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Fragile X Syndrome in Practice: A Clinical Dysmorphology Guide for Diagnosis Without Genetic Testing

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Abstract

Background: Fragile X syndrome is one of the most common inherited causes of mental retardation and a leading monogenic cause of autism spectrum disorder. Despite its well-established genetic basis, diagnosis in many low-and middle-income countries remains limited due to restricted access to molecular testing. Historically, the condition was first described by James Purdon Martin and Julia Bell in 1943, with subsequent cytogenetic characterization by Herbert Lubs. Later clinical delineation highlighted a recognizable pattern of craniofacial dysmorphism and neurodevelopmental impairment. In resource-limited settings, reliance on clinical features remains essential for diagnosis.

Objective: To describe the clinical characteristics and diagnostic features of three Iraqi male patients presenting with neurodevelopmental impairment and phenotypic findings suggestive of Fragile X syndrome, emphasizing the role of phenotype-based diagnosis in the absence of genetic confirmation.

Methods: This case series includes three male patients evaluated in 2025 in a clinical setting. Diagnosis was based on detailed clinical assessment, including developmental history, behavioral profile, and physical examination focusing on dysmorphic features. Data collected included age at presentation, neurodevelopmental status, behavioral characteristics, growth parameters, and craniofacial morphology.

Results: The patients (ages 6, 8, and 16 years) demonstrated variable neurodevelopmental impairment:

- One patient exhibited severe autism, absent eye contact, stereotypic behaviors, and growth failure.
- One patient presented with marked speech delay and hyperactivity without clear autistic features.
- One patient showed mental retardation with less prominent behavioral abnormalities.

All patients shared consistent craniofacial features, including:

- Long, narrow face
- Prominent or protruding ears
- Forehead prominence (in two patients)
- Variable mandibular changes (micrognathia or prognathism)

Additional findings included slender body habitus in two patients and absence of major congenital anomalies in all cases. Notable phenotypic variability was observed, particularly in behavioral manifestations and severity of cognitive impairment.

Conclusion: Fragile X syndrome can be diagnosed with reasonable clinical confidence based on characteristic craniofacial features and neurodevelopmental profile, even in the absence of genetic testing. This case series highlights the importance of clinician awareness and careful phenotypic. Early clinical recognition may facilitate timely intervention, appropriate management, and genetic counseling, thereby reducing underdiagnosis and improving patient outcomes.

Keywords: Fragile X Syndrome; Mental Retardation; Autism Disorder; Dysmorphic Features; Clinical Diagnosis; Iraq

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Introduction

In 1943, James Purdon Martin (Figure 1A) and Julia Bell (Figure 1B) described a pedigree consistent with X-linked mental retardation. The family they reported included mothers with normal intelligence and eleven sons with severe mental retardation (Mental ages of 2-4 years). The authors attributed the condition to a sex-linked recessive gene. In addition, two females in the family exhibited mild retardation, which was interpreted as evidence that the gene was not completely recessive.

All of the carrier mothers were daughters of two phenotypically normal brothers, except for one who was the daughter of the brothers' sister. The two brothers appeared unaffected and were considered to suppress the clinical expression of the disorder while still transmitting the causative gene [1].

In 1969, Herbert Lubs (Figure 1C) reported 4 males in three generations having X-linked mild to severe mental retardation and a marker X chromosome with a secondary constriction near the end of the long arm giving the appearance of large satellites. The marker X chromosome was present in 10%-33% of cells [2].

In 1970, R. Ellen Magenis, Frederick Hecht, and Everett W. Lovrien used term "fragile site" to describe recurrent chromosome breaks at a site [3].

In 1981, Brown and colleagues suggested screening for fragile X syndrome by testicular size measurement [4].

In 1982, Nielsen et al. reported a study which involved clinical screening of 178 male patients with mental retardation for the presence of macroorchidism using an orchidometer. 52 had a testicular volume of 25 ml and over, 11 of them had prominent macroorchidism (above 25 ml). All the 52 patients were examined cytogenetically for the fragile X. Two patients with prominent macroorchidism had fragile X chromosome [5].

In 1984, Jean-François Mattei (Figure 1D) from France and his research group emphasized the association between X-linked mental retardation and characteristic facial dysmorphism in individuals carrying a fragile site at Xq27–q28 of the X chromosome. They proposed that the syndrome followed an X-linked dominant mode of inheritance with incomplete penetrance and estimated a frequency of approximately 1 in 2000 affected males exhibiting Fra(X) (q).

Mattei et al., provided one of the earliest consolidated clinical descriptions of what is now recognized as Fragile X syndrome, highlighting a recognizable but variable facial phenotype characterized by a long, narrow face, large ears, and a prominent forehead and jaw. They also emphasized the variability of expression and its age-dependent evolution, contributing to the recognition of this condition as a clinically identifiable syndrome rather than solely a cytogenetic finding.

