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# Analysis of the prion protein gene in thalamic dementia

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## Abstract

Thalamic degenerations or dementias are poorly understood conditions. The familial forms are (1) selective thalamic degenerations and (2) thalamic degenerations associated with multiple system atrophy. Selective thalamic degenerations share clinical and pathologic features with fatal familial insomnia, an autosomal dominant disease linked to a mutation at codon 178 of the prion protein (PrP) gene that causes the substitution of asparagine for aspartic acid ($178^{Asn}$ mutation). We amplified the carboxyl terminal coding region of the PrP gene from subjects with selective thalamic dementia or thalamic dementia associated with multiple system atrophy. Three of the four kindreds with selective thalamic dementia and none of the three kindreds with thalamic dementia associated with multiple system atrophy had the PrP $178^{Asn}$ mutation. Thus, analysis of the PrP gene may be useful in diagnosing the subtypes of thalamic dementia. Moreover, since selective thalamic dementia with the PrP $178^{Asn}$ mutation and fatal familial insomnia share clinical and histopathologic features, we propose that they are the same disease.

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Thalamic degenerations or dementias comprise a group of ill-defined conditions commonly subdivided into three types.[1,2] The first type, “selective thalamic degeneration,” includes conditions characterized by severe symmetric thalamic atrophy and minimal or no extrathalamic pathology. The second type, identified as “thalamic degeneration associated with multiple system atrophies,” includes more complex conditions such as Friedreich’s ataxia, spinocerebellar degenerations, and Werdnig-Hoffman spinal muscular atrophy.[1] In a third type, thalamic degeneration is associated with a significant amount of gliosis or spongiosis in the cerebral cortex and probably corresponds to the “thalamic type” of Creutzfeldt-Jakob disease.[1] Distinguishing types 1 and 3 is difficult, if not impossible, with clinical and histopathologic criteria alone. Types 1 and 2 include sporadic and familial forms, whereas, to our knowledge, there are no reports of a familial form of the thalamic type of Creutzfeldt-Jakob disease.

Thalamic degeneration is the histopathologic hallmark of fatal familial insomnia (FFI), an autosomal dominant prion disease linked to a mutation in codon 178 of the prion protein (PrP) gene.[3-5] We analyzed the PrP gene in members of seven unrelated kindreds previously classified as having thalamic degenerations of types 1 and 2.

## Methods.

### Kindreds examined.

We reviewed the records of six kindreds previously published as having either selective thalamic degeneration or thalamic degeneration associated with multiple system atrophy, [2,6-10] and one unpublished kindred (identified by L. Berg) classified as having selective thalamic degeneration. The pedigree of the previously unpublished kindred is shown in figure 1. The original classifications were retained with the exception of the one for the subject described by Oda.[10] This subject had been classified in either type of thalamic degeneration due to the mild extrathalamic histopathology.[2,10] However, he also had sclerosis of the white matter in the centrum ovale. In addition, a cousin who died after a 7-year history of dementia and motor signs had thalamic atrophy associated with "sudanophilic leukodystrophy."[11] Therefore, this kindred is currently classified in the group of the thalamic degenerations associated with multiple system atrophy (J.J. Martin, personal communication). The first three of the four kindreds with selective thalamic degeneration had clinical features similar to those observed in the two kindreds with previously published FFI (table 1), including age of onset, course, and motor and memory impairments. Moreover, dysautonomia and lack of EEG sleep patterns were demonstrated in subject III-2 of the first kindred (table 1), and an overnight polysomnogram also showed the absence of EEG sleep patterns in subject IV-4 of the second kindred (table 1). Both subjects of the third kindred had sleep disturbances, and EEG recording during sleep in one of them "revealed an atypical stage 5 sleep pattern." The thalamic and extrathalamic lesions present in the subjects from these three kindreds who had histopathologic examination were also similar to those of FFI. None of these cases had widespread spongiosis. However, subject IV-4 of Berg's kindred had a single microscopic area of spongiosis.

Attempts to detect protease-resistant prion protein on brain tissue from the Berg kindred, case IV-I, using an immunochemical assay, and to transmit the disease to susceptible animals with brain tissue from members of the Little et al kindred, have been unsuccessful (L. Berg, personal communication, and reference 7).

