



Short Report

Fragile X-associated tremor/ataxia syndrome (FXTAS) in grey zone carriers

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The grey zone (GZ; 45–54 CGG repeats in the *FMRI* gene) is considered a normal allele; however, several studies have found a high frequency of GZ in movement disordered populations. Here, we describe neurological features of fragile X-associated tremor/ataxia syndrome (FXTAS) in two carriers of GZ alleles, although FXTAS has been defined as occurring only in premutation carriers (55–200 CGG repeats). Both patients had family members who had premutation and were diagnosed with FXTAS. The presence of relatively high GZ alleles with elevated fragile X mental retardation 1 mRNA (*FMRI*-mRNA) combined with a family history of FXTAS that may represent a facilitating genetic background for FXTAS are the factors that led to the presence of FXTAS in these individuals with a GZ allele. Further research into clinical involvement of GZ alleles is recommended and the definition of FXTAS may require revision.

Conflict of interest

Dr Hagerman's work has been funded by the NIH. Other funding has been received for clinical trials from Seaside Therapeutics, Roche, Forest, Curemark, and Novartis. Dr. Zhang's work has been funded by the NIH. Other funding has been received for clinical trials from Boehringer-Ingelheim, and Allergan. Dr. Zhang serves as consultant and/or adviser for Allergan, Dysport, Teva Neuroscience, and Merz. Dr. Zhang serves as speaker for Allergan, Novartis, and Teva Neuroscience. Dr. Ying Liu's work has been funded by Teva Neuroscience and Allergan. There are no other conflicts of interest from the authors.

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In 2001, the first five cases of the fragile X-associated tremor ataxia syndrome (FXTAS) were described and subsequent studies have validated the clinical features of intention tremor, cerebellar ataxia, autonomic dysfunction, neuropathy, and cognitive decline (1, 2). The cause of FXTAS is thought to be the elevated fragile X mental retardation 1 mRNA (*FMRI*-mRNA) levels observed in all premutation carriers (55–200 CGG repeats in the *FMRI* gene) leading to RNA toxicity in the neural cells (3).

The grey zone (GZ, 45–54 CGG repeats) allele is considered normal. However, several researchers have studied involvement in the GZ. Loesch et al. reported

more than twofold increased incidence of the GZ allele in patients with Parkinsonism, one of the features in FXTAS, and suggested a potential role for GZ in neurodegeneration (4). A slightly elevated frequency of GZ alleles was also found in male multiple system atrophy (MSA) patients in European MSA populations (5). Kenneson et al. found reduced fragile X mental retardation protein levels in GZ alleles (6), whereas Loesch et al. observed increased *FMRI*-mRNA levels for alleles as low as 39 CGG repeats in size (7). More recently, Hall et al. reported three patients with *FMRI* GZ alleles who met diagnostic criteria for FXTAS (8). The consequence of these findings is the possibility

of the development of FXTAS or related neurological symptoms in some GZ carriers. The neurodegenerative changes including FXTAS would likely be associated with the toxic gain-of-function mechanism of raised *FMRI*-mRNA. Here, we report two carriers of GZ alleles exhibiting FXTAS.

Clinical presentation of grey zone with FXTAS

Patient 1 is a 58-year-old male with a GZ of 52 CGG repeats and his *FMRI*-mRNA level is 1.83 ± 0.08 -fold above normal. He noticed tremor at age 55 when holding a coffee cup. At age 56, he noticed balance problems and handwriting difficulties. He had numbness and tingling in his feet. He has also had erectile dysfunction. He has noticed some weakness in his hands including a weak grip. His past medical history includes sleeping problems, type II diabetes, hypertension, migraine headaches, and eye surgery related to his diabetes.

Neurological examination

Finger to nose touching shows a bilateral intention tremor with a significant terminal tremor. His motor tone is increased on the left more than on the right. He has great difficulty with tandem walking. Deep tendon reflexes are 1+ in the upper extremities, 2+ at the knees, and absent at the ankles. Vibration sense is decreased on the left side. He has a dyskinesia with the right hand and a positive pull test. Brain magnetic resonance imaging (MRI) demonstrated mild brain atrophy and some scattered white matter disease involving the pons but not the middle cerebellar peduncles (MCPs) (Fig. 1).

