Fragile X syndrome: genetic and clinical profile in the Hong Kong Chinese population

Candice WM Au, HM Luk, Stephanie Ho, SW Cheng, Stephen TS Lam, Brian HY Chung, SC Chong, Ivan FM Lo *

ABSTRACT

Introduction: Fragile X syndrome (FXS) is a common inherited cause of intellectual disability, and FXS testing is recommended as a first-line genetic investigation for global developmental delay or intellectual disability. This retrospective study evaluated the diagnostic yield of FXS testing and clinical features in Chinese patients in Hong Kong.

Methods: From 1993 to 2022, 7291 patients referred to the Clinical Genetic Service for neurodevelopmental conditions (eg, developmental delay, autism spectrum disorder, and intellectual disability) underwent FXS testing. In total, 103 individuals from 61 families were confirmed to have an *FMR1* full mutation, including 59 index cases and 44 family members. Clinical features of 70 Chinese patients with FXS, including growth, neurobehavioural features, and other co-morbidities, were evaluated.

Results: The diagnostic yield of FXS testing was 0.8%. The median age at diagnosis for index cases was 4.1 years, with a trend towards earlier diagnosis in recent years. In 27 families (44.2%), multiple members carried a full mutation. Prenatal diagnosis was arranged in 11% of families. Developmental delay was observed in all males, compared with 45.0% of females. Intellectual disability affected 86.0% of males but only 30.0% of females. Common co-morbidities included obesity, autism spectrum disorder, attention-deficit/hyperactivity disorder, epilepsy, gastrointestinal problems, and sleep disturbances. Features such as strabismus, scoliosis, and mitral valve prolapse were rarely reported.

Conclusion: Fragile X syndrome is more than a pure neurodevelopmental disorder. Our findings highlight the importance of early diagnosis and subsequent management, with awareness of relevant surveillance and management guidelines.

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New knowledge added by this study

- The local diagnostic yield of fragile X syndrome in patients referred for developmental delay/intellectual disability is 0.8%. There is a temporal trend towards earlier diagnosis. This study explored the landscape of cascade screening and prenatal diagnosis in Hong Kong.
- We examined the co-morbidity profile of patients with a full mutation in the *FMR1* gene in Hong Kong. We observed a substantial number of co-morbidities beyond neurodevelopmental issues, requiring regular follow-up and surveillance.

Implications for clinical practice or policy

- There is a need for heightened awareness of disease-specific surveillance guidelines, which may be facilitated by the development of rare disease registries.
- Integration of structured surveillance protocols into routine care for patients with fragile X syndrome may improve early identification and management of co-morbidities, thereby enhancing long-term health outcomes.

Introduction

Fragile X syndrome (FXS; OMIM #300624), an X-linked dominant condition, is one of the most common inherited causes of intellectual disability (ID)[1-3] and autism spectrum disorder (ASD).[2-5] The prevalence of FXS is most widely regarded as 1 in 4000 for males and 1 in 8000 for females.[6-9] Fragile X syndrome is within the spectrum of *FMR1*-related

脆性X綜合症：香港華人群體的遺傳與臨床特徵分析

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引言：脆性X綜合症是導致遺傳性智力障礙的常見原因之一。就整體發展遲緩和智力障礙而言，脆性X綜合症檢測是第一線基因檢測的一部分。本回顧性研究旨在評估脆性X綜合症檢測的診斷效益及本港華人患者的臨床特徵。

方法：於1993至2022年間共有7291名患者因神經發展相關疾病（如發展遲緩、自閉症譜系障礙及智力障礙）被轉介至醫學遺傳科進行脆性X綜合症檢測。當中103位來自61個家庭的患者帶有FMR1基因全突變，包括59位先證者及44位家族成員。此研究分析了70位患有脆性X綜合症的華人患者的臨床特徵，包括生長、神經行為特徵及其他共病情況。

