

# Lack of evidence for *LRP10* variants as a cause of dementia with Lewy bodies

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Quadri and colleagues<sup>1</sup> report on variants in *LRP10* as the cause of dominant Parkinson's disease (PD) in a family from Italy and then follow-on to describe rare mutations in two independent cohorts of patients (including PD, PD with dementia and dementia with Lewy bodies (DLB)) and controls. Functional *in-vitro* data suggested that variants affect expression, protein stability or localization. This is an important study as it provides a novel gene for DLB, a disease for which causative genes have been difficult to identify.

To replicate these results, we mined whole-exome sequencing data from a cohort of 1,040 DLB cases and 1,422 controls.

We identified 25 variants, 14 occurring only in controls, and 8 occurring exclusively in cases (Supplementary Table 1). Two of the variants identified by Quadri and colleagues in two Dutch individuals were present in our data, in one case each (p.Ala212fs and p.Asn517del). Our cases, obtained from The Netherlands Brain Bank, also match on gender and age at

death/disease duration. Given the extreme rarity of these variants (they are absent from gnomAD) and the same phenotype, it is very likely that our cases are the same as the ones described. Two other high impact variants were identified in our cohort (p.Gln67\* and p.Arg554\*), appearing in one case and one control respectively. No single variant was associated with DLB and the carrier frequency was identical between cases (2.5%) and controls (2.8%). To determine if there is enrichment of variants in *LRP10*, we performed group-wise associations (using SKAT-O), with sex and the first 10 principle components as covariates. Variants were grouped into: missense, missense and loss-of-function variants, and loss-of-function only categories. No groups were significantly associated with DLB ( $p=0.4$ ,  $p=0.7$ ,  $p=0.3$ , respectively).

It is difficult to conclusively disprove *LRP10* in DLB, particularly given the suggestion of incomplete penetrance and phenocopies in the studied families. The comparison with *SNCA* and *LRRK2* is not adequate - there are multiple, established threads of evidence showing that these two genes are involved in PD, and the original descriptions were based on informative co-segregation of the disease in families. Taken together, our data does not support a role for *LRP10* in DLB. We believe this is a critical and important finding and caution against functional studies to understand the role of this gene in DLB based solely on the original report.

## References

- 1 Quadri M, Mandemakers W, Grochowska MM, *et al.* LRP10 genetic variants in familial Parkinson's disease and dementia with Lewy bodies: a genome-wide linkage and sequencing study. *Lancet Neurol* 2018; published online June 6. DOI:10.1016/S1474-4422(18)30179-0.