Family history

His brother (II:3) has premutation and a GZ allele (52,68 CGG repeats; mRNA 2.62 ± 0.34) and has been diagnosed with FXTAS and previously been reported (JDBP) (9). His brother has three daughters, one (III:2) with GZ (56 repeats) and symptoms of anxiety and two are premutation carriers [56 repeats (III:6) and 67 repeats (III:7), respectively]. The daughter with GZ has two sons (IV:1 and IV:2) with premutation (61 and 69 CGG repeats) and autism. Another daughter (III:6) has a daughter (IV:4) with premutation (69 repeats) and symptoms of anxiety, attention deficit hyperactivity disorder (ADHD) and shyness which are typically seen in premutation carriers (Fig. 2).

Patient 2 is an 80-year-old female with a GZ of 53 CGG repeats and her *FMRI*-mRNA level was 1.35 ± 0.07 -fold above normal. Her neurological symptoms began at age 52 with an intermittent intention tremor in her right hand. It began to involve her left side within 2 years. At age 75, she developed balance problems. At age 79, she began using a cane on a regular basis. She had burning and numbness in her lower legs. She has had autonomic dysfunction including urinary frequency since age 55 and has also

been anorgasmic throughout her life. Other medical problems include migraine headaches, osteoarthritis, anxiety problems, and uterine and cervical cancer.

Her family history is significant in that her father and uncle had FXTAS tremor and ataxia consistent with FXTAS. Her uncle was seen before his death and his neuropathology studies were documented with the inclusions of FXTAS in both neurons and astrocytes and his MRI had a MCP sign. Her uncle has three daughters and all three have children diagnosed with fragile X syndrome (Fig. 3).

Upon examination, a 'no-no' head tremor is persistent throughout the exam. She has an intermittent resting tremor in her hands and an intention tremor bilaterally. She is ataxic, cannot tandem walk, and uses a cane. Deep tendon reflexes are 1+ and symmetrical in the upper extremities and her knees, absent at ankles. Her vibration sense is decreased in both feet. Brain MRI showed moderate to severe loss of the brain volume, enlargement of the ventricles, and limited white matter disease (Fig. 1). Significant atrophy can also occur in individuals who are 80 years old and it is likely that a combination of atrophy from age and FXTAS are present in this case, although her MRI demonstrates far more atrophy than a control of her age (Fig. 1).

Discussion

FXTAS is defined as a premutation disorder (2, 10). Patients 1 and 2 have most of the neurological features of FXTAS but not a repeat number in the premutation range as delineated by American College of Human Genetics (ACHG) (11). The lower cut off for premutation at 55 repeats was set by ACHG related to a concern for the risk of expansion to the full mutation in one generation, but this delineation of CGG repeat number does not take into account possible clinical involvement of premutation or GZ carriers related to elevation of *FMRI*-mRNA. The cause of FXTAS is thought to be the elevated *FMRI*-mRNA, which is typically twofold to eightfold in premutation carriers (12). However, elevations in *FMRI*-mRNA typically occur on a continuum that starts in the GZ range (7). Loesch et al. also observed a twofold increase of GZ alleles in males with Parkinsonism. (4). More recently, increased levels of the antisense *FMRI* (*ASFMRI*) transcript were described in a cohort of subjects with GZ and low premutation alleles and Parkinsonian phenotype suggesting a potential cytotoxic effect of elevated levels of both the *FMRI* and *ASFMRI* genes leading to mitochondrial dysfunction and neurodegenerative disorders (13).

