Tau and α-Synuclein Inclusions in a Case of Familial Frontotemporal Dementia and Progressive Aphasia

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Abstract

Recent studies have shown that neurofibrillary tangles are frequently accompanied by α-synuclein inclusions in sporadic and familial Alzheimer disease, in Down syndrome, in progressive supranuclear palsy, and Parkinsonism dementia complex of Guam. Here we report the cases of 2 brothers with familial progressive aphasia who developed features of frontotemporal dementia with predominant tau pathology but also α-synuclein pathology. The 2 patients’ brains revealed abundant tau pathology in the hippocampus and basal ganglia, whereas tau and α-synuclein aggregates coexisted only in the nucleus basalis of Meynert, the only region where α-synuclein was present. In this brain region, abundant Lewy bodies, Lewy neurites, and tau inclusions were found; the pathology was more abundant in the older than in the younger brother. Sarkosyl-insoluble tau extracted from brains of the 2 patients showed the presence of tau filaments that contained 3 major tau bands of 60, 64, and 68 kDa on Western blot analysis. These bands contained mainly tau with 3 and 4 repeats and one amino-terminal insert. No mutations were identified in the tau, α-synuclein, β-synuclein, or parkin genes. We think that this is the first report showing a specific colocalization of neurofibrillary tangles and Lewy bodies in a family with progressive aphasia.

Key Words: α-Synuclein, Frontotemporal dementia, Lewy bodies, Neurodegenerative diseases, Neurofibrillary tangles, Progressive aphasia, Tau protein.

INTRODUCTION

Tauopathies and α-synucleinopathies define 2 distinct groups of neurodegenerative diseases: Tauopathies are disorders with characteristic filamentous inclusions made of hyperphosphorylated tau, such as Alzheimer disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration, and some forms of frontotemporal dementia (FTD) (1, 2), whereas α-synucleinopathies are disorders characterized by eosinophilic inclusions composed of α-synuclein, such as Lewy bodies in Parkinson disease (PD) and dementia with Lewy bodies, and glial cytoplasmic inclusions in multiple system atrophy (3–5).

Recent studies, however, have revealed the coexistence of tau and α-synuclein pathologies in some cases of neurodegenerative diseases. For example, α-synuclein in the form of Lewy bodies and Lewy neurites has recently been identified in disorders with prominent tau pathology such as familial and sporadic AD, Down syndrome, PSP, neurodegeneration with brain iron accumulation, Parkinsonism dementia complex of Guam and a case with FTD-MND (6–13). In these disorders, neurofibrillary tangles coexist with α-synuclein-positive inclusions, and the two pathologies often colocalize in certain brain regions. In AD, for example, they colocalize primarily in the amygdala. Furthermore, tau inclusions and widespread α-synuclein aggregates have also been found in some of the brains of patients from the Contursi kindred with familial PD (14), and tau pathology has been reported in a subset of Lewy bodies in the brains of patients with PD (15). Here we report a study of 2 brothers diagnosed with progressive aphasia who developed behavioral features typical of frontotemporal dementia.

The progressive aphasias are included within the broad range of frontotemporal dementia, although some authorities prefer the general label frontotemporal lobar degeneration to describe these non-Alzheimer dementias (16, 17). Two major forms of progressive aphasia are recognized depending on speech fluency and the nature of the comprehension disorder. Sporadic cases can typically be classified as fluent (also known as semantic dementia) or nonfluent (18). The majority of cases of progressive aphasia are sporadic and only a few familial cases have been described to date (19–22).

The 2 patients described here presented with very similar profiles of language impairment classified as progressive nonfluent aphasia (23). MRI scans (23) and macroscopic and microscopic examination revealed severe left-hemisphere atrophy and neuronal loss in cortical regions of the brain in both patients. Tau pathology was the main neuropathologic feature but α-synuclein pathology was also present, in the absence of β-amloid plaques. The α-synuclein pathology was specifically localized in the nucleus basalis of...
Meynert where tau pathology was also present but usually in
distinct neurons.

Western blot analysis and electron microscopy of
sarkosyl-insoluble tau extracted from brains of the 2 patients
confirmed the presence of tau filaments, which consisted
mainly of 4-repeat tau isoforms and had the appearance of
straight and paired helical structures. No mutations were
identified in the tau, α- and β-synuclein, or the parkin coding
regions or exon-intron junctions. We think that this is the first
study showing the coexistence of tau and α-synuclein ag-
gregates in a family presenting with progressive aphasia.