結果：脆性X綜合症檢測的診斷陽性率為0.8%。先證者的中位確診年齡為4.1歲，而近年的確診年齡有提早趨勢。在27個家庭中（44.2%），有多位成員帶有全突變。11%家庭曾進行產前診斷。所有男性患者均有發展遲緩，而女性則為45.0%；86.0%男性患有智力障礙，而只有30.0%女性患者受到影響。常見共病包括肥胖、自閉症譜系障礙、專注力不足／過度活躍症、癲癇、腸胃問題及睡眠障礙。斜視、脊柱側彎及二尖瓣脫垂等情況則較為少見。

結論：脆性X綜合症不僅是純粹的神經發展障礙。我們的研究結果帶出早期診斷與後續管理的重要性，並喚起對相關監測與治療指引的認知。

disorders,[10] caused by pathogenic variants in the *FMR1* (fragile X messenger ribonucleoprotein 1) gene (OMIM #309550) mapped to the chromosome Xq27.3 region, which encodes the fragile X mental retardation protein.

Fragile X syndrome is the first genetic disorder known to be caused by trinucleotide repeat expansions—specifically, cytosine-guanine-guanine (CGG) repeats in the 5' untranslated region of the *FMR1* gene. *FMR1* alleles are categorised as normal (<45), intermediate (45-54), premutation (PM, 55-200), and full mutation (FM, >200) based on repeat size. Premutation alleles are associated with elevated levels of FMR1 messenger ribonucleic acid,[10] leading to ribonucleic acid toxicity that can result in fragile X–associated tremor/ataxia syndrome, fragile X–associated primary ovarian insufficiency, or fragile X–associated neuropsychiatric disorders.[10] Conversely, FXS typically results from FM with promoter region hypermethylation and histone protein deacetylation,[11,12] causing transcriptional silencing.[13,14] Most individuals inherit the FM from their mothers, who are PM carriers. Stability upon maternal transmission depends on the size of the PM.[15]

Characteristic signs of FXS, including prominent ears, elongated face, protruding ears, and macroorchidism, tend to evolve with age.[1,4] Facial dysmorphism can vary depending on ethnic background,[4] and females exhibit greater clinical variability.[16,17] Most patients are not diagnosed until the age of 3 years.[18,19] Fragile X syndrome is also associated with multiple medical co-morbidities, such as recurrent otitis media, mitral valve prolapse, and connective tissue problems.[3]

Clinical presentation can be further complicated by either size mosaicism or methylation mosaicism.[20] Size mosaicism refers to cell populations with variably sized CGG repeats—typically the presence of PM or intermediate/normal alleles in addition to FMs. Methylation mosaicism involves both methylated and unmethylated cell populations at the *FMR1* locus. Mosaicism in males with FXS has been reported in 12% to 41% of cases.[21-23]

While the epidemiology of FXS has been extensively studied in Western populations,[6-9] the reported prevalence of FXS among Chinese patients with developmental delay or ID showed variability (ranging from 0.43% to 12.9%).[24,25] Furthermore, the prevalence of medical co-morbidities remains understudied in the Chinese population.

In this single-centre retrospective study, we aimed to: (1) review the clinical features of FXS patients referred to the Department of Clinical Genetics of the Hospital Authority (formerly the Clinical Genetic Service of the Department of Health); (2) evaluate parameters regarding growth, medical co-morbidities, and neurobehavioural features in the Hong Kong Chinese patient population with FXS; (3) assess the diagnostic yield of FXS testing in patients with unexplained developmental delay or ID; and (4) review the diagnostic journey of such patients.

Methods

Patient data

Neurodevelopmental delay, ID, or ASD are the main reasons for ordering FXS testing. Over the 30-year period from 1993 to 2022, 7291 patients referred for such neurodevelopmental conditions underwent FXS molecular testing after clinical genetic evaluation. Maternal testing and further cascade testing were considered upon diagnosis in index cases.

