**Background:** Fragile X–associated tremor/ataxia syndrome (FXTAS), a novel disorder in male carriers of premutations of the fragile X mental retardation 1 gene (FMR1), was recently described. The clinical presentation of FXTAS most closely resembles multiple system atrophy (MSA) because both disorders manifest with cerebellar ataxia, intention tremor, autonomic dysfunction, and parkinsonism. It has been proposed that FXTAS might be a common neurodegenerative disorder.

**Objective:** To determine whether FXTAS accounts for patients currently diagnosed as having MSA or a related clinical diagnosis.

**Design:** Patients with MSA or related phenotypes were examined by experienced movement disorders neurologists, and DNA samples were obtained for genetic study.

**Setting:** Salpêtrière Hospital.

**Patients:** Seventy-seven patients clinically diagnosed as having MSA, 19 as having olivopontocerebellar atrophy, and 27 as having cerebellar ataxia.

**Main Outcome Measure:** The number of FMR1 repeats was determined in all patients by polymerase chain reaction. Alleles above 40 CGG repeats were controlled by Southern blot analysis.

**Results:** Two patients carried FMR1 premutations of 110 and 135 repeats: a man with a familial form of cerebellar ataxia and a woman diagnosed as having MSA–cerebellar type. In addition, 9 patients (7%) carried alleles in the intermediate size range, from 41 to 53 repeats.

**Conclusions:** We confirm the recent initial description of FXTAS in women. Our data suggest that FXTAS is rare in MSA and indicate that FXTAS might be less prevalent than proposed.

Fragile X syndrome is the most common heritable form of mental retardation, caused by large expansions (>200 repeats) of a CGG trinucleotide repeat in the FMR1 gene. Premutation alleles are defined by CGG expansions between 55 and 200 repeats, and they may further expand to a full mutation (>200 repeats) in the next generation. Allele sizes that range from 41 to 54 repeats are considered to be intermediate, whereas normal alleles have 40 or less CGG repeats. Premutation carriers generally do not have symptoms of typical fragile X syndrome; however, phenotypic features unique to the premutation range have been identified and include premature ovarian failure in approximately 20% of women. Fragile X–associated tremor/ataxia syndrome (FXTAS) was first described in 5 men with premutation expansions in FMR1. The main features of this clinically heterogeneous syndrome are cerebellar ataxia (CA) and intention tremor. Additional symptoms include rigidity, bradykinesia, cognitive decline, and autonomic dysfunction.

The disease with a clinical presentation that most closely resembles that of FXTAS is multiple system atrophy (MSA), a sporadic neurodegenerative disorder characterized clinically by any combination of parkinsonian, autonomic, cerebellar, and pyramidal signs. Hyperintensity on T2-weighted magnetic resonance imaging (MRIs) in the middle cerebellar peduncles and adjacent cerebellar white matter has been demonstrated in MSA and FXTAS. The objective of the present study is to examine the frequency of expanded FMR1 alleles in clinically diagnosed MSA. To investigate the possibility that patients with FXTAS have cerebellar symptoms, which do not fulfill the diagnostic criteria for MSA, we also included...
patients diagnosed as having olivopontocerebellar atrophy and CA in this study.

### METHODS

#### PATIENTS

One hundred twenty-three patients, including 17 with parental consanguinity or a family history, were selected according to clinical criteria and after exclusion of other trinucleotide repeat mutations responsible for autosomal dominant CAs, such as SCA1, SCA2, SCA3, SCA6, SCA7, DRPLA, and Friedreich ataxia. Clinical selection was performed at Salpêtrière Hospital. All the patients had cerebellar signs, and they were classified into 4 groups (Table). A diagnosis of possible or probable MSA was based on the consensus criteria established by Gilman and colleagues. These criteria have been validated for variable MSA was based on the consensus criteria established by Gilman and colleagues. These criteria have been validated for able MSA was based on the consensus criteria established by Gilman and colleagues. These criteria have been validated for these patients had cerebral MRI findings of cerebellar atrophy. Group 4 consists of 27 patients with CA diagnosis as having cerebellar atrophy on cerebral MRI associated with variable neurologic signs or with exclusion criteria such as a family history of the disease.

All participants were white (107 from France, 7 from Italy, 4 from Portugal, 3 from Spain, and 2 from Poland). Of the 106 apparently sporadic cases, 6 had 1 deceased parent with Parkinsonism, although pathological verification of Lewy body disease was not available. Fourteen patients had affected first-degree relatives, and 3 patients were consanguineous. There was no family history of mental retardation for any patient with an abnormal FMR1 allele size.

