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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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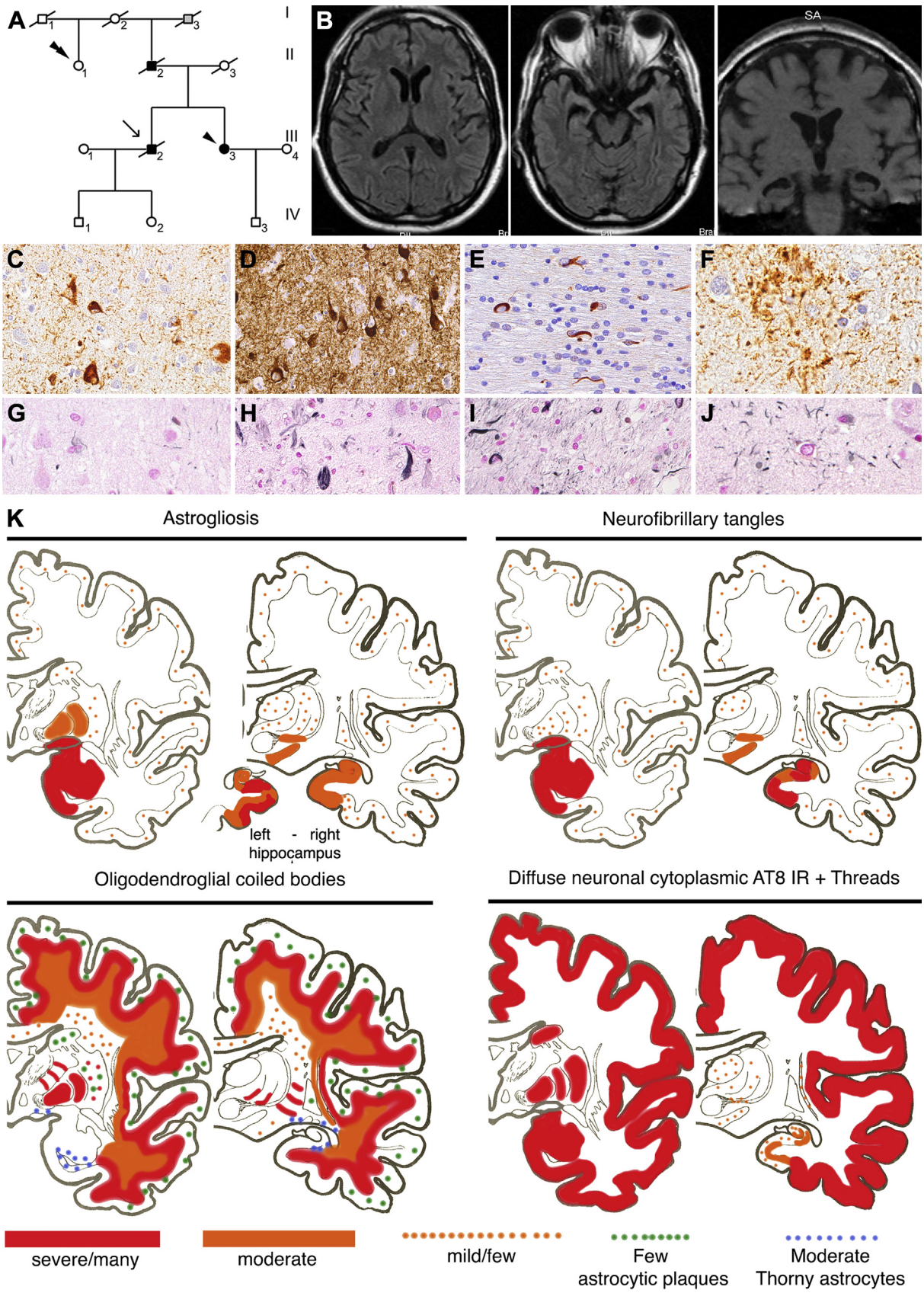


**Fig. 1.** Overview of the pedigree, brain MRI images, and neuropathology. The pedigree of the family (A), indicating the proband (black arrow), the affected proband's sister (arrowhead), and unaffected healthy aunt of the proband (double arrowhead). Filled symbols illustrate affected individuals and 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

(Kovacs, 2015). A further form, "primary age-related tauopathy" (PART) encompasses changes considered as normal aging and NFT-dementia (Crary et al., 2014).

Despite significant progress in our understanding of hereditary dementias, the list of genes associated with early-onset dementia is not yet complete. There are reports on early-onset hereditary disorders, where the absence of mutations in known genes suggests that a novel locus or loci are implicated in their pathogenesis (Clarimon et al., 2009; Ferrer et al., 2015; Fujioka et al., 2014). In this study, we present a kindred with early-onset dementia associated with a complex neuropathologic phenotype and genomic background.

