PRKAR1B mutation associated with a new neurodegenerative disorder with unique pathology

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Research question and background

What is the underlying genetic defect in a family with dementia and/or parkinsonism?

Pathological accumulation of intermediate filaments can be observed in neurodegenerative disorders, such as Alzheimer's disease, frontotemporal dementia and Parkinson's disease, and is also characteristic of neuronal intermediate filament inclusion disease. Intermediate filaments type IV include three neurofilament proteins (light, medium and heavy molecular weight neurofilament subunits) and α-internexin. The phosphorylation of intermediate filament proteins contributes to axonal growth, and is regulated by protein kinase A. Here we describe a family with a novel late-onset neurodegenerative disorder presenting with dementia and/or parkinsonism in 12 affected individuals. The disorder is characterized by a unique neuropathological phenotype displaying abundant neuronal inclusions by haematoxylin and eosin staining throughout the brain with immunoreactivity for intermediate filaments.

Methods and tissues used

Combination of linkage analysis, exome sequencing and proteomics analysis**.**

Slices of all cortical regions, hippocampus, basal ganglia, cerebellum and myelum from two patients. Fresh-frozen brain tissue of the hippocampus of two patients and two healthy controls.

Results and conclusion

We identified a heterozygous c.149T>G (p.Leu50Arg) missense mutation in the gene encoding the protein kinase A type I-beta regulatory subunit (*PRKAR1B*). The pathogenicity of the mutation is supported by segregation in the family, absence in variant databases, and the specific accumulation of PRKAR1B in the inclusions in our cases associated with a specific biochemical pattern of PRKAR1B. Screening of *PRKAR1B* in 138 patients with Parkinson's disease and 56 patients with frontotemporal dementia did not identify additional novel pathogenic mutations.

Our findings link a pathogenic *PRKAR1B* mutation to a novel hereditary neurodegenerative disorder and suggest an altered protein kinase A function through a reduced binding of the regulatory subunit to the A-kinase anchoring protein and the catalytic subunit of protein kinase A, which might result in subcellular dislocalization of the catalytic subunit and hyperphosphorylation of intermediate filaments.

Pictures, cartoons and/or graphs:

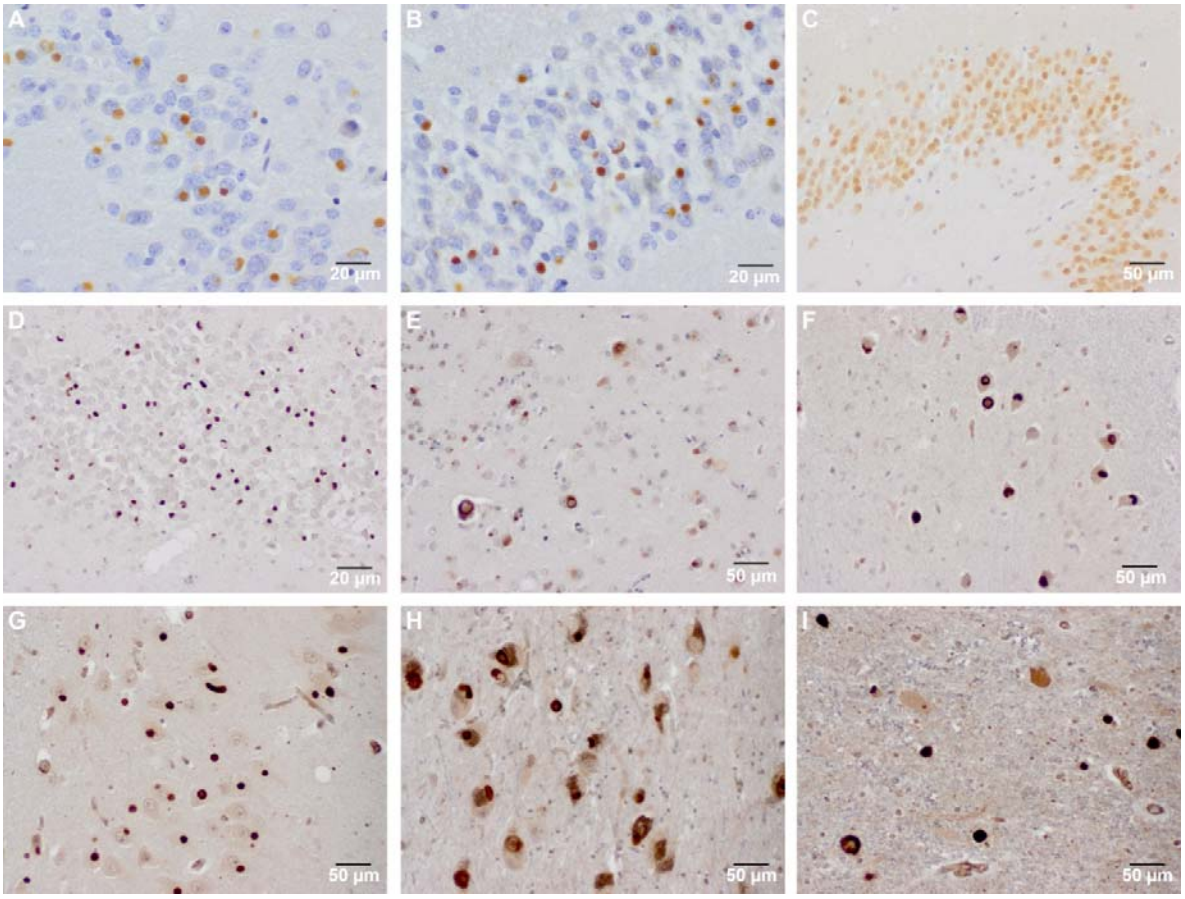

Figure 2 Distribution of neuronal cytoplasmatic inclusions found in familial neurofilamentopathy due to the mutation in the PRKAR1B
gene. Strong immunoreactivity of neuronal cytoplasmatic inclusions with antibodies against _-internexin (A) and p62 (B) in the dentate gyrus of the hippocampus is seen in Patient III:2. Granular cells of the dentate gyrus show diffuse weak nuclear staining without cytoplasmatic inclusions with FUS antibody (C). PRKAR1B-positive neuronal cytoplasmatic inclusions with various sizes are abundant in the hippocampus (D) and frontal region (E). A central unstained core surrounded by a strongly immunoreactive halo is found for larger inclusions in different cortices. Many inclusions are also found in the granular layer of the cerebellum (F). The same finding of PRKAR1Bpositive neuronal cytoplasmatic inclusions is seen in the hippocampus (G) of the second patient (Patient III:4). Substantia nigra show moderate neuron loss and positive immunoreactivity for PRKAR1B (H). These inclusions are also seen in lower motor neurons of the spinal cord (I). Scale bars: A and B = 20mm; C–I = 50mm.