The subject in the Martin et al kindred of this group differed from those in the other kindreds in several respects (table 1). Although she suffered from memory impairment, tremor, and possibly dysautonomia, she did not manifest ataxia or myoclonus. Histopathologically, however, this case is very similar to those of the other kindreds in this group except for the lack of spongiosis, which has always been found in FFI of greater than 2 years' duration.

The subjects of the three kindreds having thalamic degeneration with multiple system atrophy had heterogeneous clinical and histopathologic features distinct from those of the selective thalamic degenerations except for the aforementioned subject reported by Oda[10] (table 2). In this group, transmission to susceptible animals was unsuccessfully attempted with the subject of Deymeer et al.[8]

### DNA analysis.

One or two affected members from the seven kindreds with thalamic degeneration were analyzed. Genomic DNA was extracted from peripheral blood, fresh or fixed tissue,

according to procedures previously described.[12,13] The codon 178 mutation of the prion protein gene was detected by analysis of the carboxyl terminal coding region. We amplified this region of the gene using the following primers: 5′-CCGTTACTATCGTGAAAACATGCA-3′ and 5′-AAGGATCCCTCAAGCTGGAAAAAGA-3′. The amplification program was as follows: one cycle at 94 °C for 5 minutes; 45 cycles at 94 °C for 1 minute, 60 °C for 1 minute, and 72 °C for 1 minute; and one cycle at 72 °C for 5 minutes. To search for a mutation in the PrP gene codon 178, the amplified DNA was restricted with *TthIII* 1 and analyzed by agarose gel electrophoresis. Confirmation of the GAC-→AAC mutation in codon 178 was achieved by allele-specific oligonucleotide hybridization utilizing an oligonucleotide, with the 3′ end labeled with digoxigenin-conjugated ddUTP, homologous to either the wild-type sequence, 5′-TTGTGCACGACTGCGTC-3′, or to the mutant sequence, 5′- TTGTGCACAACTGCGTC-3′, applied to slot blots of the PCR products. The hybrids were detected using the Boehringer-Mannheim Genius system.

### Linkage analysis.

Linkage between the phenotype of selective thalamic degeneration (or FFI) and the codon 178 mutation was tested with the MLINK program.[14] The presence of the codon 178 mutation in the prion protein gene was investigated in 58 nonaffected members of the kindreds reported by Julien et al,[6] Berg, and Little et al[7] using genomic DNA extracted from peripheral blood, as above. Twenty-six members of the Julien et al[6] kindreds were included in the analysis. Five carried the mutation (two affected [table 1] and three asymptomatic), 12 members had no mutation and were asymptomatic, and nine members were uninformative for the mutation (seven asymptomatic and two with undetermined status). The 20 members examined in the Berg kindred included two who carried the mutation and were affected (table 1), 14 with no mutation and asymptomatic, and four uninformative for the mutation (two asymptomatic, two with undetermined status). Of the 12 members examined in the kindred of Little et al,[7] four carried the mutation and were affected (two are shown in table 1), eight were uninformative for the mutation (four were affected and four were asymptomatic). The three pedigrees were analyzed using age-dependent penetrance estimated on the basis of the age of onset of the disease. A total of 13 penetrance classes were used, with zero penetrance for members 0 to 19 years old and complete penetrance for those 75 or older. Members were classified as “affected” when the presence of the disease was supported by histologic or clinical examination, “undetermined status” when no medical information was available on the disease, and “asymptomatic” when there was no evidence of thalamic dementia (or FFI). The frequency of the 178 codon mutation in the normal population and the frequency of the disease were as in the previous study. [3]

## Results and Discussion.

We examined four kindreds previously classified as having selective thalamic degeneration and three classified as having thalamic degeneration associated with multiple system atrophy. Analysis of the amplified DNA with the restriction enzyme *TthIII* 1 and hybridization with allele-specific probes demonstrated a mutation at codon 178 of the PrP gene, resulting in the substitution of asparagine for aspartic acid ($178^{Asn}$ mutation) in the kindreds of Julien et al,[6] Berg, and Little et al[7] (figure 2, table 1). The $178^{Asn}$ mutation is

identical to that previously demonstrated in FFI kindreds[3,5] and, using these three families, is linked to the disease with a maximal combined lod score of 2.7 (table 3). The combined lod score, including the previous kindreds,[3] is 6.5 (unpublished data). In contrast, this mutation was not present in any of the kindreds with thalamic degeneration associated with multiple system atrophy (data not shown). Thus, analysis of the PrP gene, in conjunction with clinical data, is a useful test in differentiating type 1 and type 2 thalamic dementias.

