plastic compensatory mechanisms might explain why EOPD patients have different clinical presentation, treatment response, and disease progression. Future studies evaluating patients prospectively from the early stages of PD will be able to evaluate the differences in the dopamine neuronal loss progression in EOPD and LOPD.

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# Fragile X-Associated Tremor/Ataxia Syndrome: Intrafamilial Variability and the Size of the *FMR1* Premutation CGG Repeat

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Video 

***Abstract:*** **Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurological progressive disorder associated with the *FMR1* gene premutation. We report on variable presentation of findings associated with FXTAS in 3 brothers aged 68, 74, and 73 years, carrying premutation alleles of $(CGG)_{123}$, $(CGG)_{109}$, and $(CGG)_{91}$ triplets, respectively. Based on previously proposed diagnostic criteria for the syndrome, clinical and radiological data allowed establishing a "definite" diagnosis of FXTAS in the two carriers of the longest $(CGG)_n$. The carrier of the $(CGG)_{91}$ allele, although presenting a major radiological sign of the syndrome (symmetrical white-matter lesions in the middle cerebellar peduncles), did not have any significant neurological manifestation at 73 years of age.**

**Key words:** FXTAS; tremor/ataxia syndrome; fragile X premutation; *FMR1* gene.

The expansion of the polymorphic CGG repeat at the 5′ UTR region of the fragile X mental retardation 1 (*FMR1*) gene is associated with distinct clinical phenotypes.[1,2] In the general population, the size of the $(CGG)_n$ ranges from 6 to ~55 with the commonest alleles having

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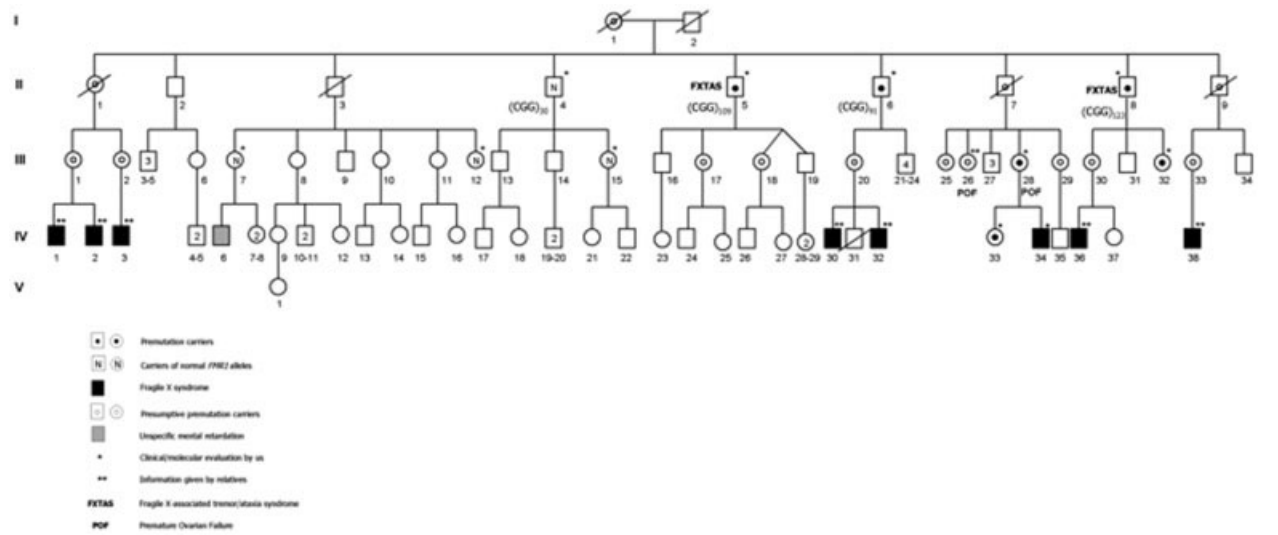