From the onset of the intention tremor, delay of onset of ataxia was 1 year in patient 1 and, 23 years in patient 2. A longitudinal study of FXTAS showed that from the onset of intention tremor, median delay of onset of ataxia was 2 years (14). When compared to the progression in the above study, patient 2 had a much slower progression, which is seen in many females with FXTAS. The X-inactivation with a diluting effect of the second normal X chromosome may have contributed to her slow progression. It is also possible that FXTAS,

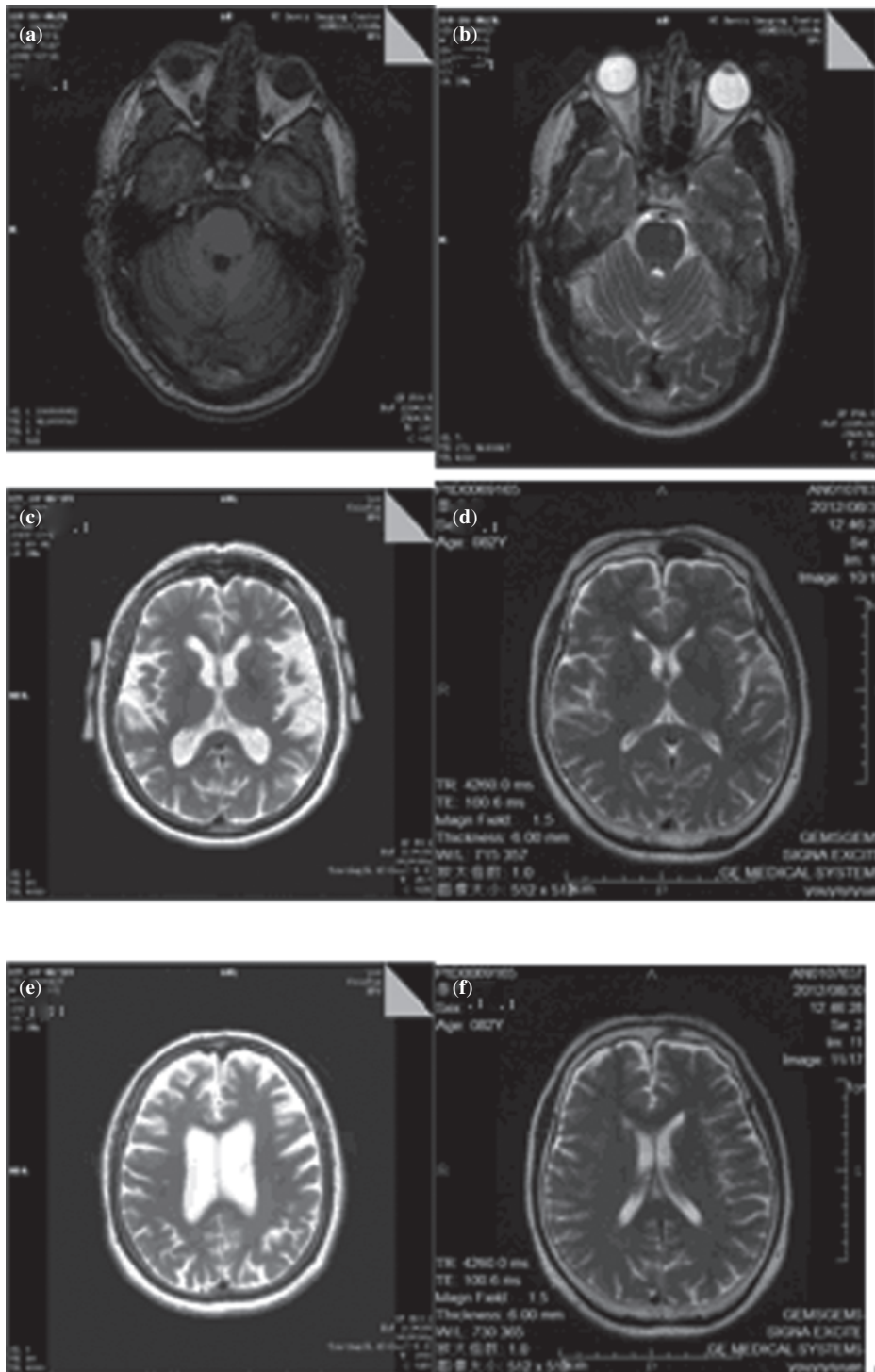


Fig. 1. T1 and T2 weighted images of case 1, case 2 and normal control. (a) Showing mild atrophy of the cerebellum in case 1. (b) Showing increased signal intensity in the left of the pons in case 1. (c) Showing atrophy of the temporal lobe in case 2. (d) Showing normal T2 weighted images of normal control (female 83 years old). (e) Showing atrophy of the frontal lobe and enlargement of the ventricles in case 2. (f) Showing normal T2 weighted images of normal control (female 83 years old).

when it occasionally occurs in GZ carriers, may exhibit a slower deterioration in the GZ than in the premutation.

