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IN BRIEF

PARKINSON DISEASE

LRRK2 variants linked to PD and Crohn's disease.

A new gene association study has found a genetic link between Parkinson disease (PD) and Crohn's disease (a form of inflammatory bowel disease), suggesting the presence of shared disease mechanisms in these two disparate disorders. Researchers carried out exome sequencing and genotyping in individuals of Ashkenazi Jewish descent, including 2,066 individuals with Crohn's disease and 3,633 healthy controls. The team found functional gene variants in *LRRK2* — the greatest known genetic contributor to PD — which conferred either increased risk or protection from Crohn's disease. A larger analysis of the *LRRK2* locus in 24,570 people of Jewish and of non-Jewish descent, which included patients with Crohn's disease, patients with PD and healthy individuals, confirmed the presence of shared alleles that confer risk or protection in Crohn's disease and PD. The findings suggest commonalities in the underlying biology of these two conditions, which could have implications for the development of future treatments.

ORIGINAL ARTICLE Hui, K. Y. *et al.* Functional variants in the *LRRK2* gene confer shared effects on risk for Crohn's disease and Parkinson's disease. *Sci. Transl Med.* **10**, eaai7795 (2018)

DEMYELINATING DISEASE

Cholesterol crystals thwart repair in old CNS

An inability to remove excess cholesterol after myelin damage could underlie the defective remyelination and recovery observed in old age, according to a new study published in *Science*. Investigators found that expression of cholesterol transporters, including apolipoprotein E, was reduced in demyelinating lesions of old mice compared with those of young mice. The deficit was associated with an accumulation of cholesterol crystals inside of the lysosomes of phagocytes, accompanied by stimulation of the inflammasome and cell death. Inflammasome activation instigated an aberrant immune response that prevented successful remyelination in the old mice. Conversely, upregulation of cholesterol exporters in the mice promoted remyelination and recovery. The findings highlight upregulation of cholesterol export as a potential regenerative therapy in demyelinating conditions.

ORIGINAL ARTICLE Cantuti-Castelvetri, L. *et al.* Defective cholesterol clearance limits remyelination in the aged central nervous system. *Science* https://doi.org/10.1126/science.aan4183 (2018)

ALZHEIMER DISEASE

BACE1 inhibitors block new Aβ plaque formation

Several clinical trials in patients with Alzheimer disease (AD) have investigated the therapeutic potential of inhibition of β-secretase 1 (BACE1), a protease involved in the production of amyloid-β (Aβ). However, these trials thus far have failed to demonstrate a reduction in cognitive decline when given to patients with mild to moderate AD. Now, results from a new longitudinal study in a transgenic mouse model of AD suggest that this treatment was ineffective because it was given too late in the disease course. The team used two-photon microscopy in live mice to assess the kinetics of Aβ plaque deposition before and during BACE1 inhibitor treatment. BACE1 inhibition potently blocked new Aβ plaque formation but was less effective in slowing the growth of existing plaques, suggesting that the optimal timing for treatment is early in the disease course, before widespread Aβ plaque formation.

ORIGINAL ARTICLE Peters, F. *et al.* BACE1 inhibition more effectively suppresses initiation than progression of β-amyloid pathology. *Acta Neuropathol.* https://doi.org/10.1007/s00401-017-1804-9 (2018)