Patients with *FMR1* FMs were included in the initial analysis, and a retrospective chart review of printed and electronic records was performed. For analysis of clinical features among Chinese patients with FXS, individuals who self-identified as non-Chinese or had co-existing copy number variants or chromosomal structural abnormalities were excluded.

Molecular data

Genomic DNA was extracted from peripheral blood leucocytes using standardised methods, in

accordance with the manufacturer's instructions. Prior to 2014, polymerase chain reaction (PCR) followed by Southern blot analysis was used to identify individuals with FXS. This approach was subsequently replaced by conventional PCR that can detect $(CGG)_n$ alleles up to 90 repeats, followed by triplet-primed PCR and methylation-specific PCR using the AmplideX kit (Asuragen, Austin [TX], US), if necessary.

Statistical analysis

Baseline demographic characteristics were descriptively summarised. Continuous variables were reported as means and standard errors for normally distributed data, and as medians and ranges/interquartile ranges (IQRs) for non-parametrically distributed data. To assess the association between age at diagnosis and year of assessment, correlation analysis was performed using the Pearson correlation coefficient (*r*), with a statistical significance threshold of 5%. Prevalence proportions were used to evaluate categorical clinical characteristics. Comparisons between males and females were made using the Chi squared test or Fisher's exact test. Statistical analysis was performed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], US).

Results

Patient demographics

Overall, 103 individuals from 61 families were confirmed to have an FM in the *FMR1* gene. Index cases were defined as patients referred from their parent institution for their condition. Among the index cases, eight individuals came from four families, with two affected members referred separately in each family. In six other families, the consultand was an unaffected member referred due to a positive family history. Family screening identified 44 additional cases in 29 families, comprising 13 males (29.5%) and 31 females (70.5%) [Table 1].

Family history

Details of family history for 55 unrelated index cases and six consultands are presented in Table 2. Overall, 41 (67.2%) had a positive family history in one or more aspects.

Diagnosis

Of 7291 patients underwent testing, 59 index cases

TABLE 1. Baseline demographic characteristics (n=103)*

	Index cases (n=59)	Additional cases detected through family screening (n=44)	Overall (n=103)
Sex			
Male	53 (89.8%)	13 (29.5%)	66 (64.1%)
Female	6 (10.2%)	31 (70.5%)	37 (35.9%)
Ethnicity			
Chinese	57 (96.6%)	41 (93.2%)	98 (95.1%)
Non-Chinese	2 (3.4%)	3 (6.8%)	5 (4.9%)
Gestation	n=59	n=7	n=66
Full-term	51 (86.4%)	6 (85.7%)	57 (86.4%)
Preterm	8 (13.6%)	1 (14.3%)	9 (13.6%)
Mean birth weight, kg (95% CI) [n=64]	n=58 3.30 (3.16-3.43)	n=6 2.83 (2.46-3.19)	n=64 3.25 (3.12-3.38)
Current age, y (n=101)	17.45 (3.65-52.85)	38.67 (7.01-66.28)	25.02 (3.65-66.28)
Source of referral			
Paediatrics/psychiatry	34 (57.6%)	N/A	34 (33.0%)
Child assessment service	21 (35.6%)	N/A	21 (20.4%)
Family clinic/private	3 (5.1%)	N/A	3 (2.9%)
Family screening	1 (1.7%)	44 (100%)	45 (43.7%)
Age at referral, y (n=55)	2.83 (1.10-24.51)	N/A	2.83 (1.10-24.51)
Age at first genetic consultation, y (n=102)	3.71 (1.56-24.78)	23.00 (1.36-52.04)	5.87 (1.36-52.04)
Age at diagnosis, y	4.10 (1.72-26.95)	23.50 (1.17-52.36)	6.73 (1.17-52.36)