The subject with selective thalamic degeneration and lacking the $178^{Asn}$ mutation had clinical features distinct from those of the subjects with the mutation: (1) an earlier onset, (2) a longer course, and (3) no ataxia or myoclonus. In contrast, clinically and histopathologically, subjects with the $178^{Asn}$ mutation appeared virtually identical to those previously described as having FFI. The combination of genotypic identity and phenotypic similarity demonstrates that the familial form of selective thalamic degeneration with the $178^{Asn}$ mutation and FFI are one and the same disease. Thus, most, but not all, of the known kindreds with selective thalamic degeneration suffer from FFI.

Brown et al recently reported six kindreds with the PrP gene $178^{Asn}$ mutation that differ from FFI patients in several features.[15] Despite a similar age of onset and duration of the disease, they apparently lack abnormalities of sleep and autonomic functions, do not show preferential involvement of the thalamus, and have widespread spongiosis of the cerebral cortex and subcortical structures regardless of the duration of the disease. In contrast to FFI, transmission of the disease has been successful in all six kindreds tested. These differences may be explained by postulating a slower rate or a more focal site of formation of the protease-resistant PrP isoform in the FFI kindreds. This is supported by the presence of protease-resistant PrP and spongiosis only in subjects with FFI of long duration,[3-5] whereas in the kindreds of Brown et al, these features are present regardless of the duration of the disease.[15] A slower rate or more focal formation of the protease-resistant PrP isoform would explain the infrequent spongiosis and lack of transmissibility in FFI. The severe involvement of the thalamus that causes untreatable, progressive insomnia and dysautonomia incompatible with a long survival may explain the relatively rapid course of FFI, despite the more focal pathology.

Clinical and pathologic features of scrapie and human prion diseases appear to be genetically regulated.[16-20] The differences between the kindreds expressing FFI and those expressing the Creutzfeldt-Jakob phenotype with the PrP gene 178 mutation are likely due to genotypic variations.

## Addendum.

After this study was completed, Goldfarb et al (*Ann Neurol* 1992;31:274-281) reported finding the $178^{Asn}$ mutation in the Little et al kindred (our table 1), which they refer to as the McK family.

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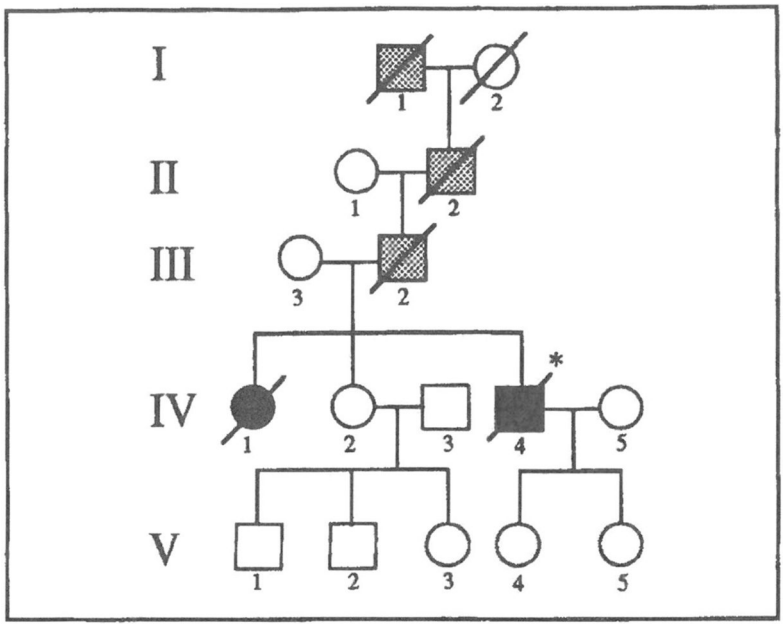


**Figure 1.**

Pedigree of the unpublished kindred (table 1, Berg). Squares represent males, circles females, and slashes indicate the deceased. Stippled symbols denote those individuals probably affected; solid symbols indicate those individuals examined clinically and demonstrated to be affected histologically in this study.

