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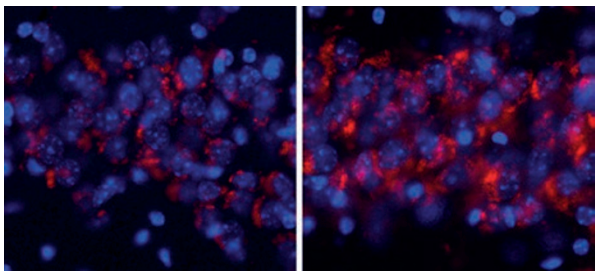
GENE THERAPY

Gene therapy targets pathology in progranulin-deficient mice

> “treatment reduced existing lipofuscinosis and microgliosis”

Gene therapy is a promising therapeutic strategy for frontotemporal dementia (FTD) and lysosomal storage disease associated with progranulin deficiency, according to a new mouse study. The treatment restored lysosomal function and reduced existing brain pathology.

Haploinsufficiency of progranulin, encoded by *GRN*, is a major cause of FTD, and complete deficiency causes neuronal ceroid lipofuscinosis, a type of lysosomal storage disease. The simple loss of gene function underlying these conditions makes them obvious candidates for gene therapy.



AAV-*Grn* AAV-GFP

Lipofuscin pathology (red) in mouse brains was reduced by adeno-associated virus delivery of the *Grn* gene to neurons (left) relative to pathology in controls that received only green fluorescent protein (right). Image courtesy of A. Arrant and E. Roberson.

“Increasing progranulin to normal levels in *GRN* mutation carriers should be an effective way to prevent or maybe even treat FTD,” says Andrew Arrant, first author of the study. “However, this hypothesis had not been tested in an in vivo model of FTD-related pathology.”

Arrant and colleagues had previously tested progranulin gene therapy in mice with *Grn* haploinsufficiency, and the treatment reduced social behaviour deficits. However, these mice do not develop lipofuscinosis or microgliosis, the pathology seen in humans with *GRN* mutations. Consequently, the effects of gene therapy on this pathology have remained unknown.

In the new study, the researchers used $Grn^{-/-}$ mice that express no progranulin and develop lipofuscinosis and microgliosis. An adeno-associated virus vector carrying the *Grn* gene was injected into the brains of these mice at age 10–12 months, when the pathology is robust, to induce expression of progranulin in neurons.

The treatment reduced existing lipofuscinosis and microgliosis. Activity of the lysosomal enzyme cathepsin D, which is increased in progranulin-deficient mice, was also normalized, indicating that restored lysosomal function was responsible for the clearance of pathology.

“Our study supports the idea that directly raising progranulin by gene therapy, an approach that has been gaining traction for other neurological diseases, will be an effective treatment strategy for *GRN* mutation carriers,” says Arrant.

Ian Fyfe

ORIGINAL ARTICLE Arrant, A. et al. Progranulin gene therapy improves lysosomal dysfunction and microglial pathology associated with frontotemporal dementia and neuronal ceroid lipofuscinosis. *J. Neurosci.* **38**, 2341–2358 (2018)