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A family with two female compound heterozygous for the *FMR1* premutation alleles

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Abstract

Premutation alleles (55-200 CGG repeats) of the fragile X mental retardation (*FMR1)* gene have been linked to various types of clinical involvement ranging from mood and anxiety disorders to immunological disorders and executive function deficits. Carrier females typically have a premutation allele and a normal allele (<55 CGG repeats). Although rare, 7 cases of females that carry two expanded alleles (compound heterozygous premutation) have been reported. Here we report on four members of a family including two compound heterozygous premutation sisters with similar CGG allele sizes, affected with different levels of clinical severity.

INTRODUCTION

Premutation carriers can present with reduced IQ, especially with a deficit of FMRP, and can also show a wide spectrum of clinical involvement including medical, neurological, immunological and psychiatric issues. In addition, there are also disorders associated with the premutation such as fragile X-associated primary ovarian insufficiency (FXPOI), which occurs in approximately 20% of premutation females and fragile X-associated tremor/ataxia syndrome (FXTAS) which occurs in ~40% of males and 8-16% of premutation females are also associated with the premutation (reviewed in (1)).

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CONFLICT OF INTEREST

F.T. is a non-paid collaborator with Asuragen, Inc. She has a patent for the detection of FMR1 allele size and category using the CGG linker PCR-based approach. R.H. has received funding for treatment trials in fragile X syndrome or autism from Novartis, Roche, Seaside Therapeutics, Curemark, Forest Pharmaceuticals, and the National Fragile X Foundation. D.H. received support from Novartis, Roche, and Seaside Therapeutics for clinical trials in fragile X syndrome. K.B., R.L., A.S., and C.Y. have no conflicts of interest to disclose.

It is rare for a female to have a premutation on both of her X-chromosomes, but this can occur when both of the female's parents carry a premutation allele themselves. This rarity is referred to as a compound heterozygous premutation if the alleles have different numbers of CGG repeats. The probability of having a daughter with a compound heterozygous premutation increases when the parents have a consanguineous relationship.

In a previously reported study, two of three sisters with compound heterozygous premutations, who were offspring from a consanguineous union, developed FXPOI (2). Another study reported that three compound heterozygous premutation sisters (non-consanguineous) did not have deficits in verbal performance, executive functions, or visual spatial domains by neuropsychological profiles (3). Another study compared a female with a compound heterozygous premutation to her premutation brother, and reported that while both individuals were similar ages and CGG-repeat sizes, they presented with different cognitive and behavioral profiles with the brother being more affected than his sister (4). To our knowledge there are only 7 heterozygous compound females described in the literature; here we present a family with two additional cases. We describe in detail the molecular and psychological evaluation of the two female siblings with the compound heterozygous *FMR1* premutation and their family.

METHODS

The family was recruited through the Fragile X Treatment and Research Center at the UC Davis MIND Institute upon approval by the IRB at UC Davis, CA.

Cognitive and molecular testing protocols were as previously described (4-7).

Structural MR images were performed on cases II-1, II-5, I-1, I-2 using a 3.0T Siemens scanner with Echo speed gradients and a Siemens 8-channel whole head coil.

RESULTS

Family History

The cases I-1 and I-2 are from a small geographically isolated village in Mexico, which is known to have ID in several members of this community. Although consanguinity is not depicted in figure 1, the mother and father of case I-2 were second cousins. Numerous other extended family members have reported ID, most likely FXS.

Case II-1

The participant is a 40 year old compound heterozygous premutation female with 93 and 128 CGG repeats and 2 AGG interruptions on each of her alleles. Her *FMR1* mRNA levels were fivefold higher than normal (Table 1). She achieved developmental milestones at appropriate ages. She has a history of anxiety, panic attacks, and depression. She attempted suicide at 30 years of age. She reported menarche at 13 years of age and has irregular menstrual cycles with severe abdominal cramps. She has chronic shoulder pain and migraine headaches. She reported memory problems for the past 3 years. Her medications included

duloxetine, naproxen and bupropion. She has a long narrow face, prominent ears and left shoulder tenderness. Her MRI findings did not show any atypical findings (Figure 2A).