The authors described a distinct, though variable, facial phenotype that closely aligns with features still recognized today:

- Long, narrow face (dolichocephalic appearance): The face is vertically elongated, giving a slender overall aspect.
- Prominent, large ears (macrotia): The ears are often enlarged and may appear protruding, representing a key clinical feature.
- Prominent forehead and jaw: A broad or high forehead and mandibular prominence (prognathism) contribute to the characteristic facial profile, particularly with increasing age.
- Elongated chin: The lower face is accentuated, reinforcing the

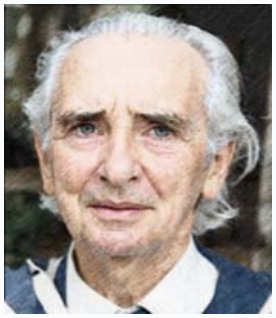

Figure 1A: James Purdon Martin neurologist (1893-1984), a neurologist from London.

Figure 1B: Julia Bell (1879-1979), an English pioneer of medical genetics.

Figure 1C: Herbert Augustus Lubs (1928 -2023), An American clinical geneticist and cytogeneticist.

Figure 1D: Jean-François Mattei (born in 1943) is a French pediatrician and geneticist.

Figure 2: A boy with Fragile X-syndrome diagnosed by chromosomal study reported by Al-Mosawi in 2020.

Figure 3: The second boy with Fragile X-syndrome diagnosed by chromosomal study reported by Al-Mosawi in 2020.

elongated facial configuration.

• Relatively underdeveloped midface: The midfacial region may appear less prominent in comparison with the upper and lower face.

From a clinical perspective, Mattei et al., also stressed that dysmorphic features may be subtle or absent in early childhood, tend to become more apparent with age especially after puberty and show considerable variability, even within affected families [6].

In 2020, Al-Mosawi reported a study which included 80 Iraqi patients with mental retardation. Down syndrome was the commonest syndromic cause of mental retardation accounting for 8.75% of the cases. Fragile X-syndrome diagnosed by chromosomal study was observed in 2 boys (Figure 2 and 3).

The aim of this paper is to describe three male patients during the year 2025, all presenting with neurodevelopmental impairment and characteristic dysmorphic features suggestive of Fragile X syndrome. The diagnosis in all cases was made clinically based on phenotypic features and behavioral profile, in the absence of genetic confirmation.

Patients and Methods

Patient-1

A 16-year-old male was first seen on 23 August 2025 (Figure 4). He was one of non-identical twins and presented with severe autism, growth failure, and dysmorphic features. His co-twin had a milder autistic phenotype but was not available for full evaluation.

The patient had delayed developmental milestones and marked autistic behaviors, including absent eye contact, lack of response to name, minimal verbal communication, and repetitive stereotypic movements. There was no history of seizures or major systemic illness.

Figure 4: A 16-year-old male was first seen on 23 August 2025.

Growth assessment revealed reduced height and weight compared to his co-twin.

On examination, he demonstrated marked motor restlessness with repetitive hand movements and stereotypies. Hand posturing (flexion and fidgeting) was noted. No limb anomalies such as clinodactyly or syndactyly were observed.

Craniofacial features included:

• Long, narrow face

• Prominent forehead

• Large, prominent ears

• Long philtrum with thin upper lip

• Prominent/pointed chin

• Subtle midface hypoplasia

• Low/posterior hairline at the nape (Figure 4)

He had a slender body habitus with long extremities. There was no hypertelorism or hypotelorism, and no congenital heart defects or palatal abnormalities were detected. No consanguinity was reported.

Patient-2

A 6-year-old boy (Figure 5) was first seen in September 2025 with marked speech delay and significant hyperactivity, despite treatment with risperidone (1 mg/day in two divided doses). He did not exhibit clear autistic features, as he responded to his name and maintained

Figure 5: A 6-year-old boy was first seen in September 2025.

Figure 6: An 8-year-old boy presented with mental retardation that was first seen late during the year 2025.

acceptable eye contact.

According to the mother, prior brain imaging (CT or MRI) was normal.

Craniofacial features included:

- Prominent, protruding ears (laterally rotated)
- Low-set and/or posteriorly rotated ears
- Long, narrow face
- Large, prominent eyes with mild periorbital fullness
- Thin upper lip
- Mildly smooth or less-defined philtrum
- Mild micrognathia
- Slender body habitus

Patient-3

An 8-year-old boy (Figure 6) presented with mental retardation who was first seen late during the year 2025

Craniofacial features included:

- Long face with elongation of the midface and mandible
- Prominent, protruding ears
- Prominent forehead (frontal bossing)
- Mild prognathism

Results

All three patients demonstrated a consistent pattern of:

- Neurodevelopmental impairment (ranging from severe autism to isolated mental retardation and speech delay)
- Characteristic craniofacial dysmorphism, particularly long face and prominent ears
- Slender body habitus (in two patients)

Notably, phenotypic variability was observed, especially regarding the presence or absence of autistic features.

