VPS35-Linked Parkinson’s Disease Resembles the Idiopathic Disease: A Review of Clinical Trials

Brim Bianca1*, Ransmayr Gerhard2, Zimprich Alexander1 and Struhal Walter1
1Department of Neurology, University Hospital Tulln, Alter Ziegelweg 10, 3430 Tulln Austria
2Department of Neurology, Kepler University Hospital Linz, Krankenhausstraße 9, 4021 Linz, Austria

Abstract

A new autosomal dominant Parkinson’s disease mutation in the VPS35 (Vacuolar sorting protein 35) gene has been discovered in 2011. The VPS35 gene encodes a key component of the membrane protein-recycling retromer complex. Consequences of the D620N mutation and retromer dysfunction are perturbations in organelle/vesicle trafficking, recycling and turnover which may result in reduction of cellular survival and gain of α-synuclein accumulation via impaired lysosomal function. VPS35-linked PD resembles the idiopathic disease. In reported cases symptoms were unilateral at the beginning in most cases and progression was slow. Initial symptoms were tremor, bradykinesia, rigidity and postural instability. Resting tremor, rigidity and bradykinesia were dominant. Almost every patient showed good response to levodopa. The frequency of VPS35 PD cases has been estimated to be rare. Until now data are missing on whether the VPS35 variant is associated with classical Lewy body pathology in the brainstem or not. We need more human case reports including neuropathology to find a specific clinical marker of VPS35 patients to allow a targeted referral to genetic testing.

Keywords: VPS35 protein; Parkinson’s disease; Genetic disease; Retromer complex; Clinical marker

Introduction

Parkinson’s disease is a progressive neurodegenerative disorder characterised by the loss of dopaminergic neurons in the substantia nigra pars compacta accompanied by reactive gliosis as well as the occurrence of eosinophilic intracytoplasmic inclusions termed Lewy bodies in brainstem neurons. This movement disorder belongs to the family of synucleinopathies that are characterized by the accumulation of aggregated α-synuclein protein.

VPS35 Mutations in Parkinson’s Disease as a Genetic Cause

A new autosomal dominant Parkinson’s disease mutation in the VPS35 (Vacuolar sorting protein 35) gene has been discovered in 2011 by two independent groups [1,2]. Only the VPS35 D620N Mutation (p.Asp620Asn) has been confirmed to be pathogenetic so far. This mutation has been identified in families in Switzerland, USA, Tunisia, Israel (Yementine Jews), UK, France, Germany and Austria. Interestingly VPS35 mutations are rare in Asian populations with the exception of Japanese populations but predominantly in families of Caucasian descent [3].

In 2012 performed a large multi center study to determine the frequency and pathogenicity of the VPS35 D620N mutation. The study population contained 8870 PD patients and 6513 controls. Among the PD cases they only found 7 subjects who carried the D620N mutation. 5 of them had a positive family history, but two of them turned out to be sporadic.

The VPS35 gene encodes a key component of the membrane protein–recycling retromer complex. The retromer complex is localized on the endosomes and has been shown to regulate several cellular pathways, including the transport of proteins to the trans-Golgi network, mitochondrial turnover, synaptic vesicle exocytosis/endocytosis, autophagy and lysosomal function. Consequences of the D620N mutation and retromer dysfunction are perturbations in organelle/vesicle trafficking, recycling and turnover which may result in reduction of cellular survival and gain of α-synuclein accumulation via impaired lysosomal function. A recent study suggests that VPS35 may interact with dopamine receptor D1 by disturbance of the dopamine – DRD1 signaling and/or cell surface recycling. They used manipulated mouse neuroblastoma cells and human embryonic kidney cells [4].

Rodents and Drosophila studies suggest that VPS35 mutations may act through a toxic gain of function or a dominant negative mechanism to induce neurotoxicity. A knock in mouse model suspects that Vps35 D620N allele is a partial-loss-of-function allele and causes an early deficit in dopamine release perhaps before the onset of neurodegeneration [5].

The mechanisms by which VPS35 and the retromer cause neurodegeneration and impact PD are not well understood. However, some recent findings give us a first idea which pathways might be involved in disease process. Two independent publications have shown that the D620N mutation impairs the association of the WASH complex with the retromer [6,7]. The WASH complex is a pentameric protein complex, which under physiological conditions associates with the retromer and facilitates sorting of a large number of different cargo proteins into distinct cellular pathways [8]. In this context it is interesting, that WASH mediated transports mainly affect proteins which are destined to the autophagosomes [Seaman MN] and one of the two reports has shown that the VPS35-D620N mutation impairs the formation of autophagosomes and the clearance of autophagy substrates [6]. Indeed

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perturbations of the autophagy system have been documented in a wide variety of neurodegenerative disorders.

