***LRP10* genetic variants in multiple system atrophy**

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We read with interest the recent article by Quadri et al., proposing *LRP10* as a novel disease-causing gene in autosomal dominant Parkinson's disease (PD) and dementia with Lewy bodies (DLB).1 Notably, the authors. use the term *α-synucleinopathies*, which entails not only Lewy body disorders, but also diseases with other patterns of alpha-synuclein pathology, such as multiple system atrophy (MSA). A mixed neuropathological picture, with elements of both PD/DLB and MSA pathology has been reported in carriers of *SNCA* p.G51D, suggesting that a simple genetic defect could potentially predispose to α-synucleinopathy in a general sense.2 To investigate the possible role of *LRP10* in MSA, we assessed potentially pathogenic variants in exome data from 264 MSA patients and 462 controls from the Healthy Exomes (HEX) database.3 Pathologically confirmed cases of definite MSA4 were obtained from the MSA Brain Bank and DNA Collaboration (see Acknowledgements). HEX controls had age at death > 60 years, no clinical symptoms of neurodegenerative disease and normal neuropathological examination. All subjects were Caucasian. Further details on methods and results are provided in an online supplement.

We concentrated on missense, stop and splicing variants in *LRP10* with a minor allele frequency < 0.01 and identified a total of 12 such variants in the combined datset from MSA patients and controls (Supplementary table). None of these overlap with any of the mutations reported by Quadri et al., but 10 out of 12 are present in the Exome Aggregation Consortium (ExAC) database (http://exac.broadinstitute.org).5 A total of seven (2·7%) MSA patients and 16 (3·5%) controls carried a variant. A stopgain mutation (p.R405X) was identified in a control individual, the rest were missense variants. Rare variant burden assessed by the sequence kernel association test - optimal (SKAT-O) (https://CRAN.R-project.org/package=SKAT) was non-significant (p=0·74).

Our limited sample size warrants cautious interpretation, but at least our data do not provide any novel evidence supporting a role for *LRP10* in MSA. The p.R405X variant is reported in two other individuals in the ExAC database, where the total number of loss-of-function *LRP10* mutation carriers is as high as 30 in ~60,000 (see Supplementary note). In our study, the HEX database control was verified as neuropathologically normal, indicating that not even subclinical changes have resulted from carrying a nonsense variant in this individual. Taken together, these observations call for some caution before accepting the hypothesis that heterozygous loss of function of *LRP10* causes haploinsufficiency and highly penetrant Mendelian α-synucleinopathy.

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**Declaration of interests**

The authors report no conflicts of interest.

**Authors' contributions**

The study was based on data from the MSA Exome Consortium, where L.S., V.C and H.H.

contributed to study design and data collection. L.P. performed data analysis and interpretation

and drafted the manuscript. All authors contributed to critical revision of the manuscript.

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