CLINICAL QUIZ (p227) ANSWER

What is the diagnosis?

Given the diagnosis of global developmental delay and autism occurring in a male child with self-injurious behavior, lax joints and obesity, both array CGH (aCGH) and Fragile X testing were arranged. The aCGH was normal, but the *FMR1* gene harbored a full mutation of >200 CGG repeats (Figure 2A) and *FMR1* gene methylation study showed full methylation, which confirms the diagnosis of Fragile X syndrome. As this is an X-linked condition,[1] his mother, maternal grandmother and maternal grandfather were referred for carrier testing (Figures 2B to 2D). Both his mother and maternal grandmother were premutation carriers, and they were encouraged to disclose the family history to extended family.

What does the *FMR1* gene do?

Function wise, the Fragile X mental retardation 1 gene (*FMR1*) encodes for the Fragile X mental retardation protein (FMRP).[2,3] FMRP is expressed in multiple tissues, and is especially important for transport of mRNA between the nucleus and cytoplasm and synaptic plasticity.[2,4] Increased CGG repeats lead to increase in production of mRNA as well as decrease in production of FMRP, eventually leading to prominent cognitive and behavioural problems,[5,6] as well as other medical issues detailed below.

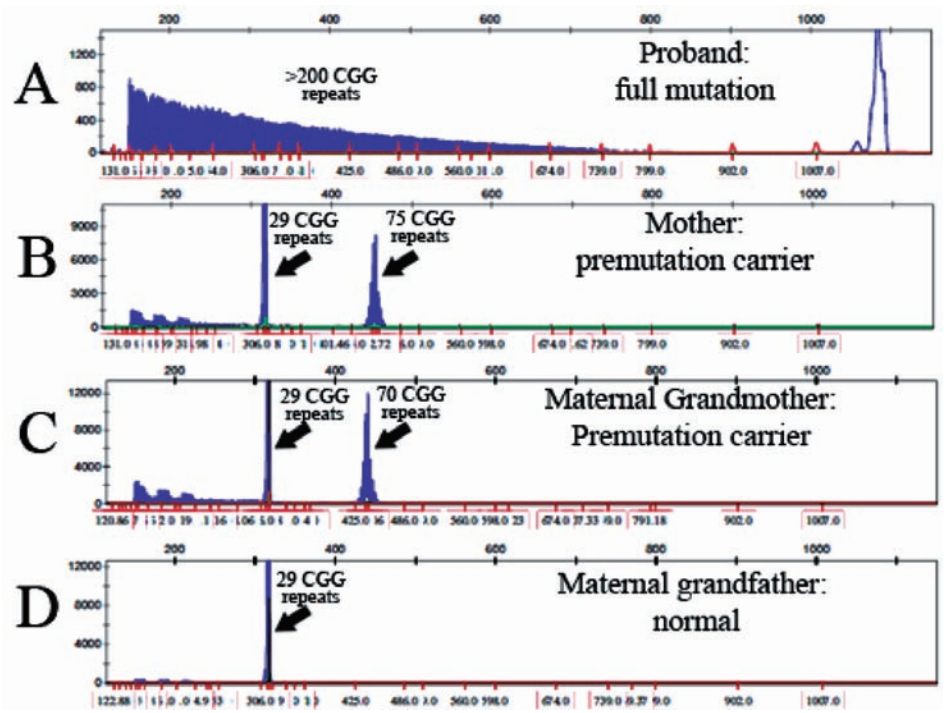

Figure 2 Fragile X testing using CGG Repeat Primed PCR amplification of the 5' untranslated region of *FMR1* gene followed by capillary electrophoresis (AmplideX™ *FMR1* PCR Kit, Asuragen, Austin, TX, USA). (A): Proband showed full mutation with >200 CGG repeats and abnormal methylation (result not shown), confirming the diagnosis of Fragile X syndrome; (B): mother showed two alleles with 29 and 75 CGG repeats, suggestive of a premutation carrier; (C): maternal grandmother showed two alleles with 29 and 70 CGG repeats, suggestive of a premutation carrier; (D) maternal grandfather showed one allele with 29 CGG repeat, which was normal.

What are the clinical features of Fragile X syndrome?

The typical dysmorphology in Fragile X syndrome consists of long face, large prominent ears, mandibular prognathism, hyperextensibility of joints as well as macroorchidism. The syndrome is also associated with cleft palate, flat feet, double jointed thumb, scoliosis and macrocephaly.[7] It should be noted, however, that up to 5-10% of these children actually have a Prader-Willi phenotype, with severe obesity, hyperphagia and hypogonadism.[2]

In general, affected females tend to have a milder phenotype as they have reduced but not complete absence of FMRP due to the presence of two X chromosomes.[7] This is especially true when it comes to cognitive functioning. Most boys with Fragile X syndrome have moderate to severe intellectual disability, with only 11% falling into the mild intellectual disability range. Most females, on the other hand, have borderline to low normal range IQ, with 25% having an IQ in the intellectual disability range.[4]

In terms of behavior, 30-50% of children with Fragile X syndrome fulfill the diagnostic criteria of autism spectrum disorder.[2,8] They tend also to be socially aversive and shy, as exemplified by the hallmark 'Fragile X handshake', which consists of shaking the interviewer's hand or acknowledging his/her presence but avoiding eye contact until he/she looks away.[6] Other mood and behavioural problems are also over represented in children with Fragile X syndrome, including aggression, depression, anxiety, social phobia and attention deficit hyperactivity disorder.[2,5,6]

Even though Fragile X syndrome is classically not associated with other malformations, studies have shown an association with recurrent otitis media, mitral valve prolapse, gastrointestinal problems (such as gastroesophageal reflux, constipation, and loose bowel movements), seizures, movement disorders, refractive errors, nystagmus, sleep problems including frequent awakening and obstructive sleep apneas.[9] It is necessary that physicians be on the lookout for these associations, and make timely referrals when appropriate.