Another cellular system which has been implicated in VPS35 associated Parkinson’s disease is the mitochondrial system. Mice lacking one copy of the VPS35 gene were shown to have a reduced amount of the mitochondrial fusion promoting protein MFN2 and consequently dopaminergic cells of these mice show extensive mitochondrial fragmentation and functional deficits [9]. The reduction of MFN2 is thought to be caused by an overactive MUL1 protein. MUL1, under normal conditions, controls MFN2 levels by promoting its degradation. A report from 2010, notably before the discovery of VPS35 as a Parkinson gene, shows that MUL1 is transported by the retromer and that inhibition of the retromer impairs MUL1 degradation [10]. It is hypothesized that the D620N mutation causes an overactive state of MUL1, which in turn causes an enhanced degradation of MFN2, which further causes mitochondrial dysfunction.

Alternatively a second study provides support for a different model for VPS35 function in the regulation of mitochondrial homeostasis and PD via interaction with the dynamin-related GTPase Drp1, which is a key protein required for mitochondrial fission. Under this model VPS35 regulates mitochondrial dynamics by removing the inactive Drp1 fission-promoting protein which leads eventually to impaired fission, resulting in dysfunctional mitochondrial homeostasis [11].

Clinical Presentation

The phenomenology appears to be clinical similar to idiopathic PD. In reported cases symptoms were unilateral at the beginning in most cases, progression was slow. Initial symptoms were tremor, bradykinesia, rigidity and postural instability. Resting tremor, rigidity and bradykinesia were dominant. Neuropsychiatric symptoms were rare. Almost every patient showed good response to levodopa. Patients in whom olfaction was tested showed mild to moderate olfactory dysfunction. Performance in the UPSIT was better than the vast majority of idiopathic PD patients. An Austrian study evaluated 14 PD patients with the VPS35 p.Asp620Asn mutation from three Austrian families. Median age at onset was 50. They found a significant positive correlation between disease duration and UPDRS II (on), III (on), Hoehn & Yahr and levodopa equivalence dose. Median sum-score in MMSE was 30 (range 26-30). They also performed well in FAB and Schwab & England Score. Most patients suffered from daytime sleepiness and urinary urgency. Dopamine transporter SPECT imaging showed asymmetric reduction of tracer uptake, indistinguishable from sporadic PD. Depression seemed to be more common than cognitive impairment. Atypical motor features were not found [12-18].

After the year 2014 there is only one precise clinical phenomenology of a single case with an association of three mutations, including VPS35: PARK 11, FBXO7 and VPS35 (gene variant c.102+33G>A, rs192115886). This patient was detected in one of three pedigrees in VPS35: PARK 11, FBXO7 and VPS35 (gene variant c.102+33G>A, rs192115886). This patient was detected in one of three pedigrees in another study. The patient presented with slowness of movement, gait initiation failure and shortened steps. Subsequently he presented with slurred speech, general rigidity, bradykinesia and bilateral resting tremor of the hands. They also found a positive applauding sign, postural instability and cognitive disorder (MMSE 23/30). During the course of disease, in addition, supranuclear gaze palsy, apraxia of lid opening, dysarthria, dysphagia severe dementia (MMSE 16/30) and inability to walk occurred [19].

In contrast to the single mutation VPS35, Levodopa response was poor. Compared with single FPXO7 associated Parkinsonism, there was no juvenile onset, no typical signs of a pyramidal disease and non-motor symptoms were not present. In brain MRI, diffuse brain atrophy and post ischemic hyper intensities bilaterally were detected. The VPS35 gene mutation was also identified in the patient’s cousin and her two daughters. While the cousin has mild late onset Parkinson’s disease – no precise clinical description provided – her two daughters do not have any clinical symptoms until now.

Neuropathology of VPS35 D620N Mutation in Parkinson’s Disease

So far, only one carrier of the VPS35 (D620N) mutation in a Swiss family has been assessed at autopsy [18]. However the neuropathological examination excluded the brainstem. They did not reveal any signs of Lewy body disease or α-synuclein immunoreactivity. Therefore, until now data are missing on whether the VPS35 variant is associated with classical Lewy body pathology in the brainstem. In animal trials with mice they found dopaminergic neuron loss and increased α-synuclein levels in the ventral midbrain [20].

The Role of Interaction of VPS35 with Other PD Linked Gene Products

Recent studies with Drosophila, yeast and worms have demonstrated that PD-linked gene products (VPS35, LRK22, SNCA, Parkin and/or PINK1) may act together in a common pathway. Possibly the influence of their combination could increase the risk of PD.

Discussion

VPS35-linked PD resembles clinically and neurochemically the idiopathic disease. There are about 50 cases of the D620N mutation mentioned in literature. The frequency has previously been estimated to be about 0.1 to 1% in patients with familial autosomal dominant PD [21], but may be rarer than that [17]. Of those patients only insufficient clinical data are available. Since we do only have very few precise case studies, the search for a clinical marker of VPS35 is hampered. Missing a clinical marker endangers VPS35 patients to be misdiagnosed as idiopathic PD patients. In addition we do not have a biomarker for the VPS35 variant. Even more it remains unclear in whether the disease in human is associated with classic Lewy body pathology. While within the last half decade we considerably learned about the genetics of VPS35 patients, we have nothing at hand to offer our clinical VPS35 patients. More human case reports including neuropathology would be needed to find a specific clinical marker of VPS35 patients to allow a targeted referral to genetic testing [22-26].

References


