# Clinical/Scientific Notes

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## COMPLEX MOVEMENT DISORDERS IN FATAL FAMILIAL INSOMNIA: A CLINICAL AND GENETIC DISCUSSION

Fatal familial insomnia (FFI) represents a rare neurodegenerative autosomal dominant prion disease, usually affecting patients between the fifth and sixth decades, evolving rapidly to death.[1,2] FFI results from a missense mutation at codon 178 (D178N) of the *PRNP* gene (located on chromosome 20p13) linked with methionine at codon 129 of the mutated allele. Its major neuropathologic features include severe neuronal loss with astrogliosis of mediodorsal and ventral anterior thalamic nuclei and inferior olivary nuclei, with variable degrees of spongiosis, especially in subiculum entorhinal cortex.[3]

Neurologic manifestations include 4 main categories: 1) sleep disturbances: refractory insomnia, agrypnia excitata, diurnal dreaming state, oneiric stupor, somniloquy, and dream enactment; 2) motor disorders: dysphagia, cerebellar ataxia, dysarthria, and myoclonus; 3) cognitive-behavioral: apathy, hallucinations, memory dysfunction, temporal disorientation, and dementia; and 4) dysautonomia. Movement disorders usually comprise myoclonus and ataxia.[1,2,4]

Herein, we describe the first Brazilian patient with molecularly proven FFI, presenting with an atypical phenotype comprising complex movement disorders and erratic ocular movements. We provide a discussion on the phenomenology, genetic features, and possible pathophysiologic mechanisms involved.

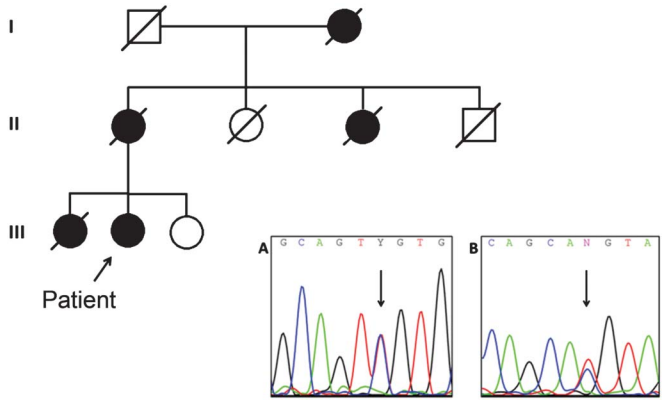
**Case description.** A 67-year-old Brazilian woman from Portuguese ancestry presented to our hospital with a 1-year history of diplopia, insomnia, excessive daytime sleepiness, progressive gait ataxia, and slurred speech, evolving to dysphagia, behavioral changes, visual and auditory hallucinations, and myoclonus. She had no dysautonomia. There was a remarkable family history for an autosomal dominantly inherited disease (figure). We were unable to evaluate other affected family members. On neurologic examination, there was Mini-Mental State Examination score of 12, gait ataxia, dysarthria, ideomotor apraxia, frontal release signs, parkinsonism (tremor, bradykinesia, rigidity, and postural instability), truncal tremor, generalized myoclonus, and spontaneous erratic multidirectional REMs (video on the *Neurology*® Web site at www.neurology.org). Serologic tests, including Whipple disease, were negative. Paraneoplastic and thyroid antibodies were normal. CSF showed mild high protein concentrations and 14-3-3 protein was negative. Brain MRI disclosed mild diffuse cortical atrophy. Brain SPECT imaging was normal. Polysomnography showed reduction in total sleep time, lack of REM sleep, and increased arousals. Genetic testing for FFI was performed and the genomic sequencing of *PRNP* disclosed the prion protein gene mutation at codon 178 (D178N). The *PRNP* polymorphic codon 129 was in heterozygosity (M129V), with mutated allele in frame with methionine (N178+M129), confirming FFI (figure). We started clonazepam for sleep disorders, with poor improvement.

**Discussion.** FFI is an extremely rare neurodegenerative disorder, and there are few families described worldwide. A clinical spectrum composed of complex movement disorders including parkinsonism, truncal tremor, and erratic ocular movements is discussed in this article. This phenotype is similar to previous ones observed in patients from the Basque Country.[4] When the aforementioned neurologic features are present, it is presumed that basal ganglia circuit may be involved. Neuropathologic data from patients with FFI have demonstrated that apoptotic neurons are mostly found in thalamus and medullary olives, while PET studies disclose severe thalamic and additionally cortical hypometabolism. Interestingly, patients presenting heterozygosity at polymorphic codon 129 (M129V) of *PRNP*, as described here, showed a more widespread cerebral change, and apoptotic neurons were also found in neocortex and striatum and a longer disease duration.[5]

There are no clear detailed clinical descriptions or pathophysiologic explanations for abnormal ocular movements in FFI. Our patient has complex movement disorders associated with involuntary, arrhythmic, chaotic, and multidirectional saccadic eye movements, rarely described in the disease.[4] When the phenomenology described here is observed, a comparison to opsoclonus-myoclonus syndrome (OMS) is inevitable. Thus, we presume that a disinhibition of the fastigial nucleus of the cerebellum or brainstem dysfunction might be involved here, as well as in OMS, to better explain abnormal ocular movements.[6]

Supplemental data at www.neurology.org

**Figure** Pedigree and genomic sequencing of *PRNP*




(A) The mutation GTC to GTT in heterozygosis that codes for amino acid 178, replacing an aspartate for an asparagine (D178N). (B) The *PRNP* polymorphic codon 129 is in heterozygosity (M129V).