### MOLECULAR AND STATISTICAL ANALYSES

DNA samples were obtained from all individuals after appropriate informed consent and institutional review board approval were obtained. Molecular analyses were performed in 2 different laboratories (98 at Laboratoire Diagnostic Génétique CHRU Strasbourg and 64 at the Department of Neuroscience, Mayo Clinic, Jacksonville). After polymerase chain reaction, alleles were sized using an automated sequencer (ABI 3100; Applied Biosystems, Foster City, Calif) and appropriate control alleles. The absence of alleles above 120 CGG repeats was controlled by Southern blot analysis for all patients with an allele above 40 repeats and for all homozygous women. The concordance of the results has been verified in 39 samples analyzed by both laboratories. A total of 181 control chromosomes from healthy white individuals (53 men and 64 women) with similar Northern European ethnicity were analyzed to determine the frequency of allele sizes in the general population. The molecular analysis protocol is available on request.

Comparisons of frequencies were performed using the Fisher exact test, and percentages are given with their 95% exact binomial confidence intervals (CIs).

#### RESULTS

We studied 28 women and 95 men with a mean (SD) age at onset of 51.7 (11.2) years (range, 26-79 years). Seventy-six patients (62%) were 50 years or older. The distribution of FMR1 allele sizes for the 151 X chromosomes analyzed (ie, 2 from each of the 28 women plus 1 from each of the 95 men) is presented in the Figure. We identified 2 patients whose FMR1 alleles were within the pre-
Mutation range: a man diagnosed as having familial CA (110 CGG repeats) and a woman diagnosed as having MSA-C (29 and 135 CGG repeats). Nine white patients (7%; 95% CI, 3.4%-13.44%) were carriers of FMR1 intermediate-sized alleles between 41 and 53 CGG repeats. This group consisted of 6 men and 3 women, whose phenotypes are shown in Table 1 (3 patients with MSA-C, 2 with MSA–parkinsonian type, 3 with olivopontocerebellar atrophy, and 1 with CA). The mean (SD) age at onset in patients with intermediate-sized alleles was 51.0 (13.3) years (range, 27-60 years). We observed a higher frequency of alleles in the intermediate size range (41-54 repeats) in men than in controls (6/94; 6%; 95% CI, 2.38%-13.38% vs 4/181; 2%; 95% CI, 0.61%-5.59%), but this difference was not statistically significant (\( P = .09 \)). Because the cutoff value of 40 repeats is an arbitrary choice, and larger alleles are more prone to be involved in the disease, we also compared groups that had more than 50 CGG repeats. The difference between patients and controls was not significant (2 of 149; 1%; 95% CI, 0.16%-4.76% vs 0 of 181; 0%; 95% CI, 0.00%-1.64%; \( P = .12 \)). There was no significant difference between carriers of a large normal allele (\( \geq 41 \) repeats, \( n = 11 \)) or a premutated allele and noncarriers (\( n = 112 \)), even after stratifying according to sex or age at onset (<50 or \( \geq 50 \) years). We report the phenotypes of the 2 patients with a premutation.

FAMILIAL CASE OF CA AND 110 FMR1 CGG REPEATS

The proband developed progressive gait ataxia at age 55 years. He had an episode of transient confusion at age 58 years. Clinical examination at age 59 years showed cerebellar gait and limb ataxia. Frontal lobe dysfunction was noted, with global slowness, attention and memory deficit, decreased verbal fluency, perseverations, and constructive apraxia. Reflexes were normal, with flexor plantar response. He had no bladder dysfunction. Brain MRI showed severe cortical, subcortical, and cerebellar atrophy, as with severe white matter lesions that involve the frontal lobes. Electromyographic findings were normal. This patient’s brother developed gait difficulties at age 62 years. On examination, he had axial and upper limb parkinsonian rigidity, bradykinesia, and right upper limb rest tremor; these symptoms responded only partially to levodopa treatment. Severe cognitive decline was noted. The Mini-Mental State Examination score was 16/30. Such cognitive decline is not compatible with a diagnosis of MSA. He had no bladder dysfunction and no pyramidal syndrome. Brain MRI revealed cortical and subcortical atrophy with marked ventricle enlargement but without any white matter lesions. He was not available for molecular testing.