**MATERIALS AND METHODS**

**Patients**

Patient 1, a right-handed security gate importer,
presented in April 1995 at the age of 50, complaining of pro-
gressive language impairment over 18 months. His speech was
nonfluent and hesitant, with frequent word-finding pauses,
phonetic paraphasias, and short phrases. He made occasional
syntactic errors in speech and had difficulty understanding
syntactically complex language. Formal testing showed a
pattern of surface dyslexia, but his visuospatial functions, as
well as memory and problem solving in nonverbal domains,
were unimpaired. There were no physical signs, and his
medical history of partially resolved depression was not
thought to be contributory. An MRI scan was performed soon
after presentation, which showed left-sided atrophy, particu-
larly marked in polar and inferior temporal areas but also
involving the frontal lobe. His deficits worsened rapidly, and
by 1997 he had no useful language. He also developed more
generalized cognitive deficits, obsessive and aggressive be-
haviors, and eventually Parkinsonism. He died in February
1999.

Patient 2, a right-handed baker, was more than 5 years
older than Patient 1, but presented only in January 1996 at 56
years of age, having noticed progressive language impairments
for the preceding 2 years. His spontaneous speech, like his
brother’s, was nonfluent, with word-finding difficulty, phonetic
paraphasia and grammatical errors, and he also showed a
surface dyslexia and dysgraphia. Syntactic comprehension
was more severely impaired than single-word comprehension.
He was less anomic than Patient 1, and at presentation per-
formed much better on tests of word production to a letter or
category cue, although his performance on all these tests was
well below normal levels. His nonverbal skills were largely
intact, and there were no physical signs. He had been di-
agnosed with temporal lobe epilepsy in 1991, which was
controlled on carbamazepine. He was also found to be de-
pressed at presentation. In comparison with Patient 1, the MRI
scan of Patient 2 showed less marked atrophy, which was
confined to the left perisylvian region, with a milder degree of
left temporal lobe involvement. His progression was rapid. He
developed marked behavioral symptoms and died in residen-
tial care in November 2000. The father of both patients died in
his 80s and suffered from dementia in late life, but there was
no other significant family history. Neither of the patients’
parents had any other children. Further details of the clinical,
cognitive, neuropsychologic, and brain imaging studies of the
two brothers are given in Croot et al (23).

**Neuropathology**

Postmortem brain examination was performed in both
cases. The brain was bisected through the corpus callosum in
the sagittal plane. Blocks of tissue were removed from all
major cortical areas of the right cerebral hemisphere before
processing through paraffin. The right cerebral hemisphere,
the right cerebellar hemisphere, and the left half of the
brainstem were sliced and then rapidly frozen on a brass plate
cooled on dry ice to −50°C. This tissue was used for DNA
analysis and for biochemical studies of tau protein. The con-
tralateral (left) cerebral hemisphere, left cerebellar hemisphere,
and right hemi-brainstem were immersed in 10% formalin
saline for four weeks prior to dissection. Subsequently, the
fixed cerebral hemisphere was cut coronally into 0.5-cm-thick
slices, the brainstem was cut into 0.5-cm-thick slices in the
horizontal plane, and the cerebellar hemisphere was cut
vertically through the dentate nucleus. The fixed brain slices
were sampled according to the CERAD protocol (24) and
tissue blocks were processed through paraffin wax. Ten-
micron sections were cut from paraffin-embedded tissue and
stained with hematoxylin and eosin or used for immunohis-
tochemistry.

**Immunohistochemistry**

Sections from the following brain areas of Patients 1 and
2 were studied: hippocampus, occipital cortex, enthorinal cor-
tex, cingulate cortex, cerebellum, basal ganglia, midbrain,
medulla, pons, amygdala, Brodmann’s area 21/22, and
Brodmann’s areas 40 and 46. Sections were treated with meth-
anol (20%) peroxide (1.5%) for 30 minutes prior to overnight
incubation with primary antibodies at 4°C. The antibody
staining was visualized using the biotin/avidin Vectastain sys-
tem (Vector Laboratories, Peterborough, UK), as previously
described (4).