**FIG. 1.** Genealogy of premutation carriers evaluated for FXTAS.

29 to 31 triplets. Transcription silencing and absence of the protein occur when the repeat exceeds 200 trinucleotides and is accompanied by methylation of the adjacent CpG island, thus characterizing the full mutation that causes the fragile X mental retardation syndrome.[3–6] Alleles in the range ~55 to ~200 triplets are known as premutations, which are transcribed, but are unstable and may expand to full mutations upon maternal transmission. Indeed the boundary between stable common alleles and unstable premutations is not well defined, and constitutes a "gray zone," which includes high-common and low-premutation alleles (~45 to ~55 CGG triplets); these intermediate alleles may or may not be inherited in a stable manner.[7] Although being functional, premutations have been associated to clinical manifestations. Premature ovarian failure is known to affect around 20% of women carrying the premutation.[2,8] More recently, the *FMR1* premutation has been associated with a neurological defined condition affecting male carriers over 50 years of age, which has been designated fragile X-associated tremor/ataxia syndrome (FXTAS).[9–11] The major features include progressive intention tremor and cerebellar ataxia, which are often accompanied by progressive cognitive and behavioral difficulties, such as memory loss, anxiety, deficits of executive functions, reclusive or irritable behavior, and a gradual course to dementia in some individuals. Other features are Parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, and autonomic dysfunction. On magnetic resonance imaging (MRI), the remarkable finding is hyperintensity of the middle cerebellar peduncle (MCP sign), which serves as a major diagnostic criterion for FXTAS.[12] Analyses of brains from patients who died with this disorder revealed the presence of eosinophilic, intranuclear inclusions in neurons and astrocytes, which predominated in the hippocampus and frontal cortical regions.[13] Elevated levels of *FMR1* mRNA constitute the only known molecular correlate with alleles in the premutation range,[14] and led to the proposal of a gain-of-function toxic effect of this excessive mRNA production.[11,15] The prevalence of FXTAS among male premutation carriers is not established. It has been estimated that the penetrance of the syndrome is about 39% in premutation carriers over 50 years of age ascertained in fragile X syndrome families.[16]

Herein we describe 3 brothers aged 68, 73, and 74 years that carry *FMR1* premutations of different sizes, and present with different neurological features of FXTAS.

## SUBJECTS AND METHODS

The ethical board of the institutions approved this study, and family provided informed consent.

### Family Data

The family was ascertained through a mentally retarded boy with the diagnosis of fragile X syndrome (Fig. 1; IV-36). The proband's mother informed that her father (II-8), aged 68, was affected by a movement disorder. His clinical exam disclosed gait ataxia and intention and resting tremor. In addition to II-8, 3 of his brothers (II-4, II-5, and II-6) were investigated for the *FMR1* premutation. Diagnostic tests and genetic counseling concerning risks for fragile X syndrome were provided to the family.

### *FMR1* CGG-Repeat Size

DNA was obtained from peripheral blood lymphocytes. The *FMR1* CGG-repeat size was determined by PCR.[17] The PCR results were confirmed by Southern blotting.[18]

### Clinical and Radiological Evaluation

Individuals II-4, II-5, II-6, and II-8 were submitted to clinical and neurological assessment, and videotaped. The section III of the Unified Parkinson's Disease Rating Scale (UPDRS)[19] and the International Cooperative Ataxia Rating Scale (ICARS)[20] were used to evaluate Parkinsonism and ataxia, respectively. MRI was performed in individuals II-5, II-6, and II-8.

## RESULTS

A $(CGG)_{123}$ premutation was detected in Patient II-8. One of his brothers (II-4), who did not show any neurological impairment at age 76 years, had a $(CGG)_{30}$ allele, the most frequently found in the general population. The remaining 2 brothers presented $(CGG)_n$ repeats in the premutation range: II-5 had a $(CGG)_{109}$ allele and II-6 had a $(CGG)_{91}$ allele. The presence of the premutations was also evidenced by Southern blotting. The three carriers had tested negative for mutations in ataxia genes *SCA1*, *SCA2*, *SCA3*, and *SCA6.*

Patient II-8, the carrier of a $(CGG)_{123}$ premutation, reported that he experienced onset of gait difficulties and frequent fallings at the age of 65 years. When he was 67 years old, tremor was present at resting in the upper limbs, worsening during intentional movements. Neurological examination at the age of 68 years revealed Mini-Mental State Examination score of 27, a normal finding for his 4 years of schooling.[21] He scored 21/100 in ICARS, presenting global cerebellar syndrome characterized by dysarthria, gait ataxia, dysmetria in the upper limbs, saccadic dysmetria during voluntary gaze, bilateral dysdiadokokinesia, and kinetic tremor in the upper limbs, in addition to parkinsonian syndrome characterized by rest tremor, which was exacerbated during the gait, and global bradikinesia (UPDRS section III 16/56). MRI axial FLAIR images showed cortical and subcortical atrophy and hyperintense lesions in the periventricular white matter, and, in the fossa posterior, a mild lesion in the MCPs (Fig. 2A,B). On the basis of the diagnostic criteria for FXTAS,[11] this patient had two major clinical symptoms (tremor and ataxia), one major (MCP sign) and two minor (cerebral white-matter lesions and generalized atrophy) radiological features, thus allowing the diagnosis of "definite" FXTAS.