PATIENT WITH MSA-C AND 29/135 FMR1 CGG REPEATS

This woman had a long history of bipolar affective disorder. She developed progressive ataxic gait with falls at age 54 years. Examination at age 58 years revealed gait and limb ataxia, forelimb rest tremor, cogwheel rigidity, enhanced reflexes with flexor plantar response, and bladder incontinence. She became confined to a wheelchair at age 60 years. Four years later, she was confined to a bed, with axial rigidity, dysarthria, retroglossis, and dysphagia. Bedside oculomotor examination showed severe square-wave jerks, marked horizontal nystagmus,  

![Figure](https://example.com/figure.png)  

**Figure.** Distribution of FMR1 allele sizes in patients with multiple system atrophy–like syndromes (intermediate-sized alleles, 41-54 repeats; the 2 premutation alleles \( \geq 55 \) repeats are not shown).
To date, FXTAS has been investigated only in families with a documented fragile X history. Nevertheless, FXTAS is believed to be a relatively common disorder, possibly affecting 1 in 3000 men older than 50 years in the general population. Fragile X–associated tremor/ataxia syndrome shares several clinical features with MSA, CA, parkinsonism, and autonomic dysfunction and generally starts after 50 years of age. Thus, we hypothesized that FXTAS may account for many patients currently diagnosed as having MSA.

To our knowledge, this study is the first to report FMRI alleles in patients with a clinical diagnosis of MSA and the first to report such alleles in familial cases of CA complicated by MSA-like features. We investigated 123 patients, including 77 diagnosed as having MSA, a large series with such a rare disorder. Only 1 patient with MSA included in this study had an expansion of an FMRI allele within the premutation range. Our data indicate that patients with FXTAS are rarely given a clinical diagnosis of MSA.

Zhang and colleagues previously reported a frequency of 9 intermediate-sized alleles in 19 patients diagnosed as having MSA. In our study, the frequency of male carriers with intermediate alleles with 41 or more repeats is not significantly different from that in controls (6 of 94 vs 4 of 181). The relationship between intermediate alleles and FXTAS has not been defined. The patients described in this study could have another disorder, or intermediate FMRI alleles could predispose to FXTAS or CA. Interestingly, none of the patients with intermediate alleles in our study had white matter abnormalities on brain MRI.

Hagerman and colleagues first described FXTAS in men with intention tremor, parkinsonism, and generalized brain atrophy in carriers of fragile X premutations. Several follow-up studies have delineated the clinical, radiologic, and neuropathologic phenotype and have estimated its penetrance in premutation carriers. The proposed major radiologic criterion for FXTAS is MRI white matter lesions in middle cerebellar peduncles, the brainstem, or both. The minor radiologic criteria are MRI white matter lesions in cerebral white matter and moderate generalized atrophy. Major clinical symptoms for a diagnosis of FXTAS are intention tremor and gait ataxia; parkinsonism and cognitive decline are minor clinical signs. The presence of 1 major radiologic and 1 major clinical sign is proposed to qualify for a diagnosis of definite FXTAS. Probable FXTAS indicates the presence of 1 major radiologic sign plus 1 minor clinical symptom or the presence of 2 major clinical symptoms.

Only 2 patients in our study carried a premutation allele in the FMRI gene. One patient was a woman diagnosed as having MSA-C. She fulfills the radiologic and clinical diagnostic criteria for definite FXTAS. Recently, FXTAS was described for the first time in women with an FMRI premutation. Unlike their male counterparts with FXTAS, none of the women in that study had cognitive decline. Our patient was never diagnosed as having cognitive deficit. Thus, cognitive decline seems to be a less prominent clinical feature in women diagnosed as having FXTAS than in men. In addition, the affected woman had severe square-wave jerks, a sign not previously described in this condition. This observation highlights the clinical variability of FXTAS.

Another patient in our study was a man whose brother has a similar neurologic disease. Both had previously received a diagnosis of familial CA. In addition to a family history, the patient had marked cognitive decline. These are exclusion criteria for a diagnosis of MSA. This patient fulfills the criteria for a diagnosis of probable FXTAS.

In the present study, all the patients were examined by a movement disorder specialist using established criteria for MSA; on retrospective postmortem examination, the same clinical criteria have an excellent positive predictive value. Although FXTAS and MSA share several features, there are important clinical differences that may account for the low frequency of FMRI premutations identified. Cognitive decline is also common in FXTAS, at least in men, and urinary incontinence and impotence are more variable features. In MSA, severe autonomic failure is common, and dementia and a family history of a similar disease are exclusion criteria for the diagnosis.

In conclusion, FMRI premutations in clinically diagnosed MSA are rare, and the phenotypes of the 2 disorders do not seem to overlap. Recent FMRI screening of patients diagnosed as having essential tremor and Parkinson disease also did not identify premutation carriers. Thus, genetic testing for expansions in the FMRI gene does not seem necessary when patients fulfill the diagnostic criteria for MSA, essential tremor, or Parkinson disease, especially when age at onset is younger than 50 years. Given the importance of diagnosing FXTAS for genetic counseling, FMRI genetic testing should be considered in patients with CA of unknown cause, especially in those with cognitive decline. Although the frequency of FXTAS in the general population remains unknown, our data indicate that FXTAS might be less prevalent than previously thought.

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