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IN BRIEF

ALZHEIMER DISEASE

CRISPR activation reveals hidden γ-secretase defect in fibroblasts from patients with familial AD

Patient skin fibroblasts can offer an easily accessible cell model of disease, but key genes relevant to neurological disorders are often expressed at insufficient levels to study the pathomechanisms of such disorders in this system. In a new study, researchers increased expression of *APP* and/or *BACE1* via CRISPR gene activation in fibroblasts from patients with familial Alzheimer disease (AD) and from healthy individuals. CRISPR activation revealed a defect in γ-secretase processing of amyloid precursor protein (APP) in fibroblasts from patients with familial AD, resulting in increased levels of amyloid-β42 (Aβ42), whereas no such defects were detectable in non-modified fibroblasts from the same patients. The results suggest that increasing the expression levels of *APP* or *BACE1* to reflect those observed in cultured neurons produces a more disease-relevant fibroblast model that is quicker and easier to establish than induced pluripotent stem cell systems.

ORIGINAL ARTICLE Inoue, K. *et al.* CRISPR transcriptional activation analysis unmasks an occult γ-secretase processivity defect in familial Alzheimer's disease skin fibroblasts. *Cell Rep.* **21**, 1727–1736 (2017)

PARKINSON DISEASE

Lysosome storage disorder risk genes linked to PD

Heterozygous mutations in *GBA*, which cause the recessive lysosomal storage disorder (LSD) Gaucher disease, are a known risk factor for Parkinson disease (PD). Previous studies have investigated whether variants linked to other LSDs might increase the risk of PD but have, thus far, been insufficiently powered to reveal an effect. Now, a new report has analysed whole-exome sequencing data from 1,156 patients with PD and 1,679 non-neurodegenerative controls. The team found that the presence of an LSD-associated variant was linked to an increased risk of PD even when *GBA* was excluded from the analysis. More than half of the individuals with PD were found to have at least one gene variant associated with an LSD, and three specific loci — *CTSD*, *SLC17A5* and *ASAH2* — were newly implicated as risk factors for PD. The study supports the hypothesis that lysosomal dysfunction plays an important part in PD pathogenesis.

ORIGINAL ARTICLE Robak, L. A. *et al.* Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. *Brain* http://dx.doi.org/10.1093/brain/awx285 (2017)

CNS INFECTIONS

Zika virus mutation associated with increased infectivity, mortality and severe microcephaly

New research suggests that a Ser138Asp substitution in prM, a structural protein of Zika virus, contributed to the 2013 outbreak of the virus in French Polynesia. Researchers found that strains of the virus isolated in 2015–2016 caused higher mortality and more severe microcephaly in neonatal mice and had a higher rate of replication in mouse and human neural progenitor cells than did an ancestral strain isolated in 2010. One of the genetic changes present in the more recent Zika strains is a Ser138Asp substitution; the team found that reversal of this mutation also reversed the increased virulence and infectivity of the strain. Analysis of Zika virus evolution revealed that the Ser138Asp mutation first appeared in May 2013, shortly before the outbreak in October 2013, and has been maintained subsequently, suggesting that it contributed to the severe microcephaly observed in the Zika virus epidemic.

ORIGINAL ARTICLE Yuan, L. *et al.* A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. *Science* **358**, 933–936 (2017)