On the WAIS-IV, this individual received standard scores of 107 on Verbal Comprehension, 98 on Perceptual Reasoning, 83 on Working Memory, 102 on Processing Speed, and a Full Scale IQ score of 98. On the WMS-IV, the participant scored 102 in auditory memory, 100 in visual memory, 97 in visual working memory, 103 in immediate memory, and 100 in delayed memory. The participant had a total score 30 on the MMSE, within the normal range. She scored 20 out of possible 27 points on the BDS-2, which is the low range of normal. On the SCID-I she met criteria for past recurrent Major Depressive Disorder in partial remission, past Substance Abuse Disorder (due to alcohol consumption), Past Panic Disorder without agoraphobia, past Specific Phobia of flying, current Generalized Anxiety Disorder, and Pain Disorder. On the SCL-90-R, she scored in the clinically significant range for self-reported obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, and paranoia. The Attention Quotient (104) and Response Control score (100) of the IVA were in the average range. Although she does not demonstrate significant neuropsychological deficits, she does have significant emotional difficulties with a suicide attempt in the past in addition to chronic pain and migraine headaches so she is on the severe end of the spectrum for premutation involvement.

This participant has 4 children from 2 different marriages. II-1 verbally reported that III-2, III-3, and III-4 have FXS, while III-1 has behavioral problems including shyness and perfectionistic features.

Case II-5

The patient is a 38 year old compound heterozygous fragile X premutation carrier with 89 and 110 CGG repeats (Figure 2). She has 2 AGG interruptions on each of her alleles. Her *FMR1* mRNA level is four fold higher than normal (Table 1). She reported menarche at 15 years and had her last menstrual period at age 27, indicative of FXPOI. She has a history of dizziness, orthostatic hypotension, sleep disturbances, insomnia, migraine headaches, and anxiety. She also has obsessive compulsive features, including excessive cleaning. She has a long face with prominent ear lobes, a mildly high arched palate, alternating exotropia, hypermobility of joints and flat feet.

On the WAIS-III, the verbal IQ was 106 (average), performance IQ of 122 (superior), and full scale IQ of 113 (average). On the WMS-III, the participant scored 99 on auditory memory, 100 in visual memory, 99 in visual working memory, 100 in immediate memory, and 107 in general memory. She scored 21 points on the BDS-2. The response control quotient in the IVA fell in the average range (105), her attention quotient is at low average range (84), with a borderline score in visual attention. The SCL-90-R showed clinically significant traits for self-reported obsessive-compulsive symptoms, anxiety, hostility, and phobia. On the Beck Anxiety Inventory (Beck, 2009), she self-reports significant anxiety symptoms. On the SCID, she met criteria for Generalized Anxiety Disorder and Panic Disorder with agoraphobia/social phobia. She also met criteria for Major Depression and Dysthymia. Her brain MRI was read as normal (Figure 2B). Overall, she does not demonstrate neuropsychological deficits but her emotional problems and neurological

problems including dizziness and orthostatic hypotension in addition to connective tissue problems are more significant that what is seen in the majority of premutation carriers at age 38.

Case I-1

This individual is a 69 year old male with 183 CGG repeats (Figure 2) containing 2 AGG interruptions. His *FMR1* mRNA levels were six fold higher than in normal individuals (Table 1). As a child he reached developmental milestones at appropriate ages. He has had depression and anxiety for the past 10 years. He has intermittent episodes of dizziness and swallowing problems, remarkable with liquids. His past medical history is remarkable for stroke without complications, at age of 60. He does not have a history of dislocation or chronic pain, but reported to have an inguinal hernia. He takes fluoxetine, atorvastatin and escitalopram oxalate. His physical exam did not show ataxia or tremors. He has a long face, large ears (>7cm) and normal testicular size. IQ testing showed verbal and performance abilities within the normal range (Table 1). On the SCL-90-R, he scored in the borderline clinically significant range for self-reported obsessive-compulsive symptoms, depression, anxiety, phobia, paranoia, and psychoticism. His structural brain MRI showed mild cerebral atrophy involving frontal and parietal regions and some hyperintensities in the white matter regions of the prefrontal lobe (Figure 2C).