What is the prevalence of Fragile X syndrome and Fragile X premutation state?

Fragile X syndrome is the leading hereditary cause of intellectual disability and autism spectrum disorders, accounting for up to 2-5% of all autism spectrum disorders.[10] It has an estimated prevalence of 1 in 4000 men and 1 in 8000 women.[11-13] The premutation state, being more common, occurs 1 in 700 men and 1 in 260 women.[5] Much variation exists, however, with its prevalence data, and a study from Taiwan estimated the premutation prevalence of male carriers at 1 in 1670 only.[14]

What is the inheritance pattern of Fragile X syndrome? How does that relate to other *FMR1*-related disorders?

The name Fragile X derives from the fragile site of the X chromosome in affected individuals, which is characterised by CGG repeats. The number of CGG repeats,[15] when exceeding beyond 45-54, tends to expand across generations, leading to the hereditary pattern of X-linked dominant disease with genetic anticipation. Individuals with >200 CGG repeats are diagnosed to have Fragile X syndrome; whereas individuals with 55-200 CGG repeats are at increased risk for behavioural and cognitive problems, Fragile X-associated tremor/ataxia syndrome (FXTAS)[2] and *FMR1*-related primary ovarian insufficiency.[16]

What are the clinical features of Fragile X premutation carriers?

Children with Fragile X premutation are not completely symptom free. They tend to show subtle facial features, have subtle executive and short term memory deficits and show a propensity for psychiatric and behavioural symptoms

Table 1 Physical and behavioural characteristics of Fragile X syndrome

Categories	Features
Facial	Broad forehead
	Large and prominent ears
	Long face
	Mandibular prognathism
	Cleft palate
	Macrocephaly
Ophthalmologic	Strabismus
	Nystagmus
	Refractive errors
Ear, nose and throat	Recurrent otitis media
	+/- hearing impairment
Neurological	Seizure
	Hypotonia
	Movement disorder
Psychiatric	**Poor eye contact**
	ASD
	ADHD
	Depression
	Anxiety
	Aggressive behaviour
Development	**Intellectual impairment**
	Executive and short term memory impairment
Orthopaedic	Flat feet
	Hyperextensibility of finger joints
	Scoliosis
	Pectus excavatum
Cardiovascular	Mitral valve prolpase
	Aortic root dilatation
Respiratory	Obstructive sleep apnoea
Gastrointestinal	Gastroesophageal reflux
	Constipation
	Frequent loose stool
Genitourinary	Macroorchidism
Others	Obesity
	Tall or short stature
	Cramped teeth
	Soft and smooth skin

Features in bold font are present in our patient

including obsessionality, cognitive decline, mood disorders, ASD and ADHD.[16] As expected, males with premutation status are usually more symptomatic than females with permutation status. As mentioned earlier on, they are also at a higher risk for FXTAS.[2] Females with premutation status are also at risk for *FMR1*-related primary ovarian insufficiency.[4,16]

What is Fragile X-associated tremor / ataxia syndrome (FXTAS)?

Amongst premutation carriers of *FMR1* gene older than the age of 50, approximately 40% males and 20% females[16] develop FXTAS.[2] It is a progressive neurodegenerative disorder characterised by progressive intention tremor, cerebellar ataxia and parkinsonism. Other features include short term memory loss, executive function deficits, cognitive decline, dementia, peripheral neuropathy, proximal muscle weakness and autonomic dysfunction.[16] Typical MRI findings include white matter lesions over the middle cerebellar peduncles and/ or brainstem on MRI brain.[4]

What is *FMR1*-related primary ovarian insufficiency (POI)?

Approximately 20% of female premutation carriers develop *FMR1*-related primary ovarian insufficiency (POI), defined as cessation of menses before the age of 40 years. This premature ovarian failure can happen as early as 11 years old. Female premutation carriers should thus consider to start their families early. It should be noted, however, that the diagnosis does not preclude subsequent pregnancy and up to 5-10% of women with POI may conceive.[16]

Clinical and diagnostic implications

As of many other syndromic conditions, anticipatory management and timely referrals for associated medical problems is important for children with Fragile X syndrome. It should be noted, however, that the hereditary pattern and implications of *FMR1*-related disorders are complicated and should be adequately explained to the family. Diagnostic evaluation should extend to other members of the family as they may be premutation carriers. They might be asymptomatic. However, not only the possibility of passing on allele with expanded CGG repeats to their offspring, they are at risk of developing POI and FXTAS in the future.

Potential treatment targets

FMRP is implicated in multiple neurobiological pathway[3,4] and research is underway to identify potential treatment for Fragile X syndrome. To date there is no medication for improving the cognitive function in patients with Fragile X syndrome. However, several medications have been utilised for behavioural and psychological problems. Valproaic acid, which is a weak reactivator of the full mutation alleles in Fragile X syndrome, has been reported to improve ADHD symptoms. Minocycline, which decreases the overproduction of metalloproteinase-9 in Fragile X syndrome, has also been demonstrated to lead to behavioural improvements. Other targeted medication such as metabotropic glutamate receptor (mGluR) antagonists are also under medication trials.[7]

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