PRKAR1B mutations are a rare cause of FUS negative neuronal intermediate filament inclusion disease

Cyril Pottier, Matt Baker, Dennis W. Dickson and Rosa Rademakers

Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA

Correspondence to: Cyril Pottier
Mayo Clinic – Neuroscience,
4500 San Pablo Road Jacksonville Florida 32224, USA
E-mail: pottier.cyril@mayo.edu

Sir,

We read with great interest the article by Wong et al., 2014 that described a novel hereditary late-onset neurodegenerative disorder. Neuronal intermediate filament inclusion disease (NIFID) is a rare neurodegenerative disorder characterized by an early-onset and heterogeneous phenotypic presentation including frontotemporal dementia, pyramidal and extra-pyramidal signs (Bigio et al., 2003; Cairns et al., 2003; Josephs et al., 2003). NIFID is characterized by cytoplasmic inclusions of variable morphology which immunostained for class IV intermediate filaments (Bigio et al., 2003; Cairns and Armstrong, 2003; Cairns et al., 2004a, b). More recently it has been shown that a large proportion of NIFID inclusions contain the fused in sarcoma (FUS) protein (Neumann et al., 2009).

Here, Wong et al. present for the first time a family with neurofilament-positive but FUS-negative neuronal inclusions. Using an original combination of linkage analysis, exome sequencing and proteomic analysis, the authors identified the p.Leu50Arg mutation in the PRKAR1B gene encoding a subunit of the cyclic AMP-dependent protein kinase A complex that regulates several biological events, including neurofilament phosphorylation. The authors also provide immunohistochemistry showing PRKAR1B inclusions and they show a dramatic enrichment of PRKAR1B in highly insoluble protein fractions further supporting a causative role for PRKAR1B in the pathophysiology of this disorder.

Following this publication we studied the presence of PRKAR1B mutations in three pathologically-confirmed NIFID cases who were FUS-negative upon immunohistochemistry. The cases studied have an age at onset between 49 and 67 years. All patients clinically presented with dementia and one of them with mild parkinsonism. Dementia in close relatives was described in two patients but not to the same extent as described in the Wong et al. paper. No new variations in PRKAR1B were identified in our samples. We also searched for genomic copy number variations encompassing the entire PRKAR1B gene by using a TaqMan® assay in exon 3 (NM_002735.2). No deletions or duplications were detected. However we cannot rule out the possibility of partial copy number variations. Consistent with our genetic results, immunostaining also failed to detect PRKAR1B inclusions. Overall these results show that PRKAR1B is not the cause of the disease in our FUS-negative NIFID patients.

Our study suggests that mutations in PRKAR1B account for only a small portion of the FUS-negative cases with NIFID. Further genetic screening in the PRKAR1B pathway may identify new genetic factors involved in the aetiology of FUS-negative NIFID.

References