Case I-2

This participant is a 69 year old female born to parents who were second cousins. She has 29 and 76 CGG repeats and an activation ratio of 0.32 (Figure 2). She has 2 AGG interruptions on each allele. *FMR1* mRNA levels were within the normal range (Table 1). She reported as a child she was shy and had tantrums. She has daily anxiety symptoms, moderate depression for the past 2 years and sleep disturbances for the past 10 years. She usually sleeps 4 - 5 hours a day. She reported memory problems for the past 2 years. She reported menarche at age 15 and had a hysterectomy at age 32 for a non-specified cause. She also has osteoporosis and hypercholesterolemia. Her physical exam was unremarkable, although she has long face and large ears (>7cm). She had no ataxia or tremor. On the WAIS-III, the full scale IQ was in the low average range (82). The MMSE score of 28 does not show any impairment in orientation, or cognitive status. The BDS-2 score of 11 fell in the moderately impaired range and points to problems with executive functioning. On the SCL-90-R, she scored in the clinically significant range for self-reported somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, phobia, and psychoticism. Her structural brain MRI showed mild atrophy in the prefrontal cortex and cerebellum.

DISCUSSION

Consanguinity and inbreeding increases the risk for X-linked syndromes in females, which in many recessive disorders results in affected females. I-1 and I-2 are from a small and isolated village with a high incidence of ID explains the presence of compound heterozygous premutation in two members of this family.

The *FMR1* premutation is the most common genetic cause of fragile X–associated primary ovarian insufficiency (FXPOI) defined as cessation of menses before age 40 and has an incidence of about 20% in female carriers (8). The pathophysiology is unclear; however FMRP in early development (before the X inactivation) may play a role in proliferation of oocytes and later in life the accumulation of *FMR1* mRNA can lead to follicular atresia. II-5 experienced symptoms consistent with FXPOI at the age of 27 while II-1 did not experience these symptoms even though II-1 had higher expression of *FMR1* mRNA levels. FXPOI is characteristic of females with the premutation and is not reported to have a higher incidence in compound heterozygous premutation females; however the number of cases reported is too small to make any conclusions.

Case I-1 and II-5 scored within the normal range for intelligence and memory, which is consistent with the previously reported compound premutation females (2, 3), however, the BDS-2 results showed a comparable low score in executive functioning for both individuals and this is consistent with previous reports of executive function deficits or ADHD symptoms in carriers (9).

Depression and anxiety are the most common psychiatric problems of adults with the premutation and normal intellectual abilities (10). The psychiatric interview (SCID-I) showed a similar profile for both individuals, emphasizing an increased rate of depression and anxiety. I-1, I-2, II-1, and II-5 presented with similar severity of anxiety and depression; interestingly the onset these symptoms was described earlier in the compound heterozygous premutation females (early 20s) than the parents with the premutation (40′s). sisters did not appear to show additive cognitive effects, but the psychiatric problems were worse than typically seen in carriers and they started earlier in life so the compounded premutation may have influenced the age of presentation and severity of their psychiatric problems. I-1, I-2, II-1, and II-5 reported chronic migraines which are commonly seen in about 50% of patients with a premutation and they are often are difficult to treat (11).

Neurological problems are common in aging premutation carriers including neuropathy, tremor, ataxia and cognitive decline, which are the symptoms of FXTAS (1). Case I-1 and I-2 did not present typical symptoms of FXTAS. This is particularly remarkable for case I-1, because his *FMR1* mRNA expression levels were elevated (Table 1), which puts him at high risk for FXTAS. It is possible he has been protected by a gene modifier, the lack of environmental toxicity, and his healthy lifestyle. He has a healthy diet, exercises regularly and does not smoke or drink alcohol. The 183 CGG repeats allele decreased during transmission to his two daughters (II-1, II-5); contraction has been commonly observed during paternal transmission (12). The maternal transmission remained stable, which is most likely due to the presence of 2 AGG anchors in agreement with the predicted risk model (7).

In conclusion, we report on an interesting family with 2 compound heterozygous premutation females with similar molecular results but vary in severity of medical symptoms and psychopathological involvement. MRI imaging results shows that both I-1 and I-2 do not present any FXTAS-specific findings, which suggest of a protective factor in this family.

Acknowledgments

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This work is dedicated to the memory of Matteo.

