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Progressive Nonfluent Aphasia Associated With a New Mutation V363I in Tau Gene

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Reported here is a new missense mutation V363I in exon 12 of the microtubule-associated protein tau (MAPT) gene associated with progressive nonfluent aphasia, with onset at the age of 69 years in a woman. Although near mute, she maintained complex activities and had no discernible deficits outside of language until the age of 75 years, when progressive gait and swallowing disturbances appeared. There was a history of late-onset aphasia and apraxia in her father. All of her children were asymptomatic adults, but psycholinguistic abnormalities were detected in those bearing the mutation, consisting of difficulties in comprehension, both reading (symbol discrimination and comprehension of oral spelling) and oral (matching sentences to pictures and comprehension of locative relationships). A mutation-bearing sibling showed no abnormalities at 70 years old, consistent with the limited penetrance expected in late-onset disease. The mutation, corresponding to a highly conserved residue in the fourth tubulin-binding repeat, was not present in 194 normal individuals with the same genetic background.

Keywords: frontotemporal dementia; chromosome 17; late onset; penetrance; psycholinguistics

Primary progressive aphasia (PPA) is a syndrome that is characterized by gradual selective deterioration of language, sparing other cognitive functions for at least 2 years. Impaired word finding heralds the development of an altered, usually nonfluent speech pattern, often followed by deficits in grammatical structure and comprehension. Some classifications of frontotemporal dementia (FTD) apply the term PPA to one of the presenting syndromes characterized by impaired language (the other being semantic dementia), whereas other categorizations prefer the term progressive nonfluent aphasia (PNFA). The common pathological substrate is either a lobar tauopathy (Pick’s disease or corticobasal degeneration/progressive supranuclear palsy) or frontotemporal degeneration with ubiquitin-only inclusions (FTD-U).

PPA is usually sporadic. Several families with a hereditary syndrome that includes aphasia, but also diverse combinations of behavioral disturbances, apraxia, akinesia, and muscular rigidity in linkage to chromosome 17q21, have been described, and point mutations in the microtubule-associated protein tau (MAPT) are reported in some.

On the other hand, 3 sets of siblings with at least some subjects presenting with pure PPA have been reported. Nontau pathology was identified at autopsy in 2, either described as frontotemporal degeneration or FTD-U, whereas a combination of tau and α-synuclein was reported in the third. Mutations in MAPT were ruled out in the latter 2 families. The recent description of mutations in progranulin, another gene on the same 17q21 region as MAPT, in families with FTD-U, often with the additional finding of intranuclear lentiform ubiquitin-immunoreactive inclusions, may be relevant to these families. Some or all affected members in several families with progranulin mutations have a language disorder of the PNFA type as the dominant presenting syndrome.
An additional family with autosomal dominant syndrome of motor speech loss (verbal apraxia) with preservation of language and cognition was reported with neither genetic analysis nor autopsy studies. Finally, a point mutation in presenilin 1 (R278I) results in language impairment with relative preservation of memory. We present a case of PNFA in association with a new mutation in MAPT.

Proband

Effortful, nonfluent, hesitant, stuttering speech with imprecise articulation, initially for certain words only, insidiously developed in an illiterate Castilian widow at the age of 69 years after a dental extraction. She had previously led an entirely normal life, and she continued to handle all of the household affairs, including finances, and was able to perform elementary calculations. Her difficulties progressed slowly, maintaining recitation of series (such as digits) longer than spontaneous speech. When examined at the age of 73 years, she used with great effort only approximately 6 words (yes, no, hello, good-bye, and the name of her son) inappropriately. She cried in frustration for not being understood, but was able to understand what people told her, had learned to use the recently introduced Euro currency, and was able to buy everything that she needed to run her household. She went around town by herself, kept her social contacts, and maintained her cooking and embroidery. Her memory for events and behavior were considered normal. She had received donepezil without benefit.

A physical exam was normal. Other than rare monosyllables, she did not utter any word, could not repeat words or phrases, and could not sing a popular song she knew.

She obeyed complex orders and was able to indicate by the showing fingers how many years had elapsed since important public or private events. She was well orientated in time and was able to draw a house on command and to divide a bunch of coins into 2 groups of equal value. The reminder of the neurologic exam was unremarkable.

The patient did not return for further examination, but her daughters reported that at the age of 75 years she lost the ability to communicate by gesticulation and developed progressive gait disturbances. Currently (age of 76 years), she requires the assistance of 2 people for walking and chokes when swallowing liquids. She continues to understand spoken language and laughs at funny jokes on television.

Family History

The unrelated parents originated from a small town in central Spain. The proband’s father started at the age of 75 years to refer to objects and persons by the wrong name, was unable to say what he wanted to eat, and spoke in set expressions. He developed apraxia, being unable to use a fork and knife and to dress up, although he remained aware of events. Later, urinary incontinence supervened, and he died at the age of 80 years. Her mother died at the age of 72 without any neurologic symptoms.

