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FMR1 Gene Expansion and Scans without Evidence of Dopaminergic Deficits in Parkinsonism Patients

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Abstract

Purpose—To determine if patients with parkinsonism and *fragile X mental retardation 1 (FMR1)* gene expansions have a striatal dopamine deficit similar to Parkinson disease (PD) patients.

Scope—The authors studied three patients with parkinsonism carrying small expansions in the *FMR1* gene (41–60 CGG) with [^{123}I] -CIT SPECT imaging. The patients responded to dopaminergic medications, but had preserved dopamine transporter density.

Conclusions—These results suggest that parkinsonism associated with smaller *FMR1* expansions may be related to mechanisms other than presynaptic dopaminergic changes and may represent a potential explanation for at least some parkinsonian cases with scans without evidence of dopaminergic deficits (SWEDD).

Keywords

FMR1; SPECT; FXTAS; parkinsonism; dopamine

1. Introduction

The *FMR1* gene contains a CGG repeat in the untranslated portion of the gene. Individuals with *FMR1* premutation range expansions (55–200 CGG repeats) are at risk to develop the fragile X-associated tremor/ataxia syndrome (FXTAS), which is characterized by kinetic tremor, ataxia, parkinsonism, autonomic dysfunction, peripheral neuropathy, and cognitive decline [1]. In addition, some premutation carriers have a PD phenotype [2]. Gray zone expansions (41–54 CGG repeats) in the *FMR1* gene have recently been associated with parkinsonism in females [3]. PD patients with scans without evidence of dopaminergic deficits (SWEDD) were identified in several clinical trials enrolling early PD subjects, including the Elldopa, REAL-PET, and PRECEPT studies [4–5]. In some of these parkinsonism cases, there is no explanation to account for the lack of dopamine transporter (DAT) deficit on imaging [6]. This paper describes phenotypic features of three parkinsonism patients with gray or

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premutation size *FMR1* expansions (without classic FXTAS) who have normal dopamine transporter SPECT imaging results compared to a pre-existing healthy subject data base [7].

2. Report of Cases

2.1. Case 1

A 66-year-old woman had a 10-year history of head tremor and leg tremor, when standing in one position for too long (Table 1). The tremor improved on carbidopa/levodopa. On exam, the patient had a constant no-no tremor in the head and neck, bilateral kinetic and intention tremor in the upper extremities, and a faster frequency tremor in the lower extremities after a latency period. Eighteen months later; she had rest tremor and cogwheel rigidity, bradykinesia bilaterally, stooped posture, en bloc turns, and decreased arm swing on the right. She was a carrier of a normal and a gray zone *FMR1* allele of 23 and 41 CGG repeats.

2.2. Case 2

A 68-year-old woman had a 2-year history of tremor, falls, and short term memory problems. She had two siblings with PD. She was started on carbidopa/levodopa, with marked improvement in her symptoms and energy level. Five years later, she developed difficulty with turns and wearing off of her medications. On exam, she had masked facies, head tremor, rest tremor in the left hand, and kinetic tremor symmetrically in both hands. She had increased tone on the right, bradykinesia with finger tapping and hand grasping, decreased arm swing when ambulating, en bloc turns, complete retropulsion, and difficulty with tandem. Neuropsychological testing showed severely impaired memory, moderately impaired cognitive processing speed, and mildly impaired executive function. She was a carrier of a normal and a gray zone *FMR1* allele of 21 and 51 CGG repeats.

2.3. Case 3

A 46-year old right handed man had one year of rest tremor in the right hand, with pain and stiffness. On exam, he had rigidity and rest tremor on the right, bradykinesia with finger tapping and decreased arm swing on the right. One year later, the patient reported worsening of his speech and gait freezing. Exam showed masked facies, increased tone in the head and neck, slowed gait initiation, decreased stride length, and he took three steps to turn. Pramipexole was started, with tremor resolution and improved balance. The following year, he developed head tremor, intention tremor, and blepharospasm. He was a carrier of a premutation *FMR1* allele of 60 CGG repeats.