Abbreviations: 95% CI = 95% confidence interval; N/A = not applicable

* Data are shown as No. (%) or median (range), unless otherwise specified

TABLE 2. Family history (n=61)*

	Positive family history
Delay/intellectual disability/learning disability	36 (59.0%)
Autism spectrum disorder	11 (18.0%)
Attention-deficit/hyperactivity disorder	5 (8.2%)
Neurodevelopmental issues (combined)	40 (65.6%)
Premature ovarian failure	4 (6.6%)
Tremor/ataxia	3 (4.9%)

* Data are shown as No. (%)

TABLE 3. Age at diagnosis*

	1993-2007	2008-2022
Age at diagnosis among index cases, y	n=27 5.47 (3.59-7.87)	n=32 3.85 (3.00-4.83)
Age at diagnosis among all cases, y	n=57 11.55 (4.77-26.38)	n=46 4.49 (3.14-9.67)

* Data are shown as median (interquartile range)

TABLE 4. Mosaicism status*

	Male (n=66)	Female (n=37)
Size mosaicism	4 (6.1%)	3 (8.1%)
Methylation mosaicism	3 (4.5%)	N/A
Size/methylation mosaicism combined	7 (10.6%)	3 (8.1%)

Abbreviation: N/A = not applicable
* Data are shown as No. (%)

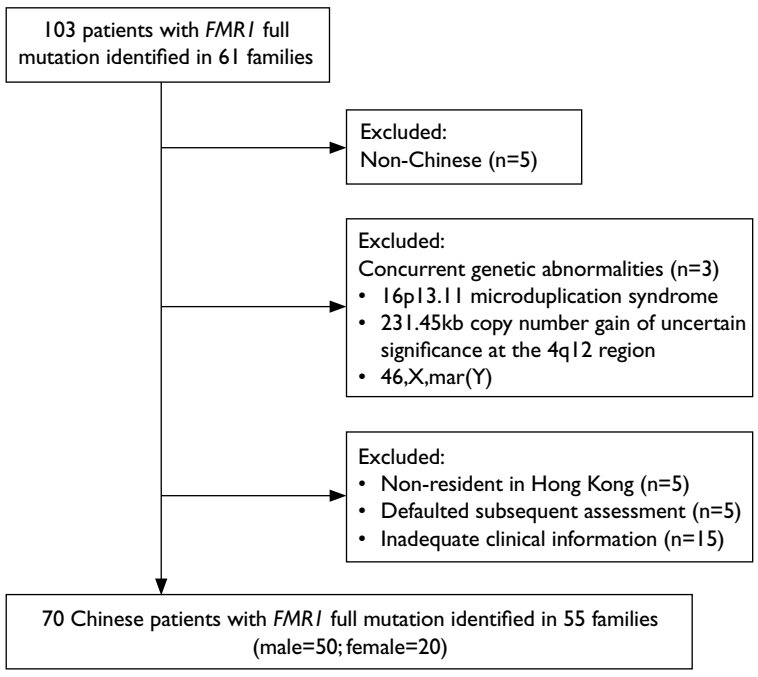

FIG. Patient selection for analysis

were identified, yielding an overall diagnostic rate of 0.8%. The sex-specific diagnostic yields were 1.0% for males and 0.3% for females. Additionally, one male and one female patient had PMs. There was an upward trend in the number of FXS tests performed (unpublished data). The median ages at diagnosis were 6.73 years (range, 1.17-52.36) among all FXS patients (including those identified through family screening) and 4.10 years (range, 1.72-26.95) when considering index cases alone. The median diagnostic lag time for index cases, defined as the time elapsed between referral and diagnosis, was 11.0 months (IQR=6.53-20.0, n=54).

The temporal trends in diagnosis are shown in Table 3. A weak negative correlation between age and assessment year was observed for all cases (r=-0.267, n=103; P=0.006). Regarding index cases, a moderate negative correlation was observed (r=-0.396, n=59; P=0.0019), suggesting a trend towards earlier diagnosis over time.

The mosaicism statuses of our patients are summarised in Table 4.

