) Drosophila Vps35 function is necessary for normal endocytic trafficking and actin cytoskeleton organisation. J Cell Sci 120:4367–4376. https://doi.org/10.1242/jcs.012336.

Koschmidder E, Mollenhauer B, Kasten M, Klein C, Lohmann K (2014) Mutations in VPS26A are not a frequent cause of Parkinson's disease. Neurobiol Aging 35. https://doi.org/10.1016/j.neurobiolaging.2013.12.016. 1512.e1-2.

Kovtun O, Leneva N, Bykov YS, Ariotti N, Teasdale RD, Schaffer M, Engel BD, Owen DJ, Briggs JAG, Collins BM (2018) Structure of the membrane-assembled retromer coat determined by cryo-electron tomography. Nature 561:561–564. https://doi.org/10.1038/s41586-018-0526-z.

Krishna A, Biryukov M, Trefois C, Antony PMA, Hussong R, Lin J, Heinäniemi M, Glusman G, Köglsberger S, Boyd O, van den Berg BHJ, Linke D, Huang D, Wang K, Hood L, Tholey A, Schneider R, Galas DJ, Balling R, May P (2014) Systems genomics evaluation of the SH-SY5Y neuroblastoma cell line as a model for Parkinson's disease. BMC Genomics 15:1154. https://doi.org/10.1186/1471-2164-15-1154.

Kumar KR, Weissbach A, Heldmann M, Kasten M, Tunc S, Sue CM, Svetel M, Kostić VS, Segura-Aguilar J, Ramirez A, Simon DK, Vieregge P, Münte TF, Hagenah J, Klein C, Lohmann K (2012) Frequency of the D620N mutation in VPS35 in Parkinson disease.