## 2. Materials and methods

### 2.1. Clinical assessment

Clinical evaluation included neurologic, neuropsychological, and magnetic resonance imaging scans of the brain for 2 individuals. An unaffected aunt underwent neurologic and neuropsychologic examinations. The studies were performed with the informed consent of the family.

### 2.2. Neuropathology and biochemistry

The neuropathologic study (proband) was performed on formalin-fixed, paraffin-embedded blocks. Tau analysis in sarkosyl-insoluble fractions was performed using fresh samples from the frontal cortex of 2 AD cases, 1 FTLD-tau (4R) case, and frontal cortex of the proband. For details on methods and applied antibodies see Supplementary data 1.

### 2.3. DNA sample preparation and whole-exome sequencing

Exome sequencing was performed on the Illumina HiSeq 2000 platform. Sequence alignment and variant calling was performed using the pipeline of the Genome Analysis Toolkit (McKenna et al., 2010). ANNOVAR (Wang et al., 2010) was used for the annotation of functional variants. We identified regions identical by descent (IBD; Rodelsperger et al., 2011) in the affected siblings and filtered out mutations shared with the aunt. To facilitate the ranking of variants in genomic data sets, integrating information from multiple sources, we developed a novel tool that we are also making publicly available at http://paschou-lab.mbg.duth.gr/Software.html. We applied the Combined Annotation Dependent Depletion method to prioritize the importance of variants based on natural selection (Kircher et al., 2014). To combine the different gene lists from various prioritization methods, we created a numeric ranked matrix of genes and their scores from the various rankings assigning a combined score to each variant. Gene ontology and pathway analysis were performed using DAVID (Database for Annotation, Visualization and Integrated Discovery) and PANTHER (Protein ANalysis THrough Evolutionary Relationships) database (Huang da et al., 2009; Supplementary data 2).

## 3. Results

### 3.1. Clinical observations

Progressive cognitive decline developed in 4 individuals in 3 generations of this family (Fig. 1A). The clinical phenotype of 3 individuals from the family consisted of behavioral change, memory impairment, executive dysfunction, and mild extrapyramidal signs associated with medial temporal lobe atrophy (Fig. 1B), detectable in the magnetic resonance imaging in 2 individuals. The duration of illness ranged from 4 to at least 13 years. For details see online Supplementary data 1.

### 3.2. Neuropathology and biochemistry

Neuropathologic examination of the proband (III-2) revealed an amygdala-hippocampal-pallido-Luysian-nigral degeneration. The most prominent neuropathologic alteration was tau pathology characterized by diffuse neuronal cytoplasmic immunoreactivity, NFTs, grains, neuropil and white matter threads, oligodendroglial coiled bodies, and astrocytic plaques (Fig. 1C–F). Except for the pretangles, these were visible in Gallyas silver staining (Fig. 1G–J). Immunostaining for different anti-tau antibodies revealed that most of the tau pathologies were 4R-tau immunoreactive. However, 3R-tau positive NFTs were seen in the hippocampus and entorhinal cortex and nucleus basalis Meynert but also in the granule cell layer of the dentate gyrus as well as striatum and substantia nigra. The distribution of tau immunoreactivities (Fig. 1K) was compatible with PART (NFT-dementia) overlapping with CBD, PSP, and argyrophilic grain disease. Although 4R-tau pathology clearly predominated, the presence of subcortical 3R-tau immunoreactive NFTs were interpreted as an unusual feature. Only in the left side, we noted hippocampal sclerosis associated with TDP-43 proteinopathy reminiscent of FTLD-TDP type A (Mackenzie et al., 2011) involving also the limbic system, frontal cortex, and basal ganglia. Immunostaining for Aβ and α-synuclein was negative in all examined regions. Sarkosyl-insoluble fractions blotted with anti-phospho-tau Ser422 revealed 2 main bands of 68 kDa and 64 kDa. For details see online Supplementary data 1.