The following primary antibodies were used: phosphor-
ylation-dependent anti-tau monoclonal antibodies AT8,
AT100 (Autogen Bioclear, Imagenetics, Calne, UK) and
12E8 (kind gift of P. Seubert, Athena Neurosciences, Worcester, MA), antisera against amyloid-β (kind gift of V.
M.-Y. Lee, University of Pennsylvania, USA), anti-ubiquitin
(Dakocytomation, Ely, UK) and anti-α-synuclein Per7 (kind
gift of V. M.-Y. Lee, University of Pennsylvania, USA), anti-ubiquitin
(Dakocytomation, Ely, UK) and anti-α-synuclein Per7 (kind
gift of M. Goedert, Medical Research Council, Laboratory of
Molecular Biology, UK ) and S129 (kind gift of T. Iwatsubo,
University of Tokyo, Japan). AT8 recognizes tau phosphor-
ylated at S202 and T205, AT100 recognizes tau phosphor-
ylated at S262 and/or S356 (using the numbering of the longest
human brain tau isoform). Per7 recognizes the middle region
of human α-synuclein. S129 recognizes α-synuclein phosphor-
ylated at S129. All of the above primary antibodies were
used at 1/1,000. Secondary antibodies (Vector Laboratories)
were used at a dilution of 1/250 and staining was developed
using 3,3 diaminobenzidine (Vector Laboratories).

For double-labeling experiments with tau AT8 and α-
synuclein Per7 antibodies, AT8 staining was visualized using
diaminobenzidine and Per7 staining was visualized with the
peroxidase substrate kit Vector SG (Vector Laboratories). Sections stained with the anti-Aβ antiserum were pretreated with 90% formic acid for 5 minutes. Immunohistochemistry with 12E8 was carried out in parallel on AD sections, which were used as a positive control for the antibody staining.

**DNA Extraction and Sequence Analysis**

Genomic DNA was extracted from blood samples of Patients 1 and 2 using DNA extraction kit (Qiagen, Crawley, UK). The following DNA sequences were analyzed: *Tau* exons 1, 2, 3, 4, 7, 9, 10, 11, 12, and 13; *parkin* exons 1–13; *α-synuclein* exons 1–4; as well as exon-intron junctions. The coding region of *β-synuclein* was also analyzed by PCR amplification and sequencing of cDNA from Patients 1 and 2.

The sequences were amplified using 10 ng of genomic DNA or 5 ng of cDNA in 50 μL PCR reactions. The primers for tau, parkin, and α-synuclein were designed to target the intron-exon boundaries of each exon as described previously (25–27). For the amplification of β-synuclein cDNA, the following primers were used: forward primer, 5’-AGGCCGCGCTTCCATCCCC-3’; reverse primer, 5’-ACAGGGACAAATGTGCTGC-3’. Amplification was performed for 35 cycles under the following conditions: Denaturation 95°C for 1 minute; annealing 50°C to 65°C (depending on the primer pair used) for 0.5 minutes; extension 72°C for 1.5 minutes, with a final 10 minute extension at 72°C. Dideoxynucleotide sequencing of double-stranded DNA was performed using the Thermosequenase kit and 32P-dideoxynucleotides (Amersham Biosciences, Chalfont St. Giles, UK).

**Semiquantitative PCR**

Genomic DNA from the 2 patients and from 2 un-affected controls was used for semiquantitative PCR experiments to investigate the number of tau gene copies present in the 2 patients. Forty nanograms of genomic DNA were used in 50 μL PCR reactions. Amplification was performed for 24, 27, and 30 cycles under the following conditions: denaturation 95°C for 1 minute; annealing 55°C for 0.5 minutes, extension 72°C for 1 minute, with a final 10 minute extension at 72°C. Tau gene exons 7, 9, and 13 were amplified. The actin gene was also amplified in each PCR reaction tube and was used as an internal control for equal DNA amplification and comparison between the samples. The primer sequences used for the amplification of the actin gene are: forward primer, 5’-AGCCATGTCACGACCCATCC-3’; reverse primer, 5’-TTTTATGTTCCAGCATCCATCC-3’. α-Synuclein gene copy number was determined using Taq Man PCR Kit (Amersham Biosciences) to specifically amplify exons 2 and 4 of the *α-synuclein* gene in the patients and 2 controls. Furthermore, as control, exons 2 and 4 of the GAPDH gene were also amplified in both patients and control genomic DNAs.