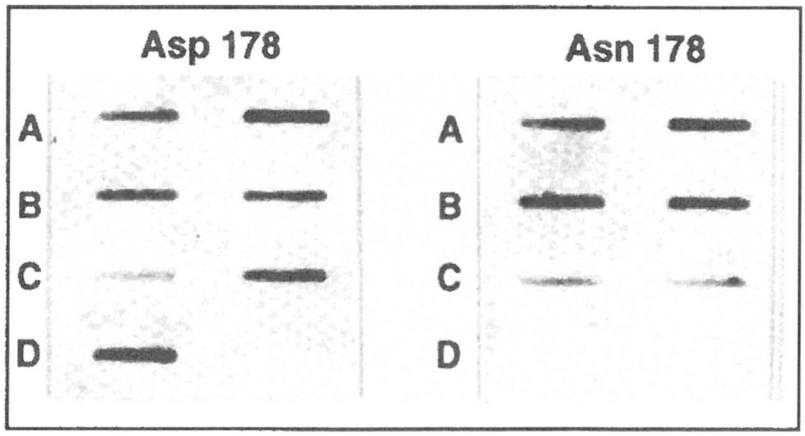


**Figure 2.**

Demonstration of codon 178 mutation by allele-specific oligonucleotide hybridization. Duplicate filters were hybridized with oligonucleotides that recognize either the wild type allele, Asp 178 on the left, or the mutant allele, Asn 178 on the right. (A-C) The two columns show hybridization of the oligonucleotides to DNA amplified from two affected members with the Asn 178 mutation from the first three kindreds in table 1.(D) An unaffected member from the Berg kindred (IV-2, figure 1).

**Table 1.**

Selective thalamic degeneration

| Pedigree (ancestry) | Case identification | Onset/ duration | Clinical presentation | Midcourse | Terminal conditions | EEG | Histopathology* |
|---|---|---|---|---|---|---|---|
| Julien et al[6] (French) | III-1 | 50 yr/8 mo | Apathy, disorientation | Insomnia with nocturnal agitation, abnormal movements, memory deficit, dysarthria, myoclonus, decreased attention | Total insomnia, severe cognitive impairment | Slowing | Thalamus: severe atrophy of AV, MD Other structures: severe atrophy of olives. No spongiosis |
| | III-2 | 45 yr/11 mo | Insomnia with nocturnal agitation, memory deficit | Ataxia, myoclonus, enacted dreams, confusion, severe memory deficit, temporal disorientation | Total insomnia, dysautonomia, increased catecholamines, myoclonus, confabulations | Slowing, absence of sleep pattern in 24-hr recording | Thalamus: severe atrophy of AV, MD, CM, P Other structures: moderate gliosis of cerebral cortex, severe atrophy of olives. No spongiosis |
| Berg (unpublished) (American/ German) | IV-4 | 51 yr/13 mo | Tiredness, low fever, sleep disturbances with nocturnal agitation and vivid dreams, decreased memory | Dementia, dysarthria, ataxia, myoclonus, absence of cortisol circadian rhythm | Weakness, respiratory difficulties, coma | Normal, absence of sleep pattern in overnight recording | Thalamus: severe atrophy of AV, MD, CM, LD, P, VLp, mild atrophy of other nuclei Other structures: moderate gliosis of entorhinal cortex and caudate; severe gliosis of sup. collie; focal spongiosis in entorhinal cortex |
| | IV-1 | 52 yr/9 mo | Altered vision, decreased memory, insomnia, hallucinations | Enacted dreams, gait disorder, myoclonus, dementia, lethargy | Stupor | Slowing | Thalamus: severe atrophy of AV, MD, P Other structures: moderate gliosis of entorhinal cortex and caudate. No spongiosis |
| Little et al[7] (American/ British) | IV-7 | 46 yr/17 mo | Somnolence, bizarre movements, hallucinations | Speech impairment, decreased memory, sleep episodes with agitation, disorientation, insomnia myoclonus | Coma | "Consistent with narcolepsy," atypical stage 5 sleep pattern during "sleep episodes" | Thalamus: atrophy of MD, P, VPI, CM Other structures: mild gliosis of cerebral cortex and basal ganglia; severe atrophy of olives. No spongiosis |
| | V-14 | 25 yr/12 mo | Ataxia, somnolence | Increased ataxia, dysarthria, decreased memory, hallucinations, myoclonus | Respiratory distress | Unremarkable | Thalamus: severe atrophy of AV, MD, VA, VPI, LD, P Other structures: as IV-7 |