### 3.3. Genetic and genomic observations

Sanger sequencing of *MAPT*, *TARDBP*, *GRN*, *PRNP*, *PSEN* 1 and 2, and *AβPP* genes did not reveal any pathogenic mutation, therefore, we performed whole-exome sequencing. After sequence alignment and quality control steps, we were left with a total of 1,375,081 variants observed across the 2 studied patients and their unaffected aunt (27,599 exonic variants as annotated by the NCBI Reference Sequence database; online Supplementary data 3 Table S1). We identified portions of the genome that have been inherited IBD in the patients and proceeded to filter out those variants that had an identical genotype in the aunt and sibs, thus reducing the dataset to 121,492 variants (9835 exonic variants as annotated by NCBI Reference Sequence database including 4483 nonsynonymous, 39 stop-gain and 4 stop-loss variants). For the list of genes harboring, the longest IBD segments carrying at least one exonic or splicing variant shared among the affected siblings see Supplementary data 3 Table S2–S3; many of the top 20 genes have been implicated in AD (e.g., *CNTN5*, *LUZP2*, *CSMD1*, *CTNNA3*, *CDH2*).

We found 3 genes carrying novel stop-gain variants inherited IBD only in the affected sibs: *DDI1*, *KRBA1*, and *TOR1A* (Supplementary data 3 Table S4–S5). However, it was evident that the genetic etiology of the phenotype could not easily be attributed to a single gene. We took a closer look on genomic segments inherited IBD among affected siblings. Most important, we

pretangles in the temporal cortex (C and G), neurofibrillary tangles in the hippocampus CA1 (D and H), oligodendroglial coiled bodies in the white matter (E and I), and astrocytic plaques in the frontal cortex (F and J). Magnification for panels C-J is ×400. Color-coded representation of neuropathologic variables (K). Green dots indicate the regions where few astrocytic plaques were observed; blue dots indicate presence of thorny astrocytes. Note that only for astrogliosis left and right side of the hippocampus is shown due to asymmetry. Abbreviation: MRI, magnetic resonance imaging. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

encountered multiple genes that have been previously implicated in the etiology of neurodevelopmental or neuropsychiatric phenotypes. On gene ontology analysis (Supplementary data 3 Table S6) a theme of enrichment in cell adhesion molecules emerged; including classical cadherins (*CDH18* and *CDH2*), protocadherins (*PCDH7* and *PCDH15*), and molecules implicated in synaptic transmission (e.g., *NRXN1*, *CTNNA3*, *CNTN5*, and associated *CNTNAP5*).

Next, we ranked variants inherited IBD in the affected siblings and not shared by their aunt, to prioritize potentially causative genes. Applying a novel software tool (http://paschou-lab.mbg.duth.gr/Software.html), we combined information from multiple sources including databases predicting variant function, conservation level, and novelty (Table 1 and Supplementary data 3 Table S7–S8). This analysis highlighted *SYNE2*, *CSMD3*, *LRRK2*, and *NRXN1* as the top prioritized genes. Subsequently, variants in *LRRK2* and *SYNE2* were validated using Sanger sequencing (Supplementary data 3 Table S9). Pathway analysis among the top 100–500 ranked genes (Supplementary data 3 Table S10) revealed enrichment in genes related to cadherin-signaling, nicotinic acetylcholine receptor signaling, cytoskeletal regulation by Rho GTPase, inflammation mediated by chemokine and cytokine signaling, VEGF signaling, and Wnt signaling. Gene ontology analysis on these top 500 ranked genes revealed significant enrichment in processes related to cell adhesion, developmental processes, cell structure and motility, ectoderm and mesoderm development, and neurogenesis (Supplementary data 3 Table S11). Constructing a network among the top implicated genes also revealed interactions with AD-associated genes (Supplementary data 3 Table S12–S15, and Supplementary data 4).

## 4. Discussion

Based on the clinical symptoms and neuropsychologic profile, the predominantly medial temporal but less frontal lobe atrophy, we interpreted the phenotype in the frame of a behavioral and/or dysexecutive variant of AD (Dubois et al., 2014; Ossenkoppele et al., 2015). Neuropathologic examination of the proband did not reveal the hallmark lesion of AD as characterized by Aβ-deposition in the brain but combined features of primary tauopathies. The presence of astrocytic plaques together with oligodendroglial coiled bodies, threads, and abundant neuronal cytoplasmic tau immunoreactivity were interpreted as CBD-like features (Dickson et al., 2002). In addition, globose NFTs in the basal ganglia, subthalamic nucleus, and brainstem suggested PSP (Kovacs, 2015). Notably, the lack of tufted astrocytes and the presence of immunoreactivity for the 3R isoform of tau in subcortical NFTs are unusual for PSP. Abundant NFT pathology was seen in the hippocampus and basal nucleus of Meynert. All subregions of the hippocampus exhibited prominent neuronal tau pathology, with both 3R and 4R-tau isoform immunoreactivity compatible with NFT-dementia or as recently termed PART (Crary et al., 2014; Jellinger and Attems, 2007). Because of the age of the proband, this pathology could rather be interpreted as accelerated brain aging. Alterations in several genes may associate with tau pathology (Kovacs, 2015), which did not show up as candidates. Instead, our whole-exome analysis revealed a complex genomic background. The top prioritized genes included multiple genes that have been previously associated with AD and Parkinson's disease (PD) with *LRRK2* as one of the top candidates. Interestingly, *LRRK2* mutations have been described in association with limbic NFTs or PSP-like pathology (Poulopoulos et al., 2012; Santpere and Ferrer, 2009; Wider et al., 2010; Zimprich et al., 2004). In addition, experimental studies suggest that tau can be a Lrrk2 substrate and that this interaction can enhance salient features of human disease (Bailey et al., 2013; Kawakami and Ichikawa, 2015). We also observed TDP-43 pathology, which has been also described in *LRRK2* gene variations (Covy et al., 2009). Interestingly, the 2 affected siblings carried variant S1647T, a nonsynonymous mutation that has been associated with PD in China (Zheng et al., 2011), but they did not share haplotype 1647T-2397T which has been shown to have a protective effect against PD (Wu et al., 2013). The other variant detected (M2397T) has been recently associated to multiple system atrophy (Heckman et al., 2014).

