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Brief communication

Familial early-onset dementia with complex neuropathologic phenotype and genomic background

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ABSTRACT

Despite significant progress in our understanding of hereditary neurodegenerative diseases, the list of genes associated with early-onset dementia is not yet complete. In the present study, we describe a familial neurodegenerative disorder characterized clinically as the behavioral and/or dysexecutive variant of Alzheimer's disease with neuroradiologic features of Alzheimer's disease, however, lacking amyloid-β deposits in the brain. Instead, we observed a complex, 4 repeat predominant, tauopathy, together with a TAR DNA-binding protein of 43 kDa proteinopathy. Whole-exome sequencing on 2 affected siblings and 1 unaffected aunt uncovered a large number of candidate genes, including *LRRK2* and *SYNE2*. In addition, *DDI1*, *KRBA1*, and *TOR1A* genes possessed novel stop-gain mutations only in the patients. Pathway, gene ontology, and network interaction analysis indicated the involvement of pathways related to neurodegeneration but revealed novel aspects also. This condition does not fit into any well-characterized category of neurodegenerative disorders. Exome sequencing did not disclose a single disease-specific gene mutation suggesting that a set of genes working together in different pathways may contribute to the etiology of the complex phenotype.

1. Introduction

Individuals with early-onset dementia (aged <65 years) have mostly either Alzheimer's disease (AD) or frontotemporal dementia (FTD). FTD is often associated with motor neuron disease or an extrapyramidal movement syndrome (Snowden et al., 2011). AD is characterized neuropathologically by the intracellular deposition of tau in the form of neurofibrillary tangles (NFTs) and by extracellular amyloid-β (Aβ) deposits (Montine et al., 2012). Early-onset AD is currently related to 3 major genes (*AβPP*: amyloid precursor protein gene; *PSEN1* and *2*: presenilin 1, 2), whereas several polymorphisms are reported as associated to sporadic late-onset AD (Schellenberg and Montine, 2012). The established term for the group of diseases with FTD is frontotemporal lobar degeneration (FTLD). The molecular pathologic classification of FTLD is protein-based (e.g., tau; TAR DNA-binding protein of 43 kDa, TAR DNA-binding protein of 43 kDa (TDP-43); and fused in sarcoma protein; Mackenzie et al., 2010). FTLD mostly associates with TDP-43 proteinopathy or tauopathy (Josephs et al., 2011). At least 4 subtypes of FTLD-TDP are distinguished (Mackenzie et al., 2011). FTLD-tau is classified based on the predominance of tau isoforms as 3-repeat (R) or 4R predominant or mixed 3R+4 R types. Pick disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease, and globular glial tauopathies are the major forms

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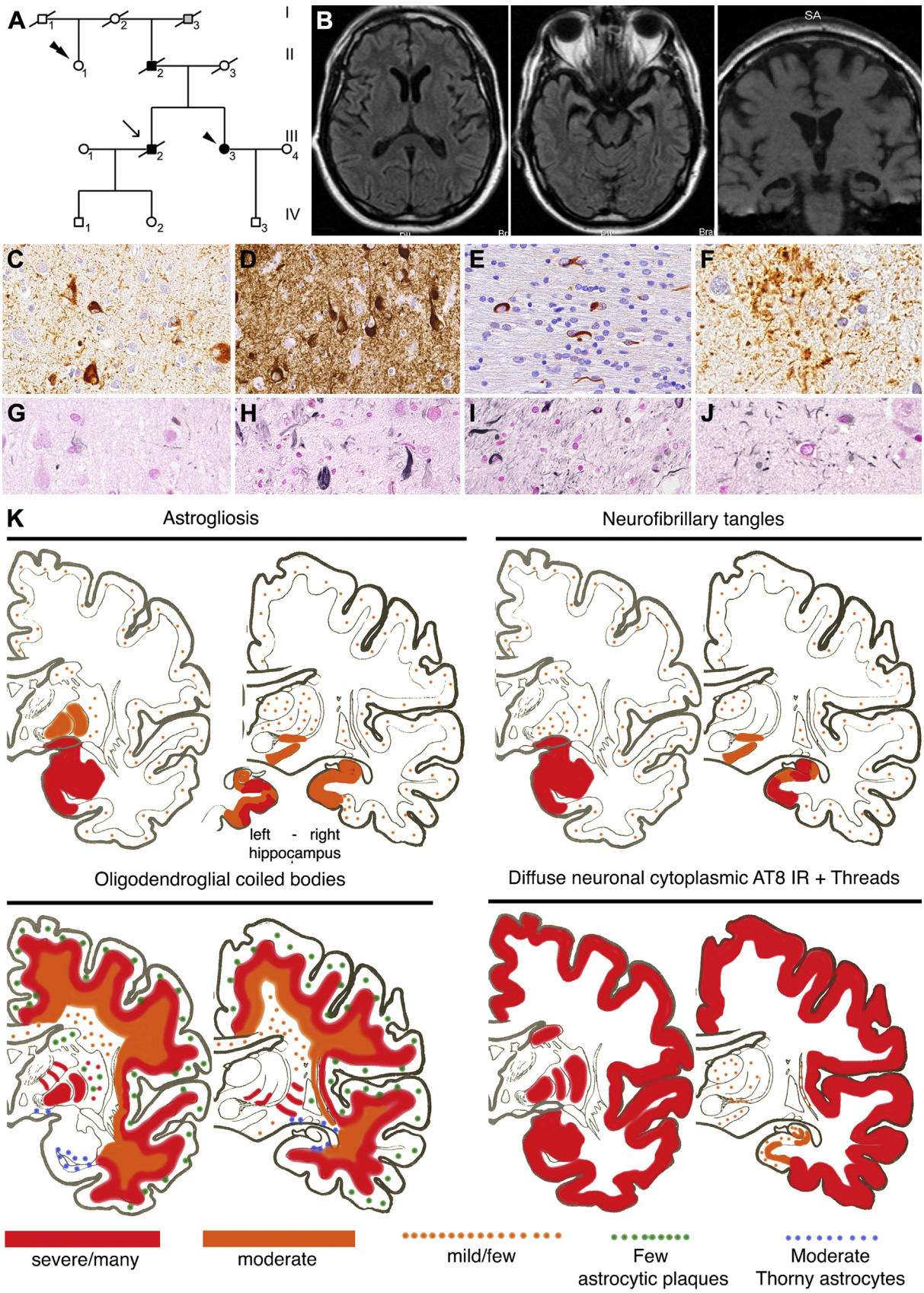

Fig. 1. Overview of the pedigree, brain MRI images, and neuropathology. The pedigree of the family (A), indicating the proband (black arrow), the affected proband's sister (arrowhead), and unaffected healthy aunt of the proband (double arrowhead). Filled symbols illustrate affected individuals and stricken out symbols indicate deceased individuals; squares, men; and circles, women. Gray colored box (I/3) indicates that there is a lack of detailed information on the clinical presentation. Brain MRI images (B) of the proband's sister (III-3; Fluid-attenuated inversion recovery). Note the atrophy in the medial temporal lobe. Immunostaining for pTau (AT8; C–F) and Gallyas silver staining (G–J) representing