No neurologic signs or symptoms were reported or identified on examination of the proband’s 2 living sisters (ages of 77 and 58 years) and 1 brother (age of 73 years) or reported on a brother deceased at the age of 62 years. The proband’s 4 children, all well-adjusted working adults, aged 43, 42, and 39 years (dizygotic, different sex twins), were likewise asymptomatic. Informed consent for genetic analysis and neuropsychologic exam was obtained from the patient, her living siblings, and 3 of her 4 children (one of the twins refused testing).
Molecular Genetics

High molecular weight genomic DNA was purified by standard techniques. Tau exons 1, 9, 10, 11, 12, and 13 were amplified by using primers designed to flanking intronic sequences and the polymerase chain reaction as described.13 Polymerase chain reaction-amplified fragments of all exons were directly sequenced in both directions on a Perkin-Elmer ABI PRISM 377 automated DNA sequencer. DNA sequencing of the MAPT gene showed a transition 2274 G→A in exon 12, leading to replacement of valine 363 for isoleucine in heterozygosis in the proband, 2 of the 3 children, and 1 of her siblings, but not in 194 healthy individuals from a population sample in central Spain or other family members tested. We determined tau haplotypes and APOE alleles to explore any possible association with the clinical expression of the mutation. The results were not informative, as tau haplotypes of the proband, all of her children, and her mutation-bearing sibling were H1/H1, and their APOE alleles were 3/3.

Neuropsychological Exam

A neuropsychological exam was carried out without knowledge of genetic results in the 3 consenting children and all 3 living siblings of the proband. One of the children, examined at the age of 43 years, had high school education; the other 2, aged 42 and 39 years, had completed grade school. Individual results are not provided to prevent identification of carriers. All children obtained normal scores in the Wechsler Adult Intelligence Scale, the Wechsler Memory Scale, the Hopkins Verbal Learning Test, Rey’s Complex Figure Test, the Frontal Assessment Battery, the Stroop Test, the Trial Making Tests A and B, the Verbal Fluency, and the Boston Naming Test.14 In the Boston Diagnostic Aphasia Examination,15 the spontaneous speech was within normal limits; however, 1 of the 2 children with the mutation demonstrated subtle definite abnormalities in specific subtests addressing verbal fluency (articulation rating and verbal agility), naming (responsive and confrontation), letter discrimination, and reading comprehension (symbol discrimination and comprehension of oral spelling). In the Psycholinguistic Assessment of Language Processing in Aphasia,16 this subject (C in Figure 2) scored below 2 SD from the norm in 3 subtests: letter discrimination and mirror reversal, matching sentences to pictures, and comprehension of locative relationships. The other mutation-bearing sibling scored just above -2 SD in the latter 2 tests, whereas all scores in the non-mutation–bearing sibling were above the mean (Figure 2). In both affected siblings, the deficit in comprehension of locative relationships was selective for abstract elements (shapes, as in “the square is under the triangle”), rather than colors, a pattern identified in agrammatism.17

A similar test battery was used the siblings of the proband, eliminating subtests that require reading or writing because of their limited literacy. All, including the mutation carrier, scored within the normal range in all tests.

Conclusions

To the best of our knowledge, this is the first time a mutation in MAPT has been associated with isolated PNFA for a prolonged period. The mutation is located in a highly conserved residue in the fourth tubulin-binding repeat. The conservative replacement of valine for the similar neutral amino acid isoleucine may explain the late clinical presentation and the consequent limited penetrance, as shown by the absence of abnormalities in a mutation-bearing sibling over 70 years old. The late onset of genetically determined disease is usually associated with reduced penetrance, as carriers may die before developing symptoms, and large differences in age of onset in carriers of the same mutation are common, even within a single family.18 Incomplete penetrance19 and late onset of disease20 have been reported in other MAPT mutations. We propose that the V363I mutation is responsible for the proband’s PNFA and likely the abnormalities in language processing demonstrated definitely in one, and possibly in another, of her mutation-bearing children. It is possible that the proband’s father’s aphasia and apraxia were also related to the presence of the mutation, but the asymptomatic mother has not been excluded as the mutation carrier. Based on the known variation in clinical presentation of hereditary FTD even among affected members of the same family,10,18 we consider unlikely that the prolonged restriction of deficits to a single domain, language, observed in the proband, will be consistently present in other symptomatic cases bearing the mutation. Tau haplotypes and APOE alleles did not differ between the symptomatic proband and her asymptomatic sibling or between a mutation-bearing child with severely impaired performance on psycholinguistic test and another child.
Figure 2. Raw scores in representative Psycholinguistic Assessment of Language Processing in Aphasia psycholinguistic subtests (letter discrimination: mirror reversal, matching sentences to pictures, and comprehension of locative relationships), obtained by the proband’s children, ages 43 to 39 years, presented in random order to hide identity. Subject A, a noncarrier of the mutation, scored in the normal range, whereas subject C, a mutation carrier with deficits in subtests of the Boston Diagnostic Aphasia Examination addressing verbal fluency, consistently scored below -2 SD. The other mutation carrier (B) obtained a normal score in letter discrimination and mirror reversal and low, but above -2 SD scores in matching sentences to pictures, and comprehension of locative relationships.
with low, but within normal limits, scores in these tests, suggesting that neither tau haplotypes nor APOE alleles play a role in the observed differences in clinical expression.

The clinical presentation of the proband is reminiscent of the syndrome of progressive motor-speech loss without dementia described as an autosomal trait and the PNFA syndrome in 2 families with progranulin mutations and differs from the language deficits described in MAPT mutations, in which fluent speech is maintained, in spite of deficits in confrontational naming. Thus, the PNFA syndrome cannot be used to predict the mutated gene in affected families.

The pathological substrate can be confidently predicted based on the fact that all known mutations in MAPT in exons other than 10 result in deposition of tau in cortical neurons with relatively minor deposition in glial cells. The type of tau cannot be predicted, as 3 known mutations in exon 12 (Q336R, E342V, K369I) result in the development of neuronal round cytoplasmic silver positive inclusions, either very similar or considered indistinguishable from those of sporadic Pick’s disease, whereas V337M produces widespread neurofibrillary tangles.

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References