Arch Neurol 69:1360–1364. https://doi.org/10.1001/archneurol.2011.3367.
Lau LML De, Breteler MMB (2006) Epidemiology of Parkinson's disease. Lancet Neurol 5:525–535. https://doi.org/10.1016/S1474-4422(06)70471-9.
Lesage S, Condroyer C, Klebe S, Honore A, Tison F, Brefel-Courbon C, Durr A, Brice A (2012) Identification of VPS35 mutations replicated in French families with Parkinson disease. Neurology 78:1449–1450. https://doi.org/10.1212/WNL.0b013e318253d5f2.
Li C, Shah SZA, Zhao D, Yang L (2016) Role of the retromer complex in neurodegenerative diseases. Front Aging Neurosci 8:42. https://doi.org/10.3389/fnagi.2016.00042.
Li J-Y, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Björklund A, Widner H, Revesz T, Lindvall O, Brundin P (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 14:501–503. https://doi.org/10.1038/nm1746.
Linhart R, Wong S, Cao J, Tran M, Huynh A, Ardrey C, Park J, Hsu C, Taha S, Peterson R, Shea S, Kurian J, Venderova K (2014) Vacuolar protein sorting 35 (Vps35) rescues locomotor deficits and shortened lifespan in Drosophila expressing a Parkinson's disease mutant of Leucine-rich repeat kinase 2 (LRRK2). Mol Neurodegener 9:23. https://doi.org/10.1186/1750-1326-9-23.
Loring JF (2018) Autologous Induced Pluripotent Stem Cell-Derived Neurons to Treat Parkinson's Disease. Stem Cells Dev 27:958–959. https://doi.org/10.1089/scd.2018.0107.
Lucas M, Gershlick DC, Vidaurrazaga A, Rojas AL, Bonifacino JS, Hierro A (2016) Structural Mechanism for Cargo Recognition by the Retromer Complex. Cell 167:1623–1635.e14. https://doi.org/10.1016/j.cell.2016.10.056.
Lucin KM, O'Brien CE, Bieri G, Czirr E, Mosher KI, Abbey RJ, Mastroeni DF, Rogers J, Spencer B, Masliah E, Wyss-Coray T (2013) Microglial Beclin 1 Regulates Retromer Trafficking and Phagocytosis and Is Impaired in Alzheimer's Disease. Neuron 79:873–886. https://doi.org/10.1016/j.neuron.2013.06.046.
Lynch-Day MA, Mao K, Wang K, Zhao M, Klionsky DJ (2012) The role of autophagy in Parkinson's disease. Cold Spring Harb Perspect Med 2. https://doi.org/10.1101/cshperspect.a009357.
MacLeod DA, Rhinn H, Kuwahara T, Zolin A, Di Paolo G, McCabe BD, MacCabe BD, Marder KS, Honig LS, Clark LN, Small SA, Abeliovich A (2013) RAB7L1 interacts with LRRK2 to modify intraneuronal protein sorting and Parkinson's disease risk. Neuron 77:425–439. https://doi.org/10.1016/j.neuron.2012.11.033.
Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW, Abbott RD, Savica R, Van Den Eeden SK, Willis AW, Tanner C (2018) Prevalence of Parkinson's disease across North America. npj Park Dis 4:21. https://doi.org/10.1038/s41531-018-0058-0.
McGarvey JC, Xiao K, Bowman SL, Mamonova T, Zhang Q, Bisello A, Sneddon WB, Ardura JA, Jean-Alphonse F, Vilardaga J-P, Puthenveedu MA, Friedman PA (2016) Actin-sorting Nexin 27 (SNX27)-retromer complex mediates rapid parathyroid hormone receptor recycling. J Biol Chem 291:10986–11002. https://doi.org/10.1074/jbc.M115.697045.
McGough IJ, Cullen PJ (2011) Recent advances in retromer biology. Traffic 12:963–971. https://doi.org/10.1111/j.1600-0854.2011.01201.x.
Mcgough IJ, Steinberg F, Jia D, Barbuti PA, Mcmillan KJ, Heesom KJ, Whone AL, Caldwell MA, Billadeau DD, Rosen MK, Cullen PJ (2014) Report retromer binding to FAM21 and the WASH complex is perturbed by the parkinson disease-linked VPS35 (D620N) mutation. Curr Biol 24:1670–1676. https://doi.org/10.1016/j.cub.2014.06.024.
Menšíková K, Tučková L, Kolařiková K, Bartoníková T, Vodička R, Ehrmann J, Vrtěl R, Procházka M, Kaňovský P, Kovacs GG (2018) Atypical parkinsonism of progressive supranuclear palsy–parkinsonism (PSP-P) phenotype with rare variants in FBXO7 and VPS35 genes associated with Lewy body pathology. Acta Neuropathol. https://doi.org/10.1007/s00401-018-1923-y.
Mir R, Tonelli F, Lis P, Macartney T, Polinski NK, Martinez TN, Chou M-Y, Howden AJM, König T, Hotzy C, Milenkovic I, Brücke T, Zimprich A, Sammler E, Alessi DR (2018) The Parkinson's disease VPS35[D620N] mutation enhances LRRK2-mediated Rab protein phosphorylation in mouse and human. Biochem J 475:1861–1883. https://doi.org/10.1042/BCJ20180248.
Miura E, Hasegawa T, Konno M, Suzuki M, Sugeno N, Fujikake N, Geisler S, Tabuchi M, Oshima R, Kikuchi A, Baba T, Wada K, Nagai Y, Takeda A, Aoki M (2014) VPS35 dysfunction impairs lysosomal degradation of α-synuclein and exacerbates neurotoxicity in a Drosophila model of Parkinson's disease. Neurobiol Dis 71:1–13. https://doi.org/10.1016/j.nbd.2014.07.014.
Mullin S, Schapira A (2013) α-Synuclein and mitochondrial dysfunction in Parkinson's disease. Mol Neurobiol 47:587–597. https://doi.org/10.1007/s12035-013-8394-x.
Munsie LN, Milnerwood AJ, Seibler P, Beccano-Kelly DA, Tatarnikov I, Khinda J, Volta M, Kadgien C, Cao LP, Tapia L, Klein C, Farrer MJ (2015) Retromer-dependent neurotransmitter receptor trafficking to synapses is altered by the Parkinson's disease VPS35 mutation p. D620N. Hum Mol Genet 24:1691–1703. https://doi.org/10.1093/hmg/ddu582.
Nayerossadat N, Maedeh T, Ali PA (2012) Viral and nonviral delivery systems for gene delivery. Adv Biomed Res 1:27. https://doi.org/10.4103/2277-9175.98152.
Patel D, Witt SN (2018) Sorting out the role of α-synuclein in retromer-mediated endosomal protein sorting. J Exp Neurosci 12. https://doi.org/10.1177/1179069518796215. 117906951879621.
Pavlos NJ, Friedman PA (2017) GPCR Signaling and Trafficking: The Long and Short of It. Trends Endocrinol Metab 28:213–226. https://doi.org/10.1016/j.tem.2016.10.007.
Prasad BC, Clark SG (2006) Wnt signaling establishes anteroposterior neuronal polarity and requires retromer in C. elegans. Development 133:1757–1766. https://doi.org/10.1242/dev.02357.
Pringsheim T, Jette N, Frolkis A, Steeves TDL (2014) The prevalence of Parkinson's disease: A systematic review and meta-analysis. Mov Disord 29:1583–1590. https://doi.org/10.1002/mds.25945.
Reitz C (2018) Retromer dysfunction and neurodegenerative disease. Curr Genomics 19:279–288. https://doi.org/10.2174/1389202919666171024122809.
Salašová A, Yokota C, Potěšil D, Zdráhal Z, Bryja V, Arenas E (2017) A proteomic analysis of LRRK2 binding partners reveals interactions with multiple signaling components of the WNT/PCP pathway. Mol Neurodegener 12:54. https://doi.org/10.1186/s13024-017-0193-9.
Seaman MN, McCaffery JM, Emr SD (1998) A membrane coat complex essential for endosome-to-Golgi retrograde transport in yeast. J Cell Biol 142:665–681.
Seaman MNJ (2012) The retromer complex – endosomal protein recycling and beyond. J Cell Sci 125:4693–4702. https://doi.org/10.1242/jcs.103440.
Seaman MNJ, Harbour ME, Tattersall D, Read E, Bright N (2009) Membrane recruitment of the cargo-selective retromer subcomplex is catalysed by the small GTPase Rab7 and inhibited by the Rab-GAP TBC1D5. J Cell Sci 122:2371–2382. https://doi.org/10.1242/jcs.048686.
Shannon B, Soto-Ortolaza A, Rayaprolu S, Cannon HD, Labbé C, Benitez BA, Choi J, Lynch T, Boczarska-Jedynak M, Opala G, Krygowska-Wajs A, Barcikowska M, Van Gerpen JA, Uitti RJ, Springer W, Cruchaga C, Wszolek ZK, Ross OA (2014) Genetic variation of the retromer subunits VPS26A/B-VPS29 in Parkinson's disease. Neurobiol Aging 35:1958.e1–1958.e2. https://doi.org/10.1016/j.neurobiolaging.2014.03.004.
Sharma M, Ioannidis JPA, Aasly JO, Annesi G, Brice A, Bertram L, Bozi M, Barcikowska M, Crosiers D, Clarke CE, Facheris MF, Farrer M, Garraux G, Gispert S, Auburger G, Vilariño-Güell C, Hadjigeorgiou GM, Hicks AA, Hattori N, Jeon BS, Jamrozik Z, Krygowska-Wajs A, Lesage S, Lill CM, Lin J-J, Lynch T, Lichtner P, Lang AE, Libioulle C, Murata M, Mok V, Jasinska-Myga B, Mellick GD, Morrison KE, Meitnger T, Zimprich A, Opala G,

