A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease.

To identify rare causal variants in late-onset Parkinson disease (PD), we investigated an Austrian family with 16 affected individuals by exome sequencing. We found a missense mutation, c.1858G>A (p.Asp620Asn), in the VPS35 gene in all seven affected family members who are alive. By screening additional PD cases, we saw the same variant cosegregating with the disease in an autosomal-dominant mode with high but incomplete penetrance in two further families with five and ten affected members, respectively. The mean age of onset in the affected individuals was 53 years. Genotyping showed that the shared haplotype extends across 65 kilobases around VPS35. Screening the entire VPS35 coding sequence in an additional 860 cases and 1014 controls revealed six further nonsynonymous missense variants. Three were only present in cases, two were only present in controls, and one was present in cases and controls. The familial mutation p.Asp620Asn and a further variant, c.1570C>T (p.Arg524Trp), detected in a sporadic PD case were...
predicted to be damaging by sequence-based and molecular-dynamics analyses. VPS35 is a component of the retromer complex and mediates retrograde transport between endosomes and the trans-Golgi network, and it has recently been found to be involved in Alzheimer disease.