Family members of both patients had premutation and were earlier diagnosed with FXTAS; thus, it is

likely that these families have a facilitating genetic background acting in concert with the premutation or GZ to produce FXTAS. In both patients, the alleles were in the upper GZ range with elevated *FMRI*-mRNA combined with a family background that could

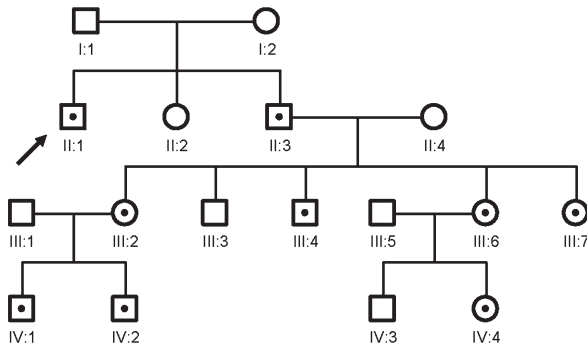


Fig. 2. Pedigree of the family of patient 1 (II:1, indicated with arrow). His brother (II:3) has the premutation and GZ allele, and has been diagnosed with FXTAS. His brother has three daughters, one with a GZ (III:2) and two are premutation carriers (III:6 and III:7). The daughter with the GZ has two sons with the premutation and autism (IV:1 and IV:2) and III:6 has a daughter with the premutation allele (IV:4).

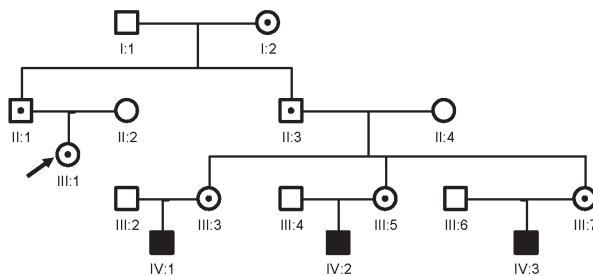


Fig. 3. Pedigree of the family of patient 2 (III:1, indicated with arrow). Her father (II:1) and her uncle (II:3) are premutation carriers and both have been diagnosed FXTAS. Her uncle (II:3) has three daughters (III:3; III:5; and III:7) who have premutation alleles and all of them have children who had been diagnosed with fragile X syndrome (IV:1; IV:2; and IV:3).

lead to the observed symptoms of FXTAS. FXTAS is the late outcome of an RNA-associated pathogenic process that in mouse models actually begins early in life, which may also be true in humans (15). However, not all premutation carriers develop FXTAS so there may be additional genetic or environmental factors that facilitate the development of FXTAS. Here, we propose that FXTAS may also be present in some GZ carriers with the addition of facilitating genetic and environmental factors.

Our report draws attention to the need for larger studies in GZ carriers who may have a clinical picture similar to FXTAS. Further neuropathological studies are needed in GZ carriers, who succumb to neurological problems, to clarify if indeed this is truly FXTAS with the characteristic neuropathological features including inclusions and spongiform changes in the white matter (16). Although our patients did not have the classic MCP sign seen in 60% of males and 13% of females with FXTAS (17), their features are otherwise classic for FXTAS and they meet criteria for probable FXTAS (2). We therefore recommend that the definition of FXTAS should not be limited to just the 55–200 repeat range, but instead this definition should be broadened to include the GZ, at least in the upper GZ allele CGG repeat range and with facilitating genetic background.

Acknowledgements

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