Pramstaller PP, Pichler I, Park SS, Quattrone A, Rogaeva E, Ross OA, Stefanis L, Stockton JD, Satake W, Silburn PA, Strom TM, Theuns J, Tan E-K, Toda T, Tomiyama H, Uitti RJ, Van Broeckhoven C, Wirdefeldt K, Wszolek Z, Xiromerisiou G, Yomono HS, Yueh K-C, Zhao Y, Gasser T, Maraganore D, Krüger R (2012) A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants. J Med Genet 49:721–726. https://doi.org/10.1136/jmedgenet-2012-101155.

Sheerin U-M, Charlesworth G, Bras J, Guerreiro R, Bhatia K, Foltynie T, Limousin P, Silveira-Moriyama L, Lees A, Wood N (2012) Screening for VPS35 mutations in Parkinson's disease. Neurobiol Aging 33. https://doi.org/10.1016/j.neurobiolaging.2011.10.032. 838.e1-5.

Shipley MM, Mangold CA, Szpara ML (2016) Differentiation of the SH-SY5Y human neuroblastoma cell line. J Vis Exp 1–11. https://doi.org/10.3791/53193.

Small SA, Kent K, Pierce A, Leung C, Kang MS, Okada H, Honig L, Vonsattel J-P, Kim T-W (2005) Model-guided microarray implicates the retromer complex in Alzheimer's disease. Ann Neurol 58:909–919. https://doi.org/10.1002/ana.20667.

Small SA, Petsko GA (2015) Retromer in Alzheimer disease, Parkinson disease and other neurological disorders. Nat Rev Neurosci 16:126–132. https://doi.org/10.1038/nrn3896.

Sposini S, Jean-Alphonse FG, Ayoub MA, Oqua A, West C, Lavery S, Brosens JJ, Reiter E, Hanyaloglu AC (2017) Integration of GPCR Signaling and Sorting from Very Early Endosomes via Opposing APPL1 Mechanisms. Cell Rep 21:2855–2867. https://doi.org/10.1016/j.celrep.2017.11.023.

Subramaniam SR, Chesselet M-F (2013) Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog Neurobiol 106–107:17–32. https://doi.org/10.1016/j.pneurobio.2013.04.004.

