IN BRIEF

MOTOR NEURON DISEASE

Antisense treatment alleviates ALS in animals

Newly developed antisense oligonucleotides (ASOs) that target superoxide dismutase 1 (*SOD1*) mRNA increase survival and improve muscle function in animal models of amyotrophic lateral sclerosis (ALS), a new study has shown. *SOD1* mutation accounts for ~20% of familial ALS. In previous studies, an ASO against *SOD1* was identified and tested, but interest in its development waned because its effects were modest and new advances promised more potent ASOs. In the new study, next-generation ASOs were identified by screening >2,000 ASOs against human *SOD1*. When these ASOs were injected into the cerebrospinal fluid of rats and mice that expressed mutant human *SOD1*, levels of human *SOD1* mRNA were reduced, disease onset was delayed and survival was prolonged by 22% in mice and up to 39% in rats. Furthermore, ASO injection improved compound muscle action potentials, indicating a reversal of disease progression. A clinical trial of the ASOs in humans with *SOD1*-mediated ALS is now ongoing.

ORIGINAL ARTICLE McCampbell, A. et al. Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models. *J. Clin. Invest.* **128**, 3558–3567 (2018)

PARKINSON DISEASE

Familial PD gene involved in idiopathic disease

Mutation of the leucine-rich repeat kinase 2 gene (*LRRK2*) causes familial Parkinson disease (PD), but new research indicates that wild-type *LRRK2* is also involved in idiopathic PD. In the new study, proximity ligation assays were developed and used to analyse LRRK2 activity in post-mortem brain tissue from patients with idiopathic PD and rat models of the disease. In human and animal tissue, LRRK2 activity in nigrostriatal dopamine neurons was greater in individuals with disease than in controls. Furthermore, in wild-type cultured human cells and in one rat model of PD, activation of LRRK2 was prevented by treatment with LRRK2 inhibitors, suggesting that these drugs could be beneficial not only for patients with *LRRK2* mutations, but also for those with idiopathic PD and no mutations in *LRRK2*.

ORIGINAL ARTICLE Di Maio, R. D. et al. LRRK2 activation in idiopathic Parkinson's disease *Sci. Transl Med.* **10**, eaar5429 (2018)

DEMENTIA

Distinct cerebellar contributions to FTD subtypes

Distinct patterns of cerebellar atrophy between different forms of frontotemporal dementia (FTD) have been identified for the first time in an MRI study. A total of 96 patients with FTD participated in the study; 45 had behavioural-variant FTD (bvFTD), 28 had semantic dementia (SD) and 23 had progressive nonfluent aphasia (PNFA). Structural MRI was used to assess whole-brain and cerebellar grey matter integrity, and the structural findings were assessed alongside cognitive performance. Bilateral grey matter atrophy was observed in all FTD subtypes, but the patterns differed and atrophy was greatest in bvFTD. The loss of cerebellar grey matter was associated with impairment of different cognitive functions in different FTD subtypes: attention and working memory in bvFTD, visuospatial cognition in SD, and language and motor cognition in PNFA. The findings demonstrate that cerebellar atrophy is syndrome-specific in FTD, rather than a result of global atrophy, and that this atrophy contributes to cognitive dysfunction in these disorders.

ORIGINAL ARTICLE Chen, Y. et al. Cerebellar atrophy and its contribution to cognition in frontotemporal dementia. *Ann. Neurol.* https://doi.org/10.1002/ana.25271 (2018)

NEURODEGENERATIVE DISEASE

MicroRNA-132 — master regulator of neuronal health?

MicroRNA-132 (miR-132) is known to be downregulated in the brains of patients with Alzheimer disease (AD). A new study published in *Acta Neuropathologica* shows that expression of this microRNA (miRNA) protects neurons against amyloid-β (Aβ) and glutamate excitotoxicity and mitigates tau pathology, thereby addressing multiple pathogenic mechanisms that contribute to AD and other neurodegenerative disorders. The findings suggest a pivotal role for miR-132 in the maintenance of neuronal health.

"The underlying hypothesis of this study was that specific miRNAs, as key regulators of gene expression, can be involved in neuromodulatory or neuroprotective pathways associated either positively or negatively with AD," explains study leader Anna Krichevsky. "We reasoned that the identification of such miRNAs will not only contribute to a better understanding of AD but might also provide new therapeutic strategies."

Krichevsky, Rachid El Fatimy and colleagues conducted a high-throughput screen in primary neuronal cultures to identify miRNAs that could either exacerbate or ameliorate neurotoxicity mediated by Aβ and/or glutamate. The screen uncovered several neuroprotective miRNAs, the most effective of which was miR-132.

The researchers found that miR-132 reduced the formation of pathological forms of the tau protein in primary neurons from PS19 mice, a standard animal model of tauopathy. Overexpression of miR-132 in the hippocampus in this mouse model slowed disease progression and enhanced synaptic plasticity.

"These new data position miR-132 as a master regulator of neuronal

ALZHEIMER DISEASE

New clues to the genetic links between AD and Down syndrome

Trisomy of chromosome 21 promotes the pathogenesis of Alzheimer disease (AD) independently of the triplication of *APP*, the gene that encodes amyloid precursor protein, new research has shown. The findings provide mechanistic insights into the high prevalence of AD in people with Down syndrome, and could lay the foundations for novel treatments in these individuals.

Trisomy of chromosome 21, which contains *APP*, is the largest genetic risk factor for AD. Almost all individuals with Down syndrome develop amyloid-β (Aβ) plaques and neurofibrillary tangles in their brains by 40 years of age, and around two-thirds of people with Down syndrome develop clinical dementia before 60 years of age. Increasing life expectancy among people with Down syndrome has led to a mounting burden of AD in this population.

"Genetic evidence has suggested that the three copies of *APP* on chromosome 21 causes early onset AD in people with Down syndrome," explains Frances Wiseman, lead author of the new study, "but no one had asked whether disease progression is modified by the extra copies of other genes on chromosome 21."

To answer this question, the team used transgenic mice that have three copies of most of the genes on chromosome 21 but lack a third copy of *APP*. Wiseman and colleagues crossed these animals with mice that develop Aβ pathology as a result of expression of human *APP* that contains mutations found in patients with familial AD.

Interestingly, expression of the partial extra copy of chromosome 21 substantially increased the deposition of Aβ in the hippocampus of *APP*-mutant mice compared with their euploid *APP*-mutant littermates. Partial trisomy