The top gene on the list of prioritized variants was *SYNE2*. Mutations in *SYNE1* and *SYNE2* (also called Nesprin-1 and 2) are associated with numerous diseases including autism, cerebellar ataxia, and muscular dystrophy (Zhang et al., 2007). Interestingly, evaluation of microarray data of AD using cluster analysis to identify biomarker genes also found *SYNE2* to associate with AD-phenotype (Guttula et al., 2012).

In addition, we found that the patients shared novel stop-gain variants inherited in IBD in 3 genes. *DDI1* belongs to a family of shuttle proteins targeting polyubiquitinated substrates for proteasomal degradation, which is a central component in the pathogenesis of neurodegenerative diseases (Nowicka et al., 2015). *KRBA1* interacts among others with glycogen synthase kinase-3beta (GSK3B; Pilot-Storck et al., 2010). Interestingly, *GSK3B* and *MAPT* (tau) genes interact in AD (Kwok et al., 2008), furthermore, GSK3B acts as putative mediator in aberrant hyperphosphorylation of the tau protein (Jayapalan and Natarajan, 2013). *TOR1A* is the causative gene for the DYT1 form of hereditary early-onset generalized

**Table 1**
Top 10 genes prioritized as potentially implicated in the phenotype under study using our "combined ranked" method

| Gene | Gene summary | Gene name |
|---|---|---|
| *SYNE2* | The encoded protein is a nuclear outer membrane protein that binds cytoplasmic F-actin. | Spectrin repeat containing, nuclear envelope 2. |
| *CSMD3* | NA | CUB and Sushi multiple domains 3. |
| *LRRK2* | Member of the leucine-rich repeat kinase family. Mutations in this gene have been associated with Parkinson's disease. | Leucine-rich repeat kinase 2. |
| *NRXN1* | Neurexins function in the vertebrate nervous system as cell adhesion molecules and receptors. | Neurexin 1. |
| *LOC401164* | NA. | NA. |
| *FRG1* | Maps to a location 100 kb centromeric of the repeat units on chromosome 4q35, which are deleted in facioscapulohumeral muscular dystrophy (FSHD). | FSHD region gene 1. |
| *CSMD1* | NA. | CUB and Sushi multiple domains 1. |
| *PCDH15* | Member of the cadherin superfamily. Mutations in this gene result in hearing loss and Usher Syndrome Type IF (USH1F). | Protocadherin-related 15. |
| *CTNNA3* | Encodes a protein that belongs to the vinculin/alpha-catenin family. The encoded protein plays a role in cell–cell adhesion in muscle cells. | Catenin, alpha 3. |
| *LPHN3* | This gene encodes a member of the latrophilin subfamily of G-protein coupled receptors (GPCR). Latrophilins may function in both cell adhesion and signal transduction. | Latrophilin 3. |

Key: CUB, complement proteins C1r/C1s, Uegf, and Bmp 1; NA, not available.

dystonia (Leung et al., 2001). A role for torsin A as an endoplasmic reticulum chaperone protein was suggested; however, neuropathologic studies did not reveal prominent tauopathy as seen in our case (Paudel et al., 2012).

In summary, we provide a list of candidate genes, which can be evaluated in early-onset dementia cases still lacking an established genetic background. Our findings are concordant with recent studies suggesting that a set of genes working together in different pathways may contribute to the etiology of complex phenotypes.

## Disclosure statement

The authors report no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version at http://dx.doi.org/10.1016/j.neurobiolaging.2016.03.012.

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