[^{123}I] -CIT SPECT imaging—Subjects underwent [^{123}I] -CIT SPECT imaging, as previously described [8]. High specific activity [^{123}I] β-CIT was prepared from the corresponding trimethylstannyl precursor, and subjects were injected with up to a 6 mCi dosage of [^{123}I] β-CIT [9]. Manual regions of interest (ROI) analysis of the [^{123}I] -CIT/SPECT scans was performed by a nuclear medicine technologist, who was masked to the clinical data, using methods described in previous studies. The primary quantitative imaging outcome measure, the specific non-displaceable putamen uptake (V3”), was determined through a standardized analysis method [9]. Based on a previously acquired database of 100 healthy subjects (aged 19–88), scans were categorized as DAT deficient (< 70% age-expected lowest putamen [^{123}I] β-CIT), or not DAT deficient (> 70% age-expected lowest putamen [^{123}I] β-CIT)[7]. Informed consent was obtained from each subject and the study was approved by Western Institutional Review Board. None of our cases met criteria for FXTAS. The uptake of [^{123}I] β-CIT was normal in all three patients (Figure 1).

1. Discussion

In our patients with small *FMR1* repeat expansions (41–60 CGG repeats), parkinsonism was mild to moderate. The patients had been diagnosed with PD and had a positive response to dopaminergic medications, but some of the patients had or developed features atypical for PD, to include kinetic tremor or tandem difficulties.

These results provide evidence that some patients with parkinsonism who are carriers of *FMR1* gray or premutation repeat expansions have a normal [^{123}I] -CIT SPECT scan. It is uncertain if patients lack a presynaptic dopamine receptor deficit like that commonly seen in PD or whether the cut-off value used to define normal [^{123}I] -CIT SPECT imaging caused us to miss smaller changes on the scans. Nigrostriatal dopaminergic function has been investigated in FXTAS [8]. [^{123}I]FP-CIT SPECT imaging was done in four *FMR1* premutation carriers with clinical parkinsonism. Repeat sizes in these patients ranged from 73–105 CGG repeats and clinical features included either action tremor or cerebellar gait ataxia, in addition to non-dopamine responsive parkinsonism. Imaging showed no difference in [^{123}I]FP-CIT uptake in the FXTAS patients compared to healthy subjects. Our patients were different than those in this study due to lower repeat sizes and better response to dopaminergic medications.

[^{123}I] -CIT SPECT imaging has been shown to be a useful tool in evaluating patients presenting with parkinsonism. In fact, it can improve diagnostic accuracy in early parkinsonism syndromes with patients in whom a diagnosis of parkinsonism is suspected but showing no dopamine transporter deficit on imaging [7]. While it appears that SWEDD subjects do not have a pre-synaptic dopaminergic deficit, the etiology of parkinsonism symptoms in these subjects is uncertain. Possible explanations include alternative neurological syndromes, such as dystonic tremor, drug induced or vascular parkinsonism, or simply non-specific mild neurologic complaints. The subjects in this study raise the possibility as well of a genetic variant different from idiopathic PD, without or with milder pre-synaptic dopaminergic loss. Of note, we identified a fourth patient with a *FMR1* gray zone expansion who was scanned as part of a different research study and did have a dopaminergic transporter deficit that worsened over time. This may suggest that not all patient with *FMR1* expansions will have normal [^{123}I] -CIT SPECT imaging or that some subjects with *FMR1* expansions may also have Parkinson disease.

It is unclear why patients who have responded to dopminergic medications would have preserved striatal dopamine transporter densities. It may be related to the cut-off threshold missing milder striatal involvement. It may be that the patients had improvement on dopaminergic therapy due to a placebo effect.

In individuals in the *FMR1* premutation range, there is elevation of *FMR1* mRNA levels and a slight depletion in fragile X mental retardation protein levels [11]. Elevated mRNA has been described as a molecular phenotype for males with the premutation and may reflect a defect in the translation of the mRNA into *FMR1* protein [11]. In gray zone *FMR1* repeat expansion carriers, there is also an increase in mRNA levels starting at 39 CGG repeats [12]. Thus, it is possible that the mechanism leading to neurological signs in FXTAS, likely RNA toxicity due to elevated levels of *FMR1* mRNA, may also lead to neurological signs in gray zone (41–54 CGG repeats) carriers.

