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VPS35: A new player in Parkinson's disease

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The identification of genetic mutations that cause Parkinson's disease (PD) in rare families has been the bedrock of investigation into the molecular pathogenesis of PD. These mutations are used to understand and model disease, in a process aimed at finding viable points of therapeutic intervention that are based on etiology, rather than being based on symptomatic relief.

Two papers, published back to back in the American Journal of Human Genetics, expand the repertoire of genetic tools with which to understand the basis of PD by the discovery of a mutation linked to PD in the gene *VPS35*.^{1, 2} Both studies used exome sequencing, a method to sequence all of the protein coding regions of the genome in parallel, in large families with PD. In the work by Vilarino-Güell and colleagues, the authors sequenced cousins from a large Swiss kindred with autosomal dominant, late onset PD. Following a series of screening and filtering steps, the authors provide evidence that a mutation in *VPS35* (p.D620N) is responsible for disease in this family and in 4 of ~4000 unrelated PD cases screened. The mutation was absent from more than 3000 control samples. In the work by Zimprich and colleagues, the authors performed exome sequencing in an Austrian family with autosomal dominant PD. This group identified the same mutation in *VPS35*, p.D620N, segregating with disease and then went on to show that this mutation was a cause of disease in two additional families. Both groups found additional mutations in *VPS35*; in contrast to the p.D620N mutation, the evidence for pathogenicity of the additional variants was not compelling, and thus their role in disease remains unclear. The clinical phenotype of *VPS35* linked disease is reported to fulfill London Brain Bank criteria, with an age at onset of disease in the early fifties.

VPS35 encodes the vacuolar protein sorting ortholog 35, a part of a large multimeric complex called the retromer complex. This complex is believed to play an integral role in retrograde transport of proteins from endosomes to the trans-Golgi network. While *VPS35* mutations appear to be quite a rare cause of PD, they provide another valuable window into the etiology of this complex disorder.

References

1. Zimprich A, Benet-Pages A, Struhal W, et al. A Mutation in *VPS35*, Encoding a Subunit of the Retromer Complex, Causes Late-Onset Parkinson Disease. *Am J Hum Genet.* 2011; 89(1):168–175. [PubMed: 21763483]
2. Vilarino-Guell C, Wider C, Ross OA, et al. *VPS35* Mutations in Parkinson Disease. *Am J Hum Genet.* 2011; 89(1):162–167. [PubMed: 21763482]