REFERENCES

1. Hagerman RJ, Hagerman PJ. The other face of the fragile X gene: Advances in clinical and molecular understanding of the FMR1 premutation and FXTAS. Lancet Neurol. In Press.
2. Esch HVBL, Race V, Matthijs G. Very early premutation ovarian failure in two sisters compound heterozygous for the FMR1 premutation. Eur J Med Genet. 2009; 52:37–40. [PubMed: 19041959]
3. Mazzocco MM, Holden JJ. Neuropsychological profiles of three sisters homozygous for the fragile X premutation. Am J Med Genet. 1996; 64:323–328. [PubMed: 8844074]
4. Basuta K, Narcisa V, Chavez A, et al. Clinical phenotypes of a juvenile sibling pair carrying the fragile X premutation. Am J Med Genet A. 2011; 155A:519–525. [PubMed: 21344625]
5. Folstein MF, Folstein SW, McHugh PR. “Mini Mental State”: A practical method of grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. [PubMed: 1202204]
6. Grigsby J, Brega AG, Engle K, et al. Cognitive profile of fragile X premutation carriers with and without fragile X-associated tremor/ataxia syndrome. Neuropsychology. 2008; 22:48–60. [PubMed: 18211155]
7. Yrigollen CM, Durbin-Johnson B, Gane L, et al. AGG interruptions within the maternal FMR1 gene reduce the risk of offspring with fragile X syndrome. Genet Med. 2012; 14:729–736. [PubMed: 22498846]
8. Sullivan SD, Welt C, Sherman S. FMR1 and the continuum of primary ovarian insufficiency. Semin Reprod Med. 2011; 29:299–307. [PubMed: 21969264]
9. Hunter JE, Epstein MP, Tinker SW, et al. The FMR1 premutation and attention-deficit hyperactivity disorder (ADHD): evidence for a complex inheritance. Behav Genet. 2012; 42:415–422. [PubMed: 22101959]
10. Bourgeois JA, Seritan AL, Casillas EM, et al. Lifetime prevalence of mood and anxiety disorders in fragile x premutation carriers. J Clin Psychiatry. 2010
11. Au J, Akins R, Berkowitz-Sutherland L, et al. Prevalence and risk of migraine headaches in adult fragile X premutation carriers. Clin Genet. 2013
12. Nolin SL, Sah S, Glicksman A, et al. Fragile X AGG analysis provides new risk predictions for 45-69 repeat alleles. Am J Med Genet A. 2013; 161:771–778. [PubMed: 23444167]