Family cascade testing

Among the 61 families, 54 underwent maternal testing—44 were PM carriers and 10 were FM carriers. Cascade testing was conducted in other family members in 45 families (73.8%). Twenty siblings were identified as affected individuals, and maternal second-/third-degree relatives constituted another 13 cases. In 27 families (44.2%), more than one FM carrier was identified—15 families (24.6%) had two affected members, nine (14.8%) had three affected members, and three (4.9%) had four affected members. Nonetheless, 16 families (26.2%) did not proceed with further cascade testing after maternal testing. Four families (6.6%) did not undergo any family testing at all.

Prenatal diagnosis was arranged for 11 families (18%), involving 10 PM carriers and two FM carriers. Two male fetuses were affected by FM, and these pregnancies were terminated. One FM carrier opted for termination of pregnancy at 10 weeks of gestation despite counselling regarding the availability of prenatal diagnosis.

Clinical features

Seventy Chinese patients with *FMR1* FM from 55 different families were included in the analysis of clinical features (Fig); details are summarised in Table 5.

The presence and severity of ID, co-morbid ASD, or attention-deficit/hyperactivity disorder were determined based on clinician reports. More than half of the male patients (54.0%) had ID of moderate or greater severity. None of the female patients had severe ID; three females had borderline intelligence not supporting a diagnosis of ID.

TABLE 5. Clinical features (n=70)

	Male (n=50)	Female (n=20)	Overall (n=70)	P value‡
Growth				
Obesity in childhood/adolescence (BMI >97th percentile for age and sex)	11 (22.0%)	3 (15.0%)	14 (20.0%)	0.74
Macrocephaly (head circumference >97th percentile for age and sex)	5 (10.0%)	1 (5.0%)	6 (8.6%)	0.65
Microcephaly (head circumference <3rd percentile for age and sex)	1 (2.0%)	1 (5.0%)	2 (2.9%)	1.0
Tall stature (body height >97th percentile for age and sex)	4 (8.0%)	0	4 (5.7%)	0.29
Short stature (body height <3rd percentile for age and sex)	3 (6.0%)	0	3 (4.3%)	0.54
Neurobehavioural features				
Developmental delay	50 (100%)	9 (45.0%)	59 (84.3%)	<0.001
Speech delay	50 (100%)	9 (45.0%)	59 (84.3%)	<0.001
Intellectual disability	43 (86.0%)	6 (30.0%)*	49 (70.0%)	0.71
Mild	10 (20.0%)	3 (15.0%)	13 (18.6%)	
Moderate	27 (54.0%)	3 (15.0%)	30 (42.9%)	
Severe	3 (6.0%)	0	3 (4.3%)	
Not specified	3 (6.0%)	0	3 (4.3%)	
Specific learning disability without intellectual disability	1 (2.0%)	5 (25.0%)	6 (8.6%)	0.0062
Autism spectrum disorder	31 (62.0%)	3 (15.0%)	34 (48.6%)	<0.001
Poor eye contact	34 (68.0%)	4 (20.0%)	38 (54.3%)	<0.001
Unusual gesture	20 (40.0%)	2 (10.0%)	22 (31.4%)	0.0212
Perseverative speech	19 (38.0%)	1 (5.0%)	20 (28.6%)	0.0071
Sensory integration issue	12 (24.0%)	3 (15.0%)	15 (21.4%)	0.53
Hand-biting	6 (12.0%)	1 (5.0%)	7 (10.0%)	0.66
ADHD	14 (28.0%)	1 (5.0%)	15 (21.4%)	0.051
Hyperactivity	30 (60.0%)	3 (15.0%)	33 (47.1%)	0.0011
Short attention span	20 (40.0%)	3 (15.0%)	23 (32.9%)	0.053
Epilepsy/seizure except febrile convulsion	11 (22.0%)	1 (5.0%)	12 (17.1%)	0.16
History of anti-convulsant use	9 (18.0%)	2 (10.0%)	11 (15.7%)	0.71
Motor tics	2 (4.0%)	1 (5.0%)	3 (4.3%)	1.0
Hypotonia	16 (32.0%)	4 (20.0%)	20 (28.6%)	0.39
Self-mutilation	12 (24.0%)	2 (10.0%)	14 (20.0%)	0.32
Aggression	21 (42.0%)	0	21 (30.0%)	0.0011
Anxiety	11 (22.0%)	3 (15.0%)	14 (20.0%)	0.74
Depression	2 (4.0%)	3 (15.0%)	5 (7.1%)	0.14
Co-morbidities				
Gastrointestinal problems†	15 (30.0%)	4 (20.0%)	19 (27.1%)	1.0
Sleeping problems	17 (34.0%)	5 (25.0%)	22 (31.4%)	0.57
Joint laxity	14 (28.0%)	3 (15.0%)	17 (24.3%)	0.36
Pes planus	9 (18.0%)	0	9 (12.9%)	0.052
Other congenital malformations	5 (10.0%)	0	5 (7.1%)	0.31
Strabismus/refractive errors	3 (6.0%)	1 (5.0%)	4 (5.7%)	1.0
Recurrent otitis media	3 (6.0%)	0	3 (4.3%)	0.55
Sinusitis	2 (4.0%)	0	2 (2.9%)	1.0
Scoliosis	1 (2.0%)	0	1 (1.4%)	1.0
Mitral valve prolapse	0	0	0	N/A
Joint dislocation	0	0	0	N/A