Patient II-5 carried a $(CGG)_{109}$ premutation. He reported experiencing onset of gait difficulties and frequent fallings at the age of 59 years. When he was 72 years old, a cane became necessary to support locomotion. At this time, tremor started in the upper limbs, being worse

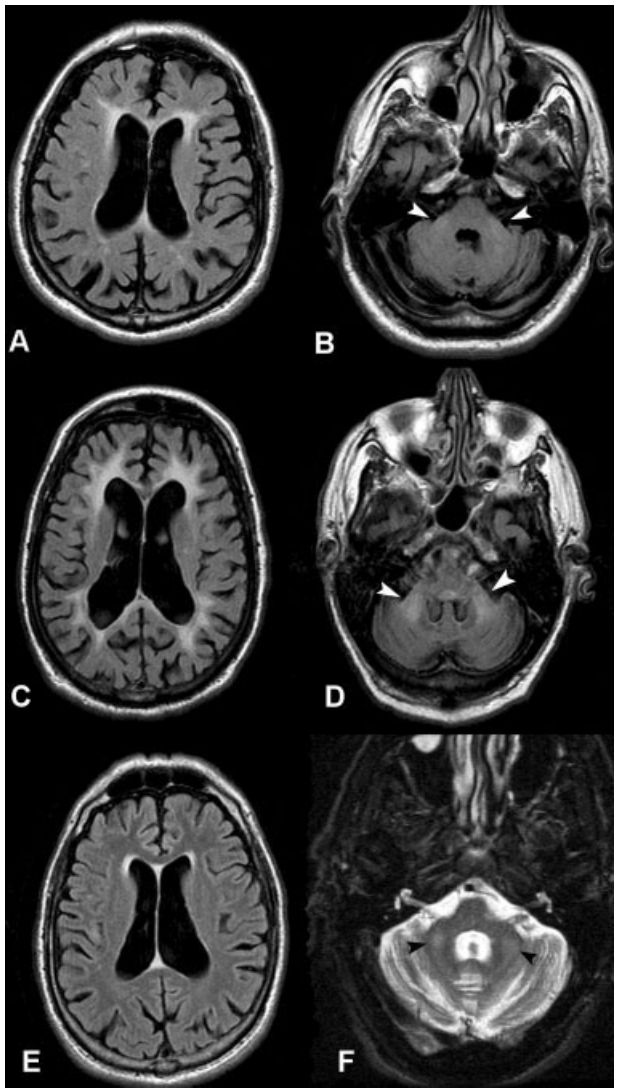


**FIG. 2.** Axial FLAIR images: in Patient II-8, (A) cortical and subcortical atrophy associated with hyperintense lesions in the periventricular white matter, and (B) in the posterior fossa, a mild lesion in the MCPs (middle cerebellar peduncles; arrowheads); in Patient II-5, (C) cortical and subcortical atrophy associated with confluent hyperintense lesions in the periventricular white matter, and (D) in the posterior fossa, hyperintense lesions in MCPs (arrowheads); in Patient II-6, (E) cortical and subcortical atrophy. Axial T2-weighted image in Patient II-6 (F) demonstrates MCP signal abnormalities (arrowheads), not evident on FLAIR images (not shown). Axial spin echo T1-weighted: TR = 500 ms, TE = 9 ms, slice thickness = 5 mm, matrix = 256 × 192, NEX = 2, FOV = 24 × 24 $cm^2$; axial fast spin echo T2-weighted: TR = 4,500 ms, TE = 83 ms, slice thickness = 5 mm, matrix = 320 × 224, NEX = 2, FOV = 24 × 24 $cm^2$; axial FLAIR images: TR = 10,000 ms, TE = 104.5 ms, TI = 2,100 ms, slice thickness = 5 mm, matrix = 256 × 224, NEX = 1, FOV = 24 × 24 $cm^2$; MRI 1.5 T equipment, Signa Horizon LX 8.2, General Electric, Milwalkee, WI.

during intentional movements. Two years later the neurological examination revealed global cerebellar syndrome, characterized by dysarthria, gait ataxia, dyssynergy, dysdiadokokinesia, and dysmetria, in addition to postural and kinetic tremor in the upper limbs, scoring 45/100 in ICARS. Besides, there was rest tremor in the right hand. He scored 18 in the Mini-Mental State Examination, a definite low score for his 8 years of schooling.[21] Furthermore, there were signs of peripheral motor syndrome, evidenced by mild weakness in the lower limbs, with absence of reflexes and urinary dysfunction characterized by incontinence. No other signs of vegetative dysfunction or pyramidal were observed. MRI examination revealed in axial FLAIR images cortical and subcortical atrophy with confluent hyperintense lesions in the periventricular white matter, and in the posterior fossa, hyperintense lesions in the MCPs (Fig. 2C,D). The presence of two major FXTAS clinical signs (tremor and ataxia) and one major radiological sign (hyperintensity in the MCP) defined the diagnosis of "definite" FXTAS.