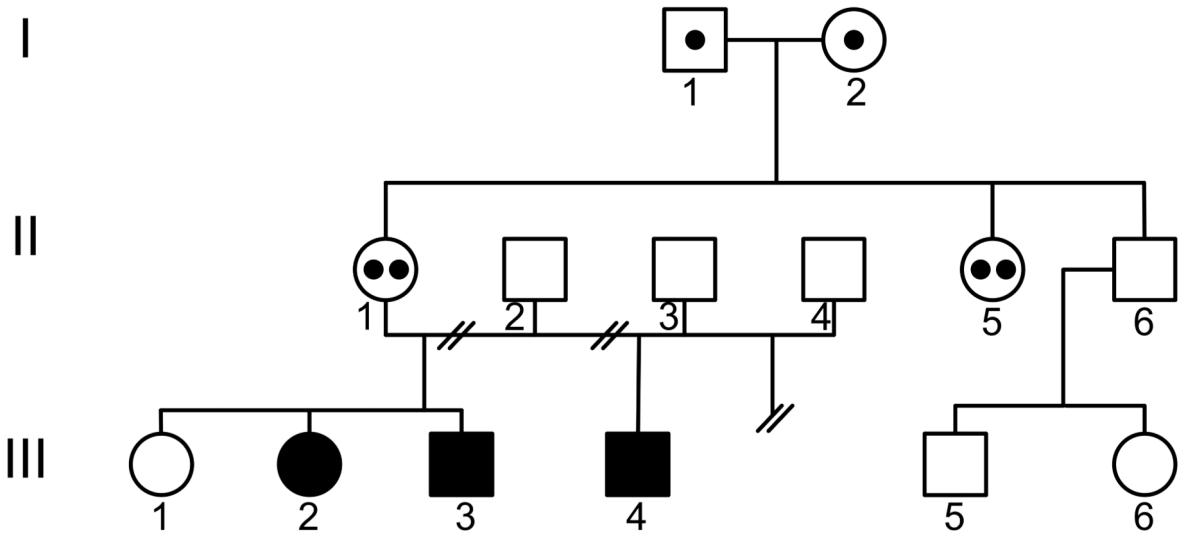

Figure 1.
Pedigree

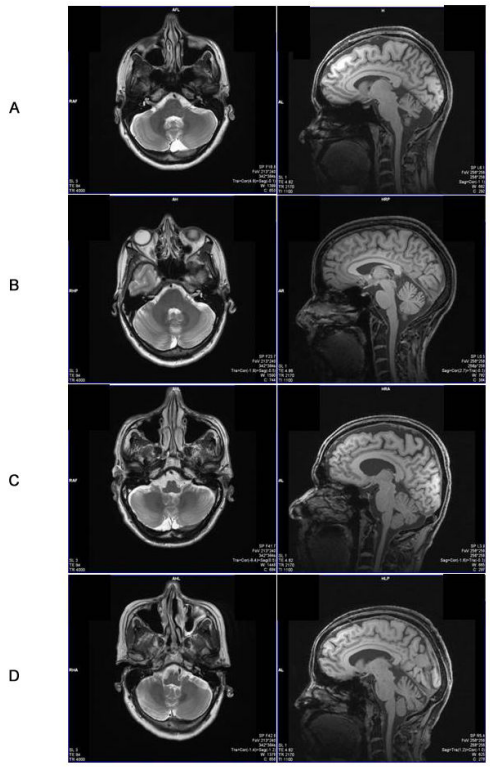

Figure 2.

Overview of T2-weighted MRIs, axial and sagittal FLAIR (fluid attenuated inversion recovery). A: MRI of II-1. B: MRI of II-5. C: MRI of I-1. D: MRI of I-2.

Table 1

Molecular and Clinical Comparison

Test		II-1	II-5	I-1	I-2
Molecular	**CGG Repeats**	93, 128	89, 110	183	29, 76
	AR	N/A	N/A	N/A	0.32
	Methylation	N/A	N/A	N/A	N/A
	AGG Interruptions	2, 1	2, 1	2	2, 2
	RNA	5.02 +/− 0.03	4.07 +/− 0.47	6.56 +/− 1.12	1.36 +/− 0.11
BDS-2 (*total*)		20	21	19	11
IVA-CPT (*Standard Score*)	**Auditory**	110	82	N/A	N/A
	Visual	111	58	N/A	N/A
MMSE (*total*)		30	N/A	29	28
IQ (*Standard Score*)	**Verbal**	107	106	94	83
	Performance	98	122	82	82
Memory (*Standard Score*)	**Full Scale**	98	113	88	82
	Auditory	102	99	N/A	N/A
	Visual	100	100	N/A	N/A
	VMS	97	99	N/A	N/A
	IM	103	100	N/A	N/A
	General	N/A	107	N/A	N/A
SCID-I	*Met criteria for:*	-Generalized Anxiety Disorder	-Generalized Anxiety Disorder	N/A	N/A
		-Major Depressive Disorder	-Major Depressive Disorder	N/A	N/A
		-Panic Disorder without Agoraphobia	-Panic Disorder with Agoraphobia	N/A	N/A
		-Specific Phobia	-Social Phobia	N/A	N/A
		-Substance Abuse	-Dysthmia	N/A	N/A
		-Pain Disorder		N/A	N/A
SCL-90-R (*T-score*)	**Somatization**	65	61	53	66
	Obsessive-Compulsive	75	71	63	71
	Interpersonal Sensitivity	72	67	53	66
	Depression	69	67	63	67
	Anxiety	74	72	62	66
	Hostility	70	71	59	57
	Phobic Anxiety	68	70	67	70
	Paranoid Ideation	70	57	62	63
	Psychoticism	74	69	63	67
	Global Severity Index	74	69	61	69
	Positive Symptom	68	66	52	56

Test		II-1	II-5	I-1	I-2
	Distress Index				
	Positive Symptom Total	74	68	62	74