

MOTOR NEURON DISEASE

Loss-of-function mutations in *TBK1* can cause familial ALS

New research published in *Nature Neuroscience* implicates specific variants of the TANK-binding kinase 1 (*TBK1*) gene in familial amyotrophic lateral sclerosis (ALS). The exome-sequencing study could have wide implications for the study of ALS, and might facilitate new approaches to diagnosis and treatment.

“Our findings ... link three ALS genes to one common pathway for autophagy regulation...”

“Currently known ALS-related genes explain only a minority of cases, but have told us a lot about the basic principles of ALS pathogenesis, such as disturbed RNA metabolism or pathological protein aggregation,” explains Jochen Weishaupt, co-supervisor of the new study.

The investigators recruited 252 patients with familial ALS who had previously tested negative for *SOD1* and *C9orf72* mutations. The patients then underwent whole-exome sequencing, and these data

were compared with sequences from 827 controls who had no family history of ALS.

Eight loss-of-function variants of *TBK1* were identified as unique to the group of patients with ALS, and achieved genome-wide significance for their association with this condition. A subsequent targeted screen for *TBK1* mutations in healthy controls and patients with sporadic ALS suggested that *TBK1* loss-of-function mutations were mostly specific to familial ALS.

The investigators then performed a series of *in vitro* tests to determine how these mutations might lead to disease. In cell lines derived from the patients with familial ALS, most of the *TBK1* loss-of-function mutations led to substantial reductions in the expression of *TBK1* mRNA and protein. Another ALS-linked mutation only truncated the C-terminus of the protein.

“On the basis of our genetic and functional findings, we could delineate mutations that affected the C-terminal coiled-coil domain 2 of *TBK1* as sufficient

to cause neurodegeneration,” explains Weishaupt. He also points out that *TBK1* interacts closely with optineurin and sequestosome-1 (also known as ubiquitin-binding protein p62), which have both been implicated in ALS pathogenesis.

“Our findings thus link three ALS genes to one common pathway for autophagy regulation,” concludes Weishaupt. This pathway might represent a therapeutic target for patients with ALS.

In the paper, the investigators also present the first autopsy data from a patient with familial *TBK1*-ALS, who had perinuclear inclusions of TAR DNA-binding protein 43 and sequestosome-1 in areas of the temporal lobe. Further postmortem analyses will be necessary to confirm the pathology of this form of familial ALS.

Alex Chase

Original article Freischmidt, A. *et al.* Haploinsufficiency of *TBK1* causes familial amyotrophic lateral sclerosis and fronto-temporal dementia. *Nat. Neurosci.* doi:10.1038/nn.4000