newborns at risk of developing cerebral palsy, and may show promise in the wider realm of neurodegenerative diseases involving glutamate-mediated excitotoxic neuronal death.

Original article Medja F *et al.* (2006) Thiorphan, a neutral endopeptidase inhibitor used for diarrhoea, is neuroprotective in newborn mice. *Brain* **129:** 3209–3223

A mutant lysosomal ATPase causes hereditary parkinsonism

The causal connection between specific genetic mutations and mendelian forms of neurodegenerative disease has been useful in determining the pathophysiological pathways underlying these disorders. In a recent study, Ramirez *et al.* described loss-of-function mutations in *ATP13A2*—a previously uncharacterized P-type ATPase gene—that cosegregate with Kufor–Rakeb syndrome (KRS), a form of early onset parkinsonism with pyramidal degeneration and dementia.

Linkage analysis and mutation screening of a large nonconsanguineous Chilean family with multiple cases of early onset parkinsonism identified a critical KRS interval of 6.6 cM containing around 40 genes. Two separate mutations in the *ATP13A2* gene cosegregated with all incidences of KRS. The causative role of the gene was confirmed in the Jordanian family in which KRS was originally described; a homozygous 22-base-pair duplication was observed in all affected individuals.

Ramirez *et al.* showed that AT132 is predominantly expressed in the brain. The wild-type protein was found to colocalize with lysosomal membrane proteins, whereas the mutant protein accumulated in the endoplasmic reticulum and was degraded by the proteasome. Levels of mutant protein were notably lower than those of the wild-type protein. The authors suggest two pathophysiological mechanisms that could cause parkinsonism: first, an overload with mutant AT132 could cause toxic aggregation leading to proteasomal dysfunction; second, loss of *ATP13A2* function could result in insufficient lysosomal protein degradation. Determining the function of *ATP13A2* would contribute to our understanding of the protein networks implicated in neurodegenerative disorders.

Original article Ramirez A *et al.* (2006) Hereditary parkinsonism with dementia is caused by mutations in *ATP13A2*, encoding a lysosomal type 5 P-type ATPase. *Nat Genet* **38:** 1184–1191

Treatment-resistant depression responds to repetitive transcranial magnetic stimulation

Several small studies have indicated that low-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) might have antidepressant properties; however, the effectiveness of this treatment in clinical practice has not been evaluated and the optimum treatment parameters are not well characterized.

In a two-arm double-blind trial, 130 patients with treatment-resistant depression were sequentially randomized to either 1 Hz or 2 Hz rTMS over the right prefrontal cortex. Patients received 10 rTMS sessions over a 2-week period. Following the tenth session, patients classified as 'initial responders' were offered a 2-week extension of treatment, while nonresponders were randomized to left prefrontal cortex rTMS at a frequency of either 5 Hz or 10 Hz.

Following 2 weeks of right-sided rTMS, 29% of patients met the response criteria (>50% reduction in the 17-item Hamilton Depression Rating Scale); 47% of patients met these criteria by week 4. Despite receiving double the 'dose', on the basis of pulse number the response rate in patients receiving 2 Hz stimulation was no higher than in those receiving 1 Hz. Notably, of the 30 patients who failed to respond to right-sided rTMS and crossed over to receive high-frequency left-sided rTMS, five met the response criteria following 4 weeks of treatment. By study completion, 51% of the entire study population had achieved the response criteria and 27% the remission criteria. In general, rTMS was acceptable to patients, as indicated by the low dropout rate. The authors conclude that low-frequency right-sided rTMS seems to be a clinically useful therapy for patients with treatment-resistant depression.

Original article Fitzgerald PB *et al.* (2006) A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmacol* **9:** 655–666

Herpes simplex virus-1 associates with changes in brain morphology in schizophrenia

A range of plausible pathogenic mechanisms that might underlie schizophrenia have been proposed, including a possible role for infectious