This study is interesting in two ways. First, it suggests that individuals with *FMR1* repeat expansions and parkinsonism responsive to dopaminergic medications and diagnosed with PD may have normal [^{123}I] -CIT SPECT imaging based on established cut-off values in PD, possibly accounting for some cases of SWEDD. Second, one of these patients developed features atypical for PD specifically kinetic tremor suggesting that this genetic abnormality may represent a subtype of parkinsonism with characteristic clinical features and imaging findings. Repeat expansions in this gene are important to recognize not only because of the

association to movement disorders but also due to the possibility of expansion of the trinucleotide in later generations leading to inherited intellectual disability or fragile X syndrome (FXS). Genetic counseling for patients should be considered, especially in those patients testing positive for an expansion. The next step will be to investigate the findings of this study by imaging a larger sample size of *FMR1* expansion carriers and by screening subjects identified as SWEDD for the genetic abnormality.

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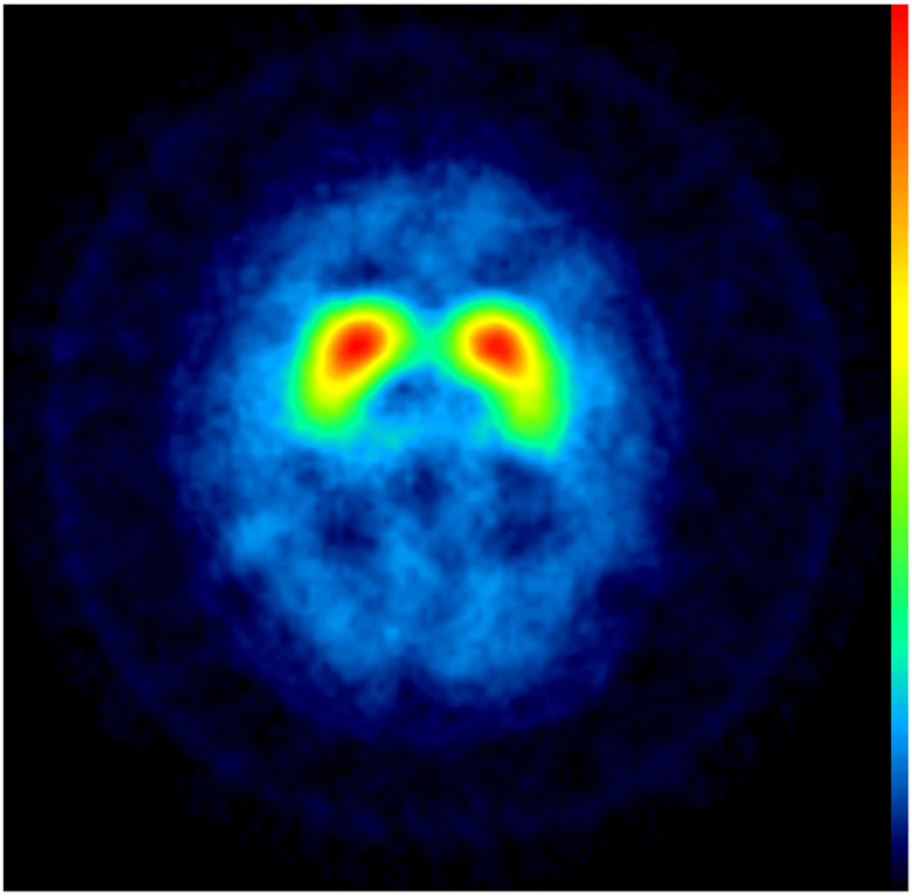