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; N/A = not applicable

* Three additional female patients (13.6%) had documented borderline intelligence

† Feeding difficulties, gastroesophageal reflux, constipation, and recurrent abdominal pain

‡ Calculated using Fisher's exact test (2×2 table) for categorical variables

Epilepsy was diagnosed in 12 patients (17.1%). One 10-year-old boy with refractory epilepsy had high-risk medulloblastoma and completed treatment at age 6 years. He developed spasm-like attacks and possible focal seizures at age 7 years. Among the remaining patients, eight had generalised seizures, two had a mixed semiology of generalised and focal seizures, and one patient had unclear seizure semiology. The age at seizure onset ranged from 2 to 19 years, with a median of 7.0 years (IQR=3.75-8.0). Three patients experienced convulsive status epilepticus triggered by infective episodes, one required intensive care unit admission.

Forty-three patients (61.4%) underwent neuroimaging (magnetic resonance imaging/computed tomography of the brain), and most results were unremarkable.

Eight patients (five males and three females) with mosaicism were eligible for analysis of clinical features after excluding individuals with inadequate data. These patients generally had less severe ID than non-mosaic patients, although proper comparison was hindered by the small sample size.

Gastrointestinal conditions and sleep problems were common co-morbidities, affecting 27.1% and 31.4% of patients, respectively. Seven patients underwent echocardiography at least once; two displayed transient aortic root dilatation. Congenital anomalies identified among our patients included Pierre Robin sequence, Klippel-Trenaunay syndrome, hemifacial asymmetry, microtia, and pigmentary mosaicism. These conditions were relatively rare in the literature.

Discussion

Clinical features

Approximately 20% of our patients developed obesity in childhood or adolescence, which aligns with the general childhood overweight/obesity prevalence in Hong Kong (~20%).[26] However, a US study[27] examining 848 families with at least one child had FXS showed that 31% of male and 15% of female children were obese. With respect to obesity alone, the frequency may be higher among our patients than in the general population, which may be attributed to physical inactivity in individuals with ID, as well as the use of psychiatric medications.

Five male patients (10.0%) and one female patient (5.0%) exhibited macrocephaly, and a few had suspected overgrowth syndrome upon referral. A subset of FXS patients has been reported to present with Sotos- or Prader-Willi–like phenotypes.[16] This feature may pose a diagnostic challenge.