**Protein Extraction and Immunoblotting**

For extraction of parkin protein, 50 mg of tissue from Patients 1 and 2 was homogenized in Tris-HCl (pH 7.4) containing protease inhibitors (Protease Inhibitors Complete Kit, Roche, Welwyn Garden City, UK). The homogenate was centrifuged at 13,000 rpm for 5 minutes and the supernatant collected. Twenty micrograms of protein were run on a 12% SDS-PAGE and immunoblotted with anti-parkin antibody (Dakocytomation) at a concentration of 1/5,000. For extraction of soluble tau, 100 mg of tissue from the frontal cortex and the hippocampus of Patients 1 and 2 and from 2 controls were homogenized in 0.5 mL 2.5% perchloric acid, as previously described (28).

Sarkosyl-insoluble tau protein was extracted from the hippocampus, as previously described (29). Insoluble tau extracted from an AD patient was used as a control. Dephosphorylation and immunoblotting were carried out as previously described (29). The phosphorylation-independent anti-tau antiserum BR133, specific for the amino-terminus of tau and the phosphorylation-dependent monoclonal antibodies AT8 and 12E8, was used for immunoblotting. BR133 and AT8 were used at a dilution of 1/10,000 and 12E8 was diluted 1/5,000. Peroxidase-linked secondary antibodies (Dakocytomation) were used at a dilution of 1/2,500 and the immunoblots were visualized using the ECL system (Amersham Biosciences).

**RESULTS**

**Neuropathology**

**Patient 1: Macroscopic and Microscopic Findings**

The brain of Patient 1 weighed 1,020 g at the time of autopsy. The cerebral gyri of the frontal lobe were severely atrophied, especially the frontal pole and the superior frontal gyrus (Fig. 1A, 1C). The anterior part of the temporal lobe was also severely atrophied. The frontotemporal atrophy was more marked in the left cerebral hemisphere than the corresponding areas on the right side. The medial temporal and parietal lobes were also atrophied. The caudate nucleus was slightly reduced in size with loss of the medial convexity, but other subcortical nuclei were unaffected. The brainstem and cerebellum were unremarkable. Notably, the substantia nigra and the locus coeruleus were normally pigmented with moderate cell loss.

Sections from left frontal and temporal cortical areas showed severe nerve cell loss, spongiosis, and reactive gliosis, whereas in sections from equivalent areas on the right side in the subiculum and in parietal cortex (BA 7 and 40), nerve cell loss was much less severe. The hippocampus and para-hippocampal gyrus were better preserved than immediately adjacent association cortex and, within these anatomic structures, the dentate fascia and entorhinal cortex were less severely affected than Sommer’s sector. The substantia nigra showed mild nerve cell loss and the rest of the brainstem and the cerebellum showed no histologic abnormality.
Patient 2: Macroscopic and Microscopic Findings

The brain of the older brother Patient 2 (whose MRI scan at presentation showed less severe atrophy compared with Patient 1) weighed only 900 g at the time of autopsy. The cerebrum was severely atrophic. The most severely atrophied regions were the superior and inferior parietal lobules, the angular gyrus, and the superior temporal gyrus (Fig. 1B, 1D). The orbital frontal cortex and the cingulate gyrus were least affected. The left cerebral hemisphere was more severely affected than the right hemisphere. The central white matter and the lateral ventricles were respectively reduced and dilated in proportion to the degree of cortical atrophy. The basal ganglia and thalamus were also atrophied. The substantia nigra and locus coeruleus were moderately pale and the cerebellum was unremarkable.

Light microscopy showed mild to severe neuronal loss and reactive astrocytic gliosis. The most severe degree of nerve cell loss occurred in left anterior hippocampus and entorhinal cortex, which contrasted with the relative preservation of nerve cells in the contralateral medial temporal lobe. Moderate to severe nerve cell loss was evident in frontal, temporal, and parietal association cortex. The most severely affected areas were BA 39 and BA 44/45. In the brainstem, the substantia nigra and locus coeruleus showed mild and moderate nerve cell loss, respectively.

Immunohistochemistry

Immunohistochemistry experiments revealed abundant tau-positive neuronal and glial inclusions in the dentate gyrus, the CA2 and CA3 areas in the hippocampus, and in the entorhinal cortex. Some tau-positive inclusions were also seen in the basal ganglia of both patients. The tau inclusions were stained with phosphorylation-dependent antibodies AT8 and AT100. In the affected areas, neurofibrillary tangles, tau neurites, and neuropil threads were observed (Fig. 2). Some tufted astrocytes were also present in the entorhinal cortex of Patient 2 (Fig. 2D).