Another hypothesis is agrypnia excitata. This is a condition characterized by loss of slow-wave sleep and abnormal eye movement, associated with motor and autonomic sympathergic activation, due to dysfunction in the thalamo-limbic circuits.[7] Although dysautonomia was not present in our patient, and taking into account that there was loss of slow-wave sleep, abnormal eye movement, and motor hyperactivation, agrypnia excitata may also be considered a possible explanation for motor hyperactivation in this case, presenting with abnormal ocular movements and truncal tremor.

On the whole, this case description calls attention to an unusual phenotype in FFI, presenting with complex movement disorders comprising parkinsonism, myoclonus, truncal tremor, ataxia, and erratic eye movements. Remarkably, although the D178N mutation in frame with 129M is defined as FFI, some patients with this genotype show a clinicopathologic phenotype of Creutzfeldt-Jakob disease.[6] Thus, the phenotypes described in prion diseases are complex, which may indicate that other genetic and environmental factors may contribute to this variability.

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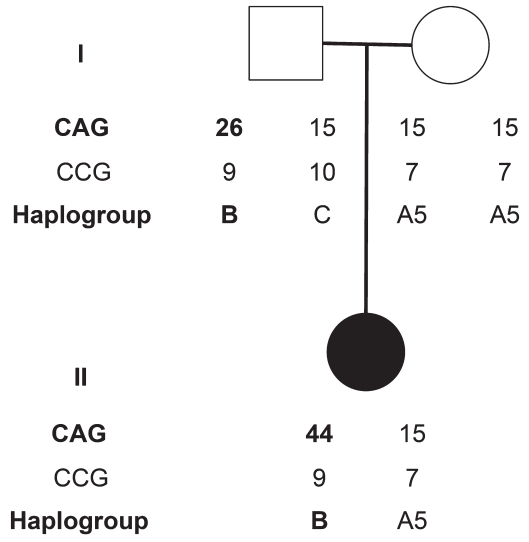
## DE NOVO HUNTINGTON DISEASE CAUSED BY 26-44 CAG REPEAT EXPANSION ON A LOW-RISK HAPLOTYPE

Huntington disease (HD, OMIM #143100) is a dominantly inherited neurodegenerative disorder due to a CAG repeat expansion in the *HTT* gene, encoding a polyglutamine tract in the N-terminal part of the huntingtin protein. Most cases are inherited from an affected parent, but in about 10% of cases the condition appears to be de novo.[1] De novo or sporadic cases are usually due to CAG repeat expansion of intermediate alleles. Intermediate alleles have 27–35 CAG repeats, and the higher the number of repeats, the higher the risk for expansion into disease range, usually upon paternal transmission.[2] In most cases, the change in repeat size is minor, and gradual increases into the disease range over several generations is the basis of new genetic mutations and stable

**Figure** **Family pedigree demonstrates paternal expansion of an allele with 26 CAG repeats into a pathologic allele with 44 CAG repeats**




The CAG and CCG repeat lengths and haplogroups are defined for each family member. The father's alleles can also be distinguished by 9 uninterrupted CGG triplets due to a common A > G polymorphism turning a CCA into (the second) CCG. For details on the determination of *HTT* haplogroups, see Warby et al.[1] Symbols: circle = female; square = male; black circle = patient.

disease prevalence. So far, the largest single-step expansions reported were from 27 to 38[3] and from 35 to 58[2] CAG repeats. It has recently been shown that intermediate alleles and disease alleles share the same haplotypes, which is expected if intermediate alleles are the main source of new mutation cases. The high-risk haplotypes are called A1 and A2, and are both prevalent among Caucasians but rare in other ethnic groups.[4]

We describe a de novo case of HD that defies this general rule. The patient is a 45-year-old white woman with advanced HD with extensive involuntary movements, unsteady gait, and dementia. Symptoms started around age 33 with swallowing problems, restlessness, asthenia, and poor concentration. Two years later, she was no longer able to work as an accountant or do activities she previously enjoyed. Four years later, increasing involuntary movements led to a diagnosis of HD, confirmed by finding 44 CAG repeats in the *HTT* gene. Family follow-up revealed allele sizes of 15/15 in the mother and 15/26 in the father (figure). This unexpected result led to uncertainty within the family concerning paternity, and the parents asked for paternity confirmation, which was verified. The HD alleles of the patient and her parents were subsequently subcloned, and an A > G polymorphism in the polyproline (CCG) tract following the polyglutamine (CAG) tract distinguished the father's 26-CAG allele from his 15-CAG allele; otherwise, the sequence surrounding the CAG repeat was identical to consensus, including a penultimate CAA following the CAG repeat. It turned out that the father's 26-CAG allele had expanded into his daughter's 44-CAG allele (figure), with no evidence of paternal mosaicism. Single nucleotide polymorphism haplotyping showed that the expansion had occurred on a low-risk B haplotype (subtype B44), not a high-risk A1 or A2 haplotype, as would be expected (figure).[4]

Our case shows that an expansion of 18 CAG repeats may occur on a low-risk haplotype from an allele size that would usually be considered stable.[5] This suggests that unknown predisposing factors, either genetic or environmental, may contribute to CAG repeat expansion in HD. The possibility that CAG repeats may unexpectedly expand into the disease range is important information when genetic counseling a family with a truly de novo case of HD.

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