Sudhaman S, Behari M, Govindappa ST, Muthane UB, Juyal RC, Thelma BK (2013) VPS35 and EIF4G1 mutations are rare in Parkinson's disease among Indians. Neurobiol Aging 34:2442.e1–2442.e3. https://doi.org/10.1016/j.neurobiolaging.2013.04.025.

Sugiura A, McLelland G-L, Fon EA, McBride HM (2014) A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J 33:2142–2156. https://doi.org/10.15252/embj.201488104.

Surmeier DJ, Obeso JA, Halliday GM (2017) Parkinson's disease is not simply a prion disorder. J Neurosci 37:9799–9807. https://doi.org/10.1523/JNEUROSCI.1787-16.2017.

Tabuchi M, Yanatori I, Kawai Y, Kishi F (2010) Retromer-mediated direct sorting is required for proper endosomal recycling of the mammalian iron transporter DMT1. J Cell Sci 123:756–766. https://doi.org/10.1242/jcs.060574.

Tang F-L, Erion JR, Tian Y, Liu W, Yin D-M, Ye J, Tang B, Mei L, Xiong W-C (2015a) VPS35 in dopamine neurons is required for endosome-to-golgi retrieval of Lamp2a, a receptor of chaperone-mediated autophagy that is critical for –synuclein degradation and prevention of pathogenesis of Parkinson's disease. J Neurosci 35:10613–10628. https://doi.org/10.1523/JNEUROSCI.0042-15.2015.

Tang F-L, Liu W, Hu J-X, Erion JR, Ye J, Mei L, Xiong W-C (2015b) VPS35 deficiency or mutation causes dopaminergic neuronal loss by impairing mitochondrial fusion and function. Cell Rep 12:1631–1643. https://doi.org/10.1016/j.celrep.2015.08.001.

Taylor KSM, Cook JA, Counsell CE (2007) Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry 78:905–906. https://doi.org/10.1136/jnnp.2006.104695.

Tian Y, Tang F-L, Sun X, Wen L, Mei L, Tang B-S, Xiong W-C (2015) VPS35-deficiency results in an impaired AMPA receptor trafficking and decreased dendritic spine maturation. Mol Brain 8:70. https://doi.org/10.1186/s13041-015-0156-4.

Tofaris GK (2012) Lysosome-dependent pathways as a unifying theme in Parkinson's disease. Mov Disord 27:1364–1369. https://doi.org/10.1002/mds.25136.

Trousdale C, Kim K (2015) Retromer: Structure, function, and roles in mammalian disease. Eur J Cell Biol 94:513–521. https://doi.org/10.1016/j.ejcb.2015.07.002.

Tsika E, Glauser L, Moser R, Fiser A, Daniel G, Sheerin U-M, Lees A, Troncoso JC, Lewis PA, Bandopadhyay R, Schneider BL, Moore DJ (2014) Parkinson's disease-linked mutations in VPS35 induce dopaminergic neurodegeneration. Hum Mol Genet 23:4621–4638. https://doi.org/10.1093/hmg/ddu178.

Tysnes OB, Storstein A (2017) Epidemiology of Parkinson's disease. J Neural Transm 124:901–905. https://doi.org/10.1007/s00702-017-1686-y.

Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, Soto-Ortolaza AI, Cobb SA, Wilhoite GJ, Bacon JA, Behrouz Bahareh, Melrose HL, Hentati E, Puschmann A, Evans DM, Conibear E, Wasserman WW, Aasly JO, Burkhard PR, Djaldetti R, Ghika J, Hentati F, Krygowska-Wajs A, Lynch T, Melamed E, Rajput A, Rajput AH, Solida A, Wu RM, Uitti RJ, Wszolek ZK, Vingerhoets F, Farrer MJ (2011) VPS35 mutations in parkinson disease. Am J Hum Genet 89:162–167. https://doi.org/10.1016/j.ajhg.2011.06.001.

Villa N, Do A, Hershey JWB, Fraser CS (2013) Human eukaryotic initiation factor 4G (eIF4G) protein binds to eIF3c, -d, and -e to promote mRNA recruitment to the ribosome. J Biol Chem 288:32932–32940. https://doi.org/10.1074/jbc.M113.517011.

Wang C-L, Tang F-L, Peng Y, Shen C-Y, Mei L, Xiong W-C (2012) VPS35 regulates developing mouse hippocampal neuronal morphogenesis by promoting retrograde trafficking of BACE1. Biol Open 1:1248–1257. https://doi.org/10.1242/bio.20122451.