Tau pathology was present in the same regions in the brains of the 2 brothers, but it was more abundant in Patient 2, with more numerous tau inclusions and denser neuropil threads. More marked neuronal loss was also observed in Patient 2 in the tau-affected areas. Anti-tau antibody 12E8 did not stain any neurons or glial deposits, although it stained tangles in an AD control brain. α-Synuclein-positive Lewy bodies and Lewy neurites, immunoreactive with Per7 and S129 antibodies, localized specifically in the area of the nucleus basalis of Meynert in both patients (Fig. 3). Hyperphosphorylated tau inclusions, in the form of neurofibrillary tangles and tau-positive neurites were also present in the same groups of cells in this area. Double immunostaining with AT8 and Per-7 antibodies showed that tau and α-synuclein inclusions usually did not colocalize within the same cell (Fig. 3). The distribution of tau and α-synuclein pathology in the 2 cases was similar, but it was overall less abundant in Patient 1 and was accompanied by less marked neuronal loss compared with Patient 2. In both patients, the amygdala was not greatly affected and mainly did not contain tau or α-synuclein inclusions. No immunoreactivity for β-amyloid was found in the brain of either patient and immunostaining for ubiquitin was normal.

Genetic Analysis

Genomic DNA sequencing of Patients 1 and 2 showed wild-type sequence for the tau gene. Patient 1 was homozygous for the less common H2 tau haplotype and Patient 2 was heterozygous H1/H2 (31). Furthermore, we performed semiquantitative PCR experiments to investigate the tau gene copy number in the 2 patients. Our experiments did not show any difference in the tau gene copy numbers compared with controls, therefore excluding the possibility of any abnormal tau gene amplification.

After the identification of α-synuclein-positive Lewy bodies and Lewy neurites in the brains of these patients, the α-synuclein gene was sequenced but no mutations were
identified. Furthermore, Taq Man PCR analysis of the α-synuclein gene showed a normal copy number.

In search of a potential genetic factor involved in the development of both tau and α-synuclein pathology in these rare cases, we screened the parkin gene sequence. Several studies have linked parkin protein dysfunction, independently, to both α-synuclein and tau in neurodegenerative disorders (26, 32–34). In our study, we identified no mutations in the sequence of the parkin gene, and from our biochemical analysis the parkin protein in the 2 patients was similar to controls on immunoblots. The β-synuclein gene was also studied as it has been suggested that dysfunction of β-synuclein can lead to α-synuclein aggregation (35). Sequencing of the β-synuclein cDNA showed wild-type sequence.

**Tau Protein Extraction, Dephosphorylation, and Immunoblotting**

Normal levels of 3-repeat and 4-repeat tau isoforms were present in soluble tau extracted from the hippocampus (Fig. 4A) and frontal cortex (not shown) in the brains of Patients 1 and 2. Sarkosyl-insoluble tau extracted from the hippocampus of Patients 1 and 2 appeared as 3 major bands of 60, 64, and 68 kDa following immunoblotting with tau antiserum BR133 (Fig. 4B). The same pattern was seen with antibody AT8. In contrast, the phosphorylation-dependent anti-tau antibody 12E8, which labeled the paired helical filament (PHF)-tau pathology of the AD control, failed to label the sarkosyl-insoluble tau bands of Patients 1 and 2 (data not shown). Following alkaline phosphatase treatment, the sarkosyl-insoluble aggregates resolved into three major bands that aligned with tau isoforms with 4R + 1N, 4R + 0N, 3R + 0N, and a very weak band that aligned with 3R + 1N, when compared with the six recombinant tau isoforms (Fig. 4C).

**Electron Microscopy of Tau Filaments**

Electron microscopy of immunolabeled preparations identified tau-positive filaments in sarkosyl-insoluble material from the hippocampus of Patients 1 and 2 (Fig. 5). Filaments were labeled by the phosphorylation-dependent monoclonal antibody AT8, and the majority of them had PHF morphology (Fig. 5A, 5B). A small minority of the filaments extracted from the brain of Patient 2 were straight filaments (Fig. 5C).
DISCUSSION

The majority of cases of progressive aphasia are sporadic, and only very few familial cases have been described to date (19–22). Furthermore, the information available on the neuropathology of familial cases is limited. Our study describes the neuropathology, genetics, and tau biochemistry of a rare case of familial FTD with progressive aphasia.