Patient II-6 carried a $(CGG)_{91}$ premutation. At 73 years of age, he did not complain of clinical symptoms, and used a bicycle for locomotion around the town he lived in. Neurological examination revealed Mini-Mental State of 28, a normal finding for his 4 years of schooling,[21] and a minor change in tandem gait, scored 1 in section I of ICARS. MRI examination (Fig. 2E,F) demonstrated in axial FLAIR images cortical and subcortical atrophy and high intensity T2 signal in the MCPs, the latter being considered a major radiological FXTAS sign.

## DISCUSSION

We describe three carriers of the *FMR1* premutation in a sibship, presenting with different features of FXTAS. Brothers II-5 and II-8 had $(CGG)_{>100}$, and their clinical features led to the diagnosis of "definite" FXTAS, according to the conventional criteria for FXTAS diagnosis.[11] Onset of symptoms occurred at late fifties/early sixties with similar progression. Patient II-5, the carrier of a $(CGG)_{109}$, at age 74 years had more severe clinical manifestations than his 68-year-old brother II-8, who carried a $(CGG)_{123}$. Age appears as the factor influencing the severity of the disorder presentation in these 2 sibs.

Patient II-6, the carrier of the smallest premutation, a $(CGG)_{91}$ allele, at 73 years of age showed only a mild difficulty in tandem gait, but he had one major radiological sign of the FXTAS, i.e., symmetric white matter lesions in the MCPs. MRI findings have been considered closely related to the clinical manifestations and FXTAS and major radiological signs were not detected in asymptomatic premutation carriers aged >50 years.[10] The correlation, however, has been recognized not to be absolute, as evidenced by one premutation carrier with a combination of intention tremor and ataxia, in the absence of MCP lesions.[10] The reverse situation is present in our patient with major radiological signs and showing a mild alteration of tandem gait as the only symptom. The absence of significant neurological symptoms in this patient might be related to his smaller number of CGG repeats in the sibship. However, premutation patients with even smaller repeats have been described with severe FXTAS.[10,22,23] Indeed, available data have not demonstrated a direct correlation between onset/course of the disorder and size of the premutation CGG repeat,[24–26] but carriers of $(CGG)_{<70}$ alleles appear less likely to have neurological manifestations.[27]

Our approach of looking for intrafamilial correlation between the size of the CGG repeat and onset age/progression of the disease might be interesting, allowing the evaluation of the influence of the repeat size on the manifestation of the syndrome within a familial genetic background. A few such instances have been reported. In a screening of patients with cerebellar ataxia for the *FMR1* premutation,[28] a male carrier of a $(CGG)_{90}$ premutation was found to have 3 brothers who were also premutation carriers. The 72-year-old proband and 2 of his brothers [63 years and a $(CGG)_{86}$ premutation; 61 years and a $(CGG)_{98}$ premutation] had neurological phenotypes considered consistent with FXTAS, whereas a 65-year-old brother who carried a $(CGG)_{86}$ premutation was asymptomatic. Although in this sibship onset of the disease was earlier in the carrier of the largest CGG repeat, this correlation was not evident when the remaining affected sibs were considered. Two other male brothers were described,[29] one of them a 60-year-old $(CGG)_{112}$ premutation carrier with "definite" FXTAS, and onset of symptoms at the age of 54 years; on the other hand, his brother who carried a $(CGG)_{166}$ premutation had mild postural/action tremor starting at age 53 years, but with little progression in 10 years; MRI showed mild cerebral atrophy and subtle changes of the cerebellar peduncles.

To our knowledge, individual II-6 is the first premutation carrier to be described presenting with white-matter lesions within the MCP and cerebellar atrophy and no significant accompanying neurological manifestation at 73 years of age. Previously, a 52-year-old premutated male has been reported with no neurological involvement, and MRI revealing florid symmetrical T2 hyperintense signal changes confined to the corona radiata.[30] Only longitudinal studies will be able to tell the eventual clinical course of the neurological manifestations in these carriers. In this context, it is noteworthy that our Patient II-6 did not have the typical FXTAS

neurological symptoms at 73 years of age. A radiological systematic study of *FMR1* premutation carriers without clinical symptoms would be necessary to evaluate the frequency of this finding.

## LEGENDS TO THE VIDEO

**Segment 1.** Patient II-8 with dysarthria during speech. Note the hypomimia and global bradikinesia. In addition, he has a global cerebellar syndrome characterized by postural and kinetic tremor, bilateral dysdiadokokinesia, saccadic dysmetria during voluntary gaze, and gait ataxia with exacerbation of rest tremor in the upper limbs.

**Segment 2.** Patient II-5 shows an intense global cerebellar syndrome with dysarthria, dysdiadokokinesia, kinetic tremor, trunk dyssynergy, dysmetria, and gait ataxia.

**Segment 3.** Patient II-6 presents a minor change in tandem gait. The remaining neurological examination was normal.

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