In our study, the frequency of developmental delay and ID was consistent with findings in other populations. Female patients displayed milder phenotypes, which is compatible with the presentation of X-linked disorders. Additionally, 48.6% of patients had a clinician-reported diagnosis of ASD. The reported prevalence of co-morbid ASD in males with FXS varies widely across studies, from 30% to 60%.[3,28] The use of different instruments has been reported to cause diagnostic inconsistency; this is further complicated by the intrinsic difficulty in diagnosing ASD among individuals with ID. The frequencies of hyperactivity and attention-deficit/hyperactivity disorder in our study are similar to rates in the literature (50%-60% and 12%-23%, respectively),[29] but smaller percentages of our patients displayed inattention, anxiety problems, or depression compared to the literature (74%-84% for inattention, 58%-86% for anxiety problems, and 8%-12% for depression).[29] The lower rates of such conditions in our study may be due to diagnostic overshadowing. Active research is underway to identify more accurate diagnostic measures for neurobehavioural co-morbidities.[28]

Overall, 17.1% of our patients displayed epilepsy, with a predilection towards generalised seizures. This is in agreement with the work of Berry-Kravis et al,[30] who characterised seizures in the largest evaluated cohort of FXS patients, although earlier case series suggested that focal onset seizures with impaired awareness were the most common semiology.[30] Notably, three patients presented with convulsive status epilepticus, which is uncommon among FXS patients.

The presence of co-morbidities such as gastrointestinal problems, sleep disturbances, joint laxity, and pes planus was consistent with commonly observed clinical patterns in individuals with FXS. Nonetheless, only a small percentage of patients in our cohort showed strabismus or refractive errors, scoliosis, or recurrent otitis media; none exhibited joint dislocations or mitral valve prolapse (Table 5). The true prevalence of mitral valve prolapse remains unclear. Loehr et al[31] reported a prevalence as high as 55% in a series of FXS patients in 1986, whereas Kidd et al[3] reported a prevalence of 0.8%; some Asian studies[32,33] did not identify any individuals with mitral valve prolapse.

A systematic approach to health supervision for FXS has been recommended by the American Academy of Pediatrics[1,28] across developmental stages. To our knowledge, there are no established surveillance guidelines in Hong Kong. Ultimately, FXS is more than a purely neurodevelopmental disorder; it is important to be aware of potential multisystemic approach and provide health supervision as needed.

Diagnosis

Our diagnostic yield of 0.8% is consistent with a local study in 1999,[34] which showed a diagnostic yield of 0.6% among 324 patients with mild ID of unspecified cause, and with a study by Chen et al

(0.93%)[35] that evaluated the diagnostic yield of FXS testing in 553 unrelated patients with moderate to severe ID of unknown cause in Beijing in 2015. Nonetheless, our yield is slightly lower than those reported by Mei et al (2.4%)[32] and Zhong et al (2.8%),[36] which were derived from relatively large-scale studies conducted in Chinese populations. Our results also revealed a slightly lower diagnostic yield compared with that of Western literature, which is around 1.5% to 2%.[37] This may be explained by reported differences in the distribution of normal, PM, and FM alleles between Asian and non-Asian populations. Various studies have identified a lower prevalence of PM alleles in East Asians compared with Western populations. One study reported that the prevalence of PM and asymptomatic FM carriers in the Hong Kong Chinese pregnant population was 1 in 883,[38] whereas another study showed a prevalence of 1 in 1113 among unaffected Chinese individuals.[39] The reported prevalence of PM alleles in Western populations varies from 1 in 113 to 1 in 382, depending on ethnicity.[39] Intriguingly, most *FMR1* alleles contain 29 or 30 CGG repeats across different populations, including ours. Alternatively, the apparent difference in PM allele prevalence may be explained by the founder haplotype hypothesis, whereby various factors contribute to disparate rates of normal-to-PM transitions, including different AGG interruption patterns across populations.[40] Although preliminary studies have explored an association between neurodevelopmental difficulties and PM status, findings have been inconclusive. In our cohort, only two patients referred for developmental delay exhibited PM status.