The 2 brothers presented at 50 and 56 years of age (Patients 1 and 2, respectively) with very similar clinical and neuropsychologic features. Their clinical history revealed that they had both suffered from depression in the years before presentation. At the time of presentation, both brothers had marked deficits in expressive language abilities, with a similar profile on linguistic neuropsychologic tests (23). In both cases, more global dementia developed quite rapidly with marked behavioral changes. The disease duration from onset to death was 4 years in both.

The classification of focal dementia syndromes remains controversial. According to the Neary et al consensus criteria (16), the brothers would fulfill criteria for progressive nonfluent aphasia, which is considered a subform of frontotemporal lobar degeneration. With the McKhann classification (17), they would be considered as language presentations of FTD. It is notable that both developed behavioral changes typical of FTD justifying their inclusion within the broad range of FTD. In both cases, more global dementia developed quite rapidly with marked behavioral changes. The disease duration from onset to death was 4 years in both.

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PHF and straight filaments, as seen by electron microscopy. A barely visible band aligning with 3R + 1N tau isoform could also be observed.

The most interesting, and previously undescribed, finding was the existence of a generalized tau pathology accompanied by the presence of α-synuclein aggregates only in the nucleus basalis of Meynert. Because this unique neuropathologic feature was present in the brains of both patients, it is unlikely that the coexistence of tau and α-synuclein aggregates is coincidental or represents a chance event in a highly affected brain region. Instead, it suggests the existence of a specific common pathway involved in the development of this disorder.

In particular, it is unlikely that this is a case of frontotemporal dementia with incidental Parkinson disease or Lewy body diseases, as Lewy bodies were not present in the substantia nigra, the area characteristically affected in PD and in amygdala or entorhinal cortex, areas affected in incidental Lewy body disease. The substantia nigra showed mild to moderate nerve cell loss in both patients, but there were no tau or α-synuclein inclusions.

The characteristic localization of the two pathologies present specifically in the Meynert nucleus also differentiates this case from other disorders with both α-synuclein and tau inclusions. Most of the cases reported to date show colocalization of the inclusions primarily in the amygdala (6); and in rare cases with PSP and PD, the tau and α-synuclein aggregates are colocalized in neurons of the substantia nigra (9, 10).

As the coexistence of tau and α-synuclein inclusions has been recently described in several cases of neurodegenerative diseases, some studies have investigated the existence of a synergistic effect in the abnormal aggregation of the two proteins (42). Although the exact mechanism leading to formation of tau and α-synuclein aggregates is not yet known, the two proteins may share interacting mechanisms of aggregate formation and α-synuclein could prompt tau aggregation.

In our study, however, tau and α-synuclein inclusions colocalize in the same brain area but usually not in the same cells. Furthermore, α-synuclein aggregates are absent in other brain regions where tau deposits are still present, questioning a straightforward synergistic effect of the two pathologies. As mentioned, it is possible that a genetic defect is the cause of both pathologies. In search for a potential genetic defect underlying the pathway that led to the development of this
disorder, we screened several genes that could have been involved.

Our genetic analysis did not identify any mutations in the tau gene. Despite the similar clinical and neuropathologic pattern of disease progression, the 2 brothers showed a different age of onset and, interestingly, the younger brother with earlier age of onset was homozygous for the H2 tau (H2/H2) haplotype, whereas his older brother was heterozygous H1/H2. Although it is not yet clear how the two distinct tau gene haplotypes may influence the FTD phenotype, it is possible that the tau H2 allele leads to an earlier age of onset in FTD patients without tau gene mutations (43). In a recent study of how the tau haplotypes may influence disease susceptibility, it has been suggested that the H1 and H2 haplotypes show different transcriptional activity in human cell lines, with H1 being more efficient at driving tau gene expression (44). No mutations were identified in the parkin, α-synuclein, or β-synuclein genes, and so the genetic factor responsible for the development of tau and α-synuclein pathology in this familial case remains unknown. Its identification will shed light on the relationship between tau and α-synuclein pathologies.

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REFERENCES