Wang C, Niu M, Zhou Z, Zheng X, Zhang L, Tian Y, Yu X, Bu G, Xu H, Ma Q, Zhang Y (2016a) VPS35 regulates cell surface recycling and signaling of dopamine receptor D1. Neurobiol Aging 46:22–31. https://doi.org/10.1016/j.neurobiolaging.2016.05.016.

Wang S, Bellen HJ (2015) The retromer complex in development and disease. Development 142:2392–2396. https://doi.org/10.1242/dev.123737.

Wang W, Wang X, Fujioka H, Hoppel C, Whone AL, Caldwell MA, Cullen PJ, Liu J, Zhu X (2016b) Parkinson's disease–associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. Nat Med 22:54–63. https://doi.org/10.1038/nm.3983.

Wen L, Tang F-L, Hong Y, Luo S-W, Wang C-L, He W, Shen C, Jung J-U, Xiong F, Lee D, Zhang Q-G, Brann D, Kim T-W, Yan R, Mei L, Xiong W-C (2011) VPS35 haploinsufficiency increases Alzheimer's disease neuropathology. J Cell Biol 195:765–779. https://doi.org/10.1083/jcb.201105109.

Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, Barker RA (2013) The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 84:1258–1264. https://doi.org/10.1136/jnnp-2013-305277.

Williams ET, Glauser L, Tsika E, Jiang H, Islam S, Moore DJ (2018) Parkin mediates the ubiquitination of VPS35 and modulates retromer-dependent endosomal sorting. Hum Mol Genet. https://doi.org/10.1093/hmg/ddy224.

Winklhofer KF (2014) Parkin and mitochondrial quality control: toward assembling the puzzle. Trends Cell Biol 24:332–341. https://doi.org/10.1016/j.tcb.2014.01.001.

Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J (2004) Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 75:637–639. https://doi.org/10.1136/JNNP.2003.020982.

Yang P-T, Lorenowicz MJ, Silhankova M, Coudreuse DYM, Betist MC, Korswagen HC (2008) Wnt signaling requires retromer-dependent recycling of MIG-14/Wntless in Wnt-producing cells. Dev Cell 14:140–147. https://doi.org/10.1016/J.DEVCEL.2007.12.004.

Yin J, Liu X, He Q, Zhou L, Yuan Z, Zhao S (2016) Vps35-dependent recycling of Trem2 regulates microglial function. Traffic 17:1286–1296. https://doi.org/10.1111/tra.12451.

Yun SP, Kim H, Ham S, Kwon S-H, Lee GH, Shin J-H, Lee SH, Ko HS, Lee Y (2017) VPS35 regulates parkin substrate AIMP2

toxicity by facilitating lysosomal clearance of AIMP2. Cell Death Dis 8:e2741. https://doi.org/10.1038/cddis.2017.157.

Zavodszky E, Seaman MNJ, Moreau K, Jimenez-Sanchez M, Breusegem SY, Harbour ME, Rubinsztein DC (2014) Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. Nat Commun 5:3828. https://doi.org/10.1038/ncomms4828.

Zhang P, Wu Y, Belenkaya TY, Lin X (2011) SNX3 controls Wingless/Wnt secretion through regulating retromer-dependent recycling of Wntless. Cell Res 21:1677–1690. https://doi.org/10.1038/cr.2011.167.

Zhang Q, Wu X, Chen P, Liu L, Xin N, Tian Y, Dillin A (2018) The mitochondrial unfolded protein response is mediated cell-non-autonomously by retromer-dependent Wnt signaling. Cell 174:870–883.e17. https://doi.org/10.1016/j.cell.2018.06.029.

Zhang Y, Chen S, Xiao Q, Cao L, Liu J, Rong T-Y, Ma J-F, Wang G, Wang Y, Chen S-D (2012) Vacuolar protein sorting 35 Asp620Asn mutation is rare in the ethnic Chinese population with Parkinson's disease. Parkinsonism Relat Disord 18:638–640. https://doi.org/10.1016/j.parkreldis.2012.02.011.

Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN, Haubenberger D, Spielberger S, Schulte EC, Lichtner P, Rossle SC, Klopp N, Wolf E, Seppi K, Pirker W, Presslauer S, Mollenhauer B, Katzenschlager R, Foki T, Hotzy C, Reinthaler E, Harutyunyan A, Kralovics R, Peters A, Zimprich F, Brücke T, Poewe W, Auff E, Trenkwalder C, Rost B, Ransmayr G, Winkelmann J, Meitinger T, Strom TM (2011) A Mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet 89:168–175. https://doi.org/10.1016/j.ajhg.2011.06.008.

(Received 22 October 2018, Accepted 8 January 2019)
(Available online 18 January 2019)