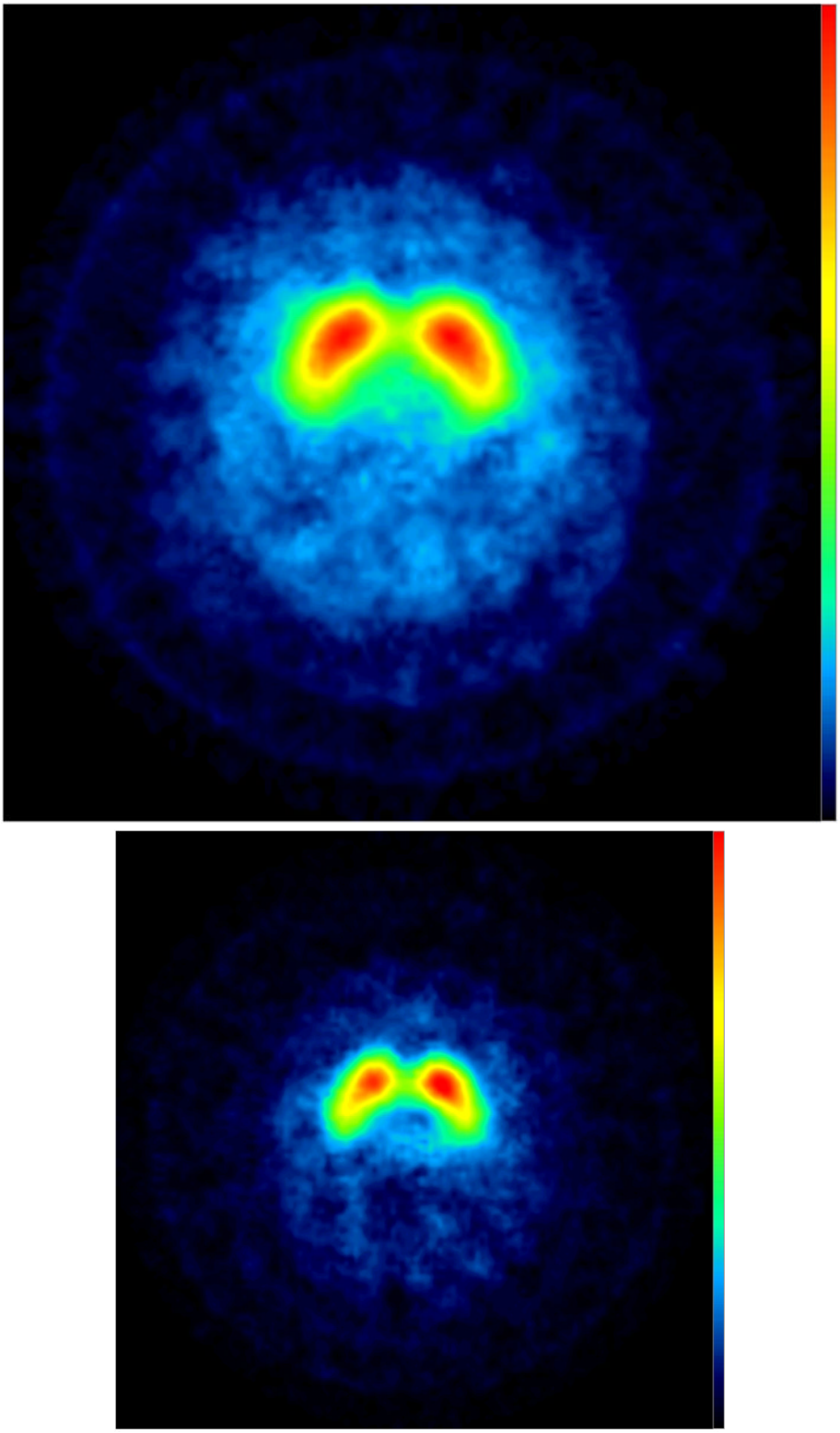

Figure 1.
[^{123}I] β-CIT SPECT Images: transverse slices at the level of the striatum show normal uptake in the three subjects.

Table 1

Clinical and neuroimaging findings in the study population

	Patient 1	Patient 2	Patient 3
Age, y	66	68	46
Age at onset, y	56	64	45
Gender	F	F	M
Clinical features	Head tremor, right arm rest tremor, kinetic arm tremor, orthostatic tremor, rigidity, bradykinesia	Head tremor, left arm rest tremor, bilateral kinetic tremor, bradykinesia, retropulsion, tandem difficulties	Head tremor, rest tremor, kinetic tremor, blepharospasm, bradykinesia and rigidity on the right, facial masking, slowed gait initiation
Family history	Cousin with hand tremor	2 siblings with PD	5 relatives with tremor and/or balance problems, niece and nephew with learning difficulties
Response to dopaminergic meds	Positive	Positive with motor fluctuations	Positive
UPDRS* (motor) score	11	13	11
UPSIT**	22	30	36
FMR1 repeat	41, 23	51, 21	60
MRI	Nonspecific white matter hyperintensities	Nonspecific white matter hyperintensities	Normal
[^{123}I]β-CIT SPECT	Normal	Normal	Normal

*UPDRS, Unified Parkinson's Disease Rating Scale;

**UPSIT, University of Pennsylvania Smell Identification Test