In a resource-limited setting where molecular testing is not readily available, careful clinical evaluation of behavioral profile and dysmorphic features remains highly valuable for the diagnosis of Fragile X syndrome.

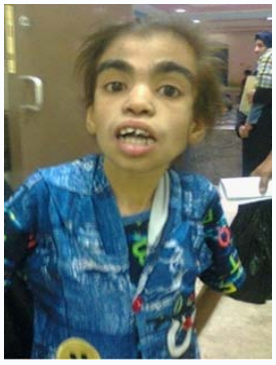

Figure 7: An Iraqi girl with Coffin Siris syndrome associated with autism. She had distinctive facial features including thick eyebrows, depressed and wide nasal bridge, and large mouth with thick everted upper and lower lips, hypertrichosis, and sparse scalp hair particularly in the temporal regions.

Figure 8: A boy from India with Williams syndrome and autism. He had a wide mouth with prominent lower lip, puffiness around the eyes, and long upper lip length.

Figure 9: An Iraqi boy with new syndromic form of autism associated with a distinct craniofacial dysmorphism.

Discussion

This case series highlights the clinical diagnosis of Fragile X syndrome in three Iraqi patients, emphasizing the continued importance of phenotype-based recognition in resource-limited settings where molecular confirmation is not readily available.

Fragile X syndrome represents one of the most common inherited causes of mental and a leading monogenic cause of autism. Despite its well-characterized genetic basis, diagnosis in many low and middle-income countries remains under-recognized and delayed, largely due to limited access to genetic testing. In such contexts, careful clinical observation remains a critical diagnostic tool.

Phenotypic consistency and variability

All three patients in this series demonstrated core craniofacial features, particularly:

- Long, narrow face
- Prominent or protruding ears

These findings are widely regarded as the most recognizable physical markers of Fragile X syndrome, especially in school-aged children and adolescents, where the phenotype becomes more pronounced.

However, the series also illustrates significant phenotypic variability:

- Patient-1 exhibited a classic and severe presentation, including profound autism, absent eye contact, stereotypies, and growth impairment.
- Patient-2 showed marked hyperactivity and speech delay without autistic features, highlighting that Fragile X syndrome does not always present with autism.
- Patient-3 demonstrated a milder neurodevelopmental phenotype with mental retardation and characteristic craniofacial features.

This variability underscores that Fragile X syndrome exists along a broad clinical spectrum, ranging from severe autistic presentations to milder cognitive and behavioral impairment.

Behavioral profile

Behavioral abnormalities were prominent across cases but differed in expression:

- Severe autistic behaviors (Patient-1)
- Hyperactivity with preserved social interaction (Patient-2)
- Mental retardation (Patient-3)

Importantly, the absence of autism does not exclude Fragile X syndrome. Clinicians should maintain suspicion in any child with speech delay, hyperactivity, and characteristic facial features, even when social engagement appears relatively preserved.

Growth and systemic findings

Growth impairment was evident in Patient-1 but not uniformly observed across all patients, further reflecting phenotypic variability. None of the patients demonstrated major congenital anomalies, consistent with the typical presentation of Fragile X syndrome as a condition primarily affecting neurodevelopment and subtle dysmorphology rather than major organ malformations.

Clinical diagnosis in resource-limited settings

A key message from this series is the feasibility and reliability of clinical diagnosis in the absence of genetic testing. The recurrent pattern of:

- Long face
- Prominent ears
- Neurodevelopmental impairment

provides a strong basis for clinical suspicion.

In countries such as Iraq, where access to molecular diagnostics may be limited, reliance on experienced clinical assessment can:

- Enable earlier identification
- Guide behavioral and educational interventions
- Support family counselling

Patients with autism generally do not display dysmorphic features. However, several dysmorphic syndromes can be associated with autism such as Coffin Siris syndrome (Figure 7) [8] and Williams syndrome (Figure 8) [9].

We have recently reported a new syndromic form of autism associated with a distinct craniofacial dysmorphism (Figure 9). He displayed multiple dysmorphic features, including:

Low-set, posteriorly rotated ears

Mild hypertelorism

Down-slanting palpebral fissures

Broad nasal bridge and bulbous nasal tip

Full cheeks with flat malar areas

Retrognathia (mild micrognathia)

Short, indistinct philtrum

Thin upper lip

Short neck

Conclusion

This case series reinforces that Fragile X syndrome can be diagnosed with reasonable confidence based on clinical findings alone, particularly in settings where genetic testing is not feasible. Recognition of the characteristic craniofacial phenotype combined with neurobehavioral features allows clinicians to identify affected individuals across a spectrum of severity.

Greater awareness of these clinical features may help reduce underdiagnosis and improve early intervention for affected children in resource-constrained environments.

Acknowledgement

The author has the copyright of all the figures and sketches included in this book.

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