

LETTER TO THE EDITOR

Reply: Lysosomal storage disorder gene variants in multiple system atrophy

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Sir,

Pihlström *et al.* (2018) examined the intriguing hypothesis that variation in genes causing lysosomal storage disorders (LSDs) might increase risk for multiple system atrophy (MSA). They adopted the same analytic strategy that we used successfully to demonstrate an aggregate burden among 54 LSD genes and Parkinson's disease susceptibility (Robak *et al.*, 2017). Since MSA is rare, with a prevalence of ~2.5 per 100 000 (Stefanova *et al.*, 2009), the investigators' effort to assemble a whole-exome sequencing cohort of more than 350 cases, including 264 with pathological confirmation, is commendable. Although the results were negative, it will be important to repeat the analysis in the future when even larger sample sizes are available. The underlying hypothesis is supported not only by emerging evidence for a connection between LSD gene variants and Parkinson's disease risk, but also studies implicating *GBA* variants in both MSA (Mitsui *et al.*, 2015; Sklerov *et al.*, 2017) and dementia with Lewy bodies (DLB) (Nalls *et al.*, 2013). Indeed, substantial phenotypic overlap is recognized among synucleinopathies. For example, cognitive impairment and autonomic dysfunction, which are core features of DLB and MSA, respectively, are also common and disabling non-motor complications of Parkinson's disease. Besides its association with Parkinson's disease risk, genetic evidence suggests that *GBA* variants may modify Parkinson's disease clinical manifestations, including incidence of dementia and rate of progression (O'Regan *et al.*, 2017). Thus, one promising future approach is to apply aggregate burden tests to

examine for a broader contribution of LSD gene variants to heterogeneous Parkinson's disease phenotypes. Evidence for association with Parkinson's disease features that also overlap with DLB (e.g. cognitive impairment, hallucinations) and/or MSA (e.g. dysautonomia, early falls, dysphagia, dysarthria) may provide clues of a shared genetic architecture underlying synucleinopathies more broadly.

References

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