| Pedigree (ancestry) | Case identification | Onset/ duration | Clinical presentation | Midcourse | Terminal conditions | EEG | Histopathology* |
|---|---|---|---|---|---|---|---|
| Martin et al[3] (Chinese) | NA | 18 yr/3 yr | Memory impairment | Abnormal behavior, apathy, shivering, sweating, urine incontinence, severe tachycardia, memory loss, tremor, *no* gait disturbances | Coma | NA | Thalamus: severe atrophy of AV, MD, less severe of P, R, VA, LD, CM<br>Other structures: gliosis of vestibular nuclei, bulbar reticular formation, olives.<br>No spongiosis |

*See table 2 for abbreviations.

**Table 2.**

Thalamic degeneration associated with multiple system atrophy

| Pedigree | Case identification | Onset/ duration | Clinical presentation | Midcourse | Terminal conditions | EEG | Histopathology |
|---|---|---|---|---|---|---|---|
| Deymeer etal[8] | NA | 46 yr/30 mo | Abnormal behavior, personality change, paranoid ideas | Dementia, dysphasia pyramidal signs, dysphagia | Paresis, muscular atrophy secondary to denervation | Normal | Thalamus: serve atrophy of MD. VA, CM Other structures: mild cortical atrophy with gliosis of cerebral cortex, white matter, hippocampus, and amygdala; marked atrophy of XII nucleus, of anterior horns and corticospinal tracts of spinal cord; neurogenic atrophy of muscle |
| Katz et al[9] | 3 | 7 yr/23 yr | Intellectual deterioration, clumsiness | Severe dementia, inappropriate behavior, optic atrophy, spastic paraparesis | Vegetative state, spasticity | Continuous generalized bursts of rhythmic delta | Thalamus: severe atrophy of MD, LD, CM Other structures: marked gliosis of white matter and neostriatum, optic atrophy, cerebellar atrophy with torpedoes, pallor of corticospinal tracts, severe atrophy of olives |
| Oda[10] | 1 | 18 yr/14 mo | Memory impairment, dreamy state, gait disturbance, tremor, ataxia, dysautonomia | Continued mental deterioration, pyramidal signs | Coma | NA | Thalamus: severe atrophy of AV, MD, CM, VA, VLp, P, LD, VLa, VM, PV Other structures: gliosis of white matter, atrophy of substantia nigra, olives, globus pallidus, vestibular nuclei, superior collicula, and reticular formation |

NA Not available.

AV Anterior ventral.

MD Mediodorsal.

CM Central median.

VA Ventral anterior.

VLp Ventral lateral posterior

P Pulvinar

LD Lateral dorsal.

R Reticular.

VPI Ventral posterior inferior.

VLa Ventral lateral anterior.

VM Ventral medial.

PV Paraventricular.

**Table 3.**

Lod scores for linkage between disease and codon 178 mutation in three kindreds*

| | Recombination fraction† | | | | |
|---|---|---|---|---|---|
| ***p*** | **0.0** | **0.05** | **0.10** | **0.15** | **0.20** |
| 0.022 | 0.614 | 0.537 | 0.460 | 0.382 | 0.304 |
| | 0.590 | 0.511 | 0.433 | 0.355 | 0.279 |
| | 1.342 | 1.192 | 1.036 | 0.875 | 0.710 |
| | **2.546** | **2.240** | **1.929** | **1.612** | **1.293** |
| 0.001 | 0.613 | 0.537 | 0.459 | 0.381 | 0.304 |
| | 0.590 | 0.511 | 0.433 | 0.355 | 0.279 |
| | 1.497 | 1.341 | 1.178 | 1.007 | 0.830 |
| | **2.700** | **2.389** | **2.070** | **1.743** | **1.413** |
| $10^{-7}$ | 0.613 | 0.537 | 0.459 | 0.381 | 0.304 |
| | 0.590 | 0.511 | 0.433 | 0.355 | 0.279 |
| | 1.505 | 1.349 | 1.185 | 1.014 | 0.836 |
| | **2.708** | **2.397** | **2.077** | **1.750** | **1.419** |

*Kindreds reported by Julien et al,[6] Berg, and Little et al[7]

†Values in the table are listed in the same order as the kindreds; values in bold type are the sum of the individual values from the three kindreds.