Novel gene variations in early-onset frontotemporal dementia with positive family history of neural ceroid lipofuscinosis-1

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Practical Implications

Consider polygenetic effects in the differential diagnosis of early-onset frontotemporal dementia.

Mutations in the palmitoyl protein thioesterase 1 gene (*PPT1*) cause classic infantile neuronal ceroid lipofuscinosis-1 (CLN1),¹ characterized by rapid visual and psychomotor deterioration, seizures, and death in early to mid-childhood. In rare cases, *PPT1* gene mutations cause visual and cognitive decline in young adulthood.^{2,3} Genetic and clinicopathologic phenotypes of frontotemporal lobar degeneration (FTLD) are markedly different from CLN1.^{4,5} We present a case of very early-onset FTLD with a positive family history of CLN1 and discuss its association with 2 novel mutations in the *PPT1* gene and a novel variation in the *MAPT* gene.

A 37-year-old man of Turkish descent presented with apathy and disinhibition over a period of 1 year. According to his relatives, onset of symptoms occurred after his 6-year-old daughter died from CLN1. The patient was diagnosed with schizophrenia prior to his admission, and he received several trials of antipsychotic medication that were all ineffective. Past medical history revealed diagnoses of nonalcoholic steatohepatitis, left-sided duplex kidney, tonsillectomy, and tobacco use. Family history was negative for other neurodegenerative disorders, positive for thalassemia, and suggestive of cystic fibrosis (figure 1). Laboratory and CSF findings were normal, including screening for infection/inflammation and CSF levels of total tau, phosphorylated tau protein (181), A β 42, A β 42/A β 40 ratio, neuron-specific enolase, and S100b. ECG demonstrated sinus rhythm at 83 bpm. EEG presented alpha oscillations.

Six months before admission, brain MRI displayed bilateral frontotemporal lobe atrophy and right-sided extension of optic nerve sheath. MRI follow-up evaluation did not show any progression (figure 2A). Fluorodeoxyglucose PET displayed frontotemporal hypometabolism (figure 2B). Ophthalmologic examination showed bilateral myopia, astigmatism, and normal fundi without signs of papilledema. Visual evoked responses were bilaterally normal. The patient scored 28/30 on the Mini-Mental State Examination (MMSE).

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Figure 1 Pedigree of the patient whose daughter was diagnosed with CLN1 disease

Patient is subject III.7. He married his second cousin. One daughter was diagnosed with CLN1 disease. The patient, his spouse, and 2 children were heterozygous for 2 *PPT1* mutations. Family history was positive for cardiovascular diseases, thalassemia, cancer, migraine, and unknown lung disease. CLN1 = neuronal ceroid lipofuscinosis-1.

Six months later, the patient was readmitted due to hyperphagia, aphasia, apraxia, and incontinence. The MMSE score had declined from 28 points to 16 points. Laboratory findings were normal. Due to agitation and uncooperative behavior, we were unable to perform another follow-up brain MRI scan. CT imaging revealed pronounced frontotemporal atrophy (figure 2C). Ophthalmologic findings and visual evoked responses remained unchanged. Tibial somatosensory evoked responses were delayed bilaterally. Light and electron microscopic analysis of skin biopsy samples demonstrated myelin debris in Schwann cells and signs of nonmyelinated nerve fiber loss.

The diagnosis of the patient's deceased daughter had been made by *PPT1* test on blood samples and evidence of homozygosity for 2 unknown-variant *PPT1* gene mutations (c.105_110dup and c.627+4A>G). Both the patient and his ex-wife (his second cousin) were found to be heterozygous for these mutations and negative for cystic fibrosis and thalassemia gene mutations.

Genetic testing for hexanucleotide mutation in chromosome 9 open reading frame 72 gene and panel testing for mutations in known genes associated with FTL⁵ (*APOE*, amyloid precursor protein, charged multivesicular body protein 2B, fused in sarcoma, granulin, prion protein, presenilin 1, presenilin 2, sortelin-related receptor, L [DLR class] A repeats containing, TAR DNA binding protein, and valosin containing protein) were negative. However, we found a heterozygosity for a novel microtubule-associated protein tau gene (*MAPT*) variation (c.664C>A) in our patient. Blood levels of *PPT1* and tripeptidyl-peptidase I and serum levels of progranulin were normal.

This is a case report of very early-onset FTL⁵ with a positive family history of CLN1 and novel mutations in 2 candidate genes: a heterozygous *MAPT* and 2 heterozygous *PPT1* gene mutations. Mutations in *MAPT* (ENSEMBL transcript ID ENST00000262410) account for about 15%–20% of familial FTL⁵ cases and are autosomal dominantly inherited.⁶ According to Exome Variant Server (<http://evs.gs.washington.edu/EVS>), the patient's sequence variant c.664C>A results in a missense mutation (p.R222S). Also, PolyPhen-2 (genetics.bwh.harvard.edu) predicted the variant to be possibly damaging (score of 0.826; sensitivity 0.84, specificity 0.93), whereas MutationTaster (mutationtaster.org) suggested a polymorphism only.

Considering the positive family history of CLN1, we also reviewed the 2 novel mutations in the *PPT1* gene (ENSEMBL transcript ID ENST00000433473). For nucleotide change c.627+4A>G, MutationTaster and Alamut predicted splice site changes. Nucleotide duplication c.105_110dup was predicted to be pathogenic via amino acid insertions. Considering

Figure 2 Neuroradiologic findings

(A) Axial T2 fluid-attenuated inversion recovery image at the level of lateral ventricles showing regional atrophy in frontotemporal lobes. (B) PET scan illustrating lower frontotemporal metabolism. (C) Follow-up CT scan indicating progression of frontotemporal atrophy 6 months after the initial admission.

the clinical phenotype, 3 cases of adult-onset CLN1 disease with *PPT1* gene mutations have been reported so far. The age at onset was 22 years in a woman from Great Britain² and 31 and 38 years in 2 sisters from France.³ In each case, the clinical phenotype was characterized by depressed mood, cognitive dysfunction, visual impairment, and retinal pigmentation. Neuroimaging revealed generalized cerebral atrophy in all cases. Atrophy of the optic nerve together with late-stage cerebellar ataxia and extrapyramidal signs were also present in the 2 French sisters. Compound heterozygosity was always present with the same nonsense mutation, c.451C>T, and either missense mutation c.134A>G² or c.322G>C,³ indicating pleiotropic effects. Since our patient was also heterozygous for 2 *PPT1* gene mutations, the frontotemporal phenotype could be one manifestation of an adult-onset CLN1 disease. However, blood levels of PPT1 were normal and the patient's spouse sharing the patient's 2 mutations was described to be healthy by relatives. Unfortunately, further examinations (e.g., whole-exome sequencing) could not be performed in this patient and his relatives because they returned to their home country soon after his hospital discharge.

Despite the differences in clinicopathology between FTLN and CLN1, a common genetic background—pleiotropic effects of progranulin mutations—has been discussed on the basis of a linkage analysis in a family with adult-onset CLN1.⁷ In our patient, however, neither progranulin exon sequencing nor serum level of progranulin was altered.

The clinical presentation of our patient resembles FTLN rather than adult-onset CLN1. The early age at onset is highly unusual for FTLN,⁴ and the family history was positive for CLN1. At this stage, although we were able to identify 2 novel *PPT1* gene mutations, it appears unlikely that the patient's condition was caused by *PPT1* gene mutations alone. While we cannot fully rule out polygenic effects of *MAPT* and *PPT1* gene mutations, our case suggests that the novel *MAPT* gene c.664C>A variation contributes to FTLN pathogenesis.

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