Our study showed a weak but statistically significant trend towards an earlier age at diagnosis, which may be attributed to increased awareness of children's developmental needs and, consequently, an earlier age at referral. The median age at diagnosis was 4.1 years for index cases alone, and 6.73 years for all cases in our study. These values are comparable to international data where the average age at diagnosis ranges from 2.9 to 6.3 years.[18,33]

There has been debate regarding whether FXS testing should be utilised as a first-line investigation to evaluate developmental delay. However, it is a simple and inexpensive test with a short turnaround time. The availability of such a test is crucial because it aids in prompt diagnosis, facilitating further cascade testing and reproductive planning. In our study, 44.2% of families had more than one affected member. Ten female PM carriers and two FM carriers from 11 families (18%) underwent prenatal diagnosis; two pregnancies were terminated after identification of FXS status. A diagnosis in one family member may influence others' decisions regarding pregnancy and subsequently affect pregnancy outcomes. Fragile X PM carrier screening is recommended by organisations such as the American College of Obstetricians and Gynecologists[41] and the American College of Medical Genetics and Genomics[42] for women with a family history suggestive of fragile X–related disorders who are either considering pregnancy or currently pregnant. Although prenatal carrier testing is free for women of childbearing age in some countries, it is currently self-financed in Hong Kong and thus not widely implemented.

An expedited diagnosis can facilitate the timely implementation of medical interventions. For PM carriers who exhibit increased risks of fragile X–associated primary ovarian insufficiency and fragile X–associated tremor/ataxia syndrome, anticipatory guidance and timely referrals can be provided. Furthermore, multiple targeted therapeutic agents with the potential to reverse some neurobiological aspects of the disorder (eg, mavoglurant, metformin, cannabidiol transdermal gel, acamprosate, and lovastatin) are undergoing active evaluation. Should any of these candidates be approved in the future, early diagnosis would prove even more beneficial.

Strengths and limitations

To our knowledge, this is the largest cohort of Chinese FXS patients reported to date. Because most FXS testing was performed at our centre, potential disease prevalence can be inferred. Our study offers a longitudinal perspective regarding the disease course and highlights areas for improvement in health supervision and management. Furthermore, we examined the landscape of cascade screening and prenatal diagnosis in our specific cultural setting.

However, this was a retrospective study and thus largely dependent on clinician-reported findings. The diagnostic yield may have been influenced by the secular trend of an increasing number of referrals for developmental delay. Furthermore, it was difficult to implement standardised diagnostic instruments for certain co-morbidities. Some patients had inadequate information or were lost to follow-up in the public sector. Finally, the lack of a standardised surveillance protocol for FXS contributed to potential confirmation bias.

Conclusion

In our study, we explored the diagnostic yield of FXS testing, as well as cascade testing and prenatal diagnosis in families with FXS in Hong Kong. Our study provides insights into the clinical features and co-morbidities of FXS in the largest cohort of Chinese patients reported to date. There has been improved awareness of children's developmental needs, as demonstrated by a trend towards earlier diagnosis, but no local surveillance protocols exist for patients with FXS. The high prevalences of neurobehavioural and medical co-morbidities highlight the need

for prompt diagnosis and structured health management. We recommend increased awareness of the multisystemic approach and targeted treatments currently under investigation, and we propose establishing rare disease registries to facilitate this process.

Considering the clinical utility of FXS testing in clinical and reproductive management, we believe it should continue to be included in the evaluation of patients with developmental delay or ID; its role in the diagnostic pathway should be determined by local resources.

Author contributions

Concept or design: CWM Au, HM Luk, IFM Lo.
Acquisition of data: CWM Au, S Ho.
Analysis or interpretation of data: CWM Au.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This research was approved by the Central Institutional Review Board of Hospital Authority, Hong Kong (Ref No.: PAED-2023-061). A waiver of informed patient consent was obtained from the Board due to the retrospective nature of the research.

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