Review

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Phenotypic variability of Fragile-X syndrome in Asian population: A systematic review

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SUMMARY: Fragile X syndrome (FXS) is the most common genetic cause of inherited intellectual disabilities. Individuals with full mutation of FXS exhibit physical and behavioral symptoms in addition to other comorbidities. The clinical features of FXS have been widely studied in Caucasians; however, they remain limited in the Asian population. This study aimed to characterize the spectrum and variability of physical and behavioral phenotypes in Asian populations. A total of 5,830 studies from the PubMed, ScienceDirect, Scopus, and Cochrane/CENTRAL databases were screened using the Covidence software. We identified FXS-specific research studies conducted in Asia that reported the clinical characteristics of individuals with FXS. This review summarizes 51 studies from different Asian regions. The frequently reported physical characteristics were large and prominent ears (72.63%), an elongated face (57.49%), and macroorchidism (45.21%). The three most prevalent behavioral characteristics were intellectual disability (ID), hyperactivity, and social withdrawal, reported in 99%, 77%, and 55% of all cases, respectively. Our findings show that the physical characteristics of FXS are variable in the Asian group but similar to those in other populations and are not recommended for early recognition. Individuals with intellectual disabilities, especially when combined with autism spectrum disorders and large prominent ears, are suggestive of further genetic testing for FXS.

Keywords: Fragile X syndrome, intellectual disability, phenotype, behavior

1. Introduction

Fragile X syndrome (FXS) is the most common genetic cause of inherited intellectual disability (ID) (*1*). An increase in the CGG trinucleotide repeat of over 200 in the promoter region of the *Fragile X Messenger Ribonucleoprotein 1 (FMR1)* gene results in the FXS phenotype (*2*). A number of CGG repeats between 5 and 44 is considered a normal allele, 45 to 54 as an intermediate allele, 55 to 200 as a premutation (PM) allele, and over 200 repeats is called a full mutation allele (*3*). Individuals with the full mutation (FM) allele have *FMR1* gene methylation, which results in transcription inhibition and a subsequent lack of Fragile X Messenger Ribonucleoprotein (FMRP). FMRP is an essential protein that affects mRNA translation and is involved in synaptic plasticity (*4*). FMRP, an RNA-binding protein, controls the translation of approximately 4% of fetal brain mRNA (*5*).

Full mutation of the *FMR1* gene results in ID and phenotypic features in affected individuals, including a long face, large prominent ears, joint hypermobility, and macroorchidism (*6*). Other physical characteristics commonly described include a high-arched palate, strabismus, flat feet, and smooth skin. Additional health issues that may occur include gastrointestinal issues (such as gastric reflux, constipation, and loose bowel movements), neurological problems (such as hypotonia, motor incoordination, and seizures), cardiovascular abnormalities, obstructive sleep apnea, and abnormal growth patterns (such as macrocephaly and increased birth weight) (*7*).

Individuals with FXS also exhibit a broad spectrum of behavioral and psychological symptoms, in addition to physical symptoms and coincident medical conditions (*8*). There are variations in the behavioral symptoms that manifest in individuals with FXS (*9*). One of the most prevalent behavioral disorders seen in FXS is autism spectrum disorder (ASD). 30 to 50% individuals with FM FXS exhibit the full DSM-IV-TR criteria for autism,

while 60%-74% adhere to the classification for ASD (*10*). Other behavioral characteristics commonly found in FXS include impulsivity, tactile defensiveness, hand flapping, poor eye contact, gaze aversion, anxiety, hyperactivity, and deficiencies in social interaction (*11*).

Estimates of the global prevalence of FXS from a meta-analysis by Hunter *et al.* (2014) were 1:7,000 for males and 1:11,000 for females (*12*). The prevalence of FM FXS is estimated to be 1:5,000 males and 1:4,000–8,000 female individuals among the population in Europe and North America (*2*). A 20-year retrospective population study of over 2000 unrelated individuals with intellectual disabilities in South Africa revealed that FM among African participants was high (5.7%) (*13*). Some Asian countries, including China and Taiwan, are estimated to have a lower prevalence of individuals with FXS than Western countries (*14*). In Indonesia, the prevalence of FXS is 0.9-1.9% in the ID population and 6.15% in the ASD group (*15*). In Thailand, the frequency of FXS among Thai boys with developmental delays is approximately 7% (*16*). Meanwhile, the predicted prevalence of FXS individuals in Japan is 1 in 10,000, which is below the expected prevalence in Caucasian populations and among the subgroup of Mediterranean and Pakistani populations (1 in 4,000 males) (*17*).

Although the clinical features of FXS have been widely studied in Caucasians, information on Asians has not been frequently reported (*7*). A study of two healthcare systems in the USA consisting of 3.8 million people discovered that the estimated underdiagnosis rate of FXS ranged between 63.60–71.94%. Additionally, more than 80 percent of patients with FXS self-reported as white (Caucasian) (*18*). The disparity between the general population and clinical practice, as well as the homogeneous population, indicates the need to identify challenges in obtaining a diagnosis, especially in diverse populations.

The limited availability of genetic testing facilities and qualified professionals is one of the major challenges related to diagnostic techniques in South Asia (*19*). The clinical variability of FXS makes diagnosis challenging. FXS has a subtle physical phenotype, particularly at birth and during infancy. Most children with FXS are not diagnosed until they are around 3 years old (*20,21*).

Considering the importance of recognizing and potential variability in clinical characteristics of individuals with FXS, this study aimed to characterize the spectrum and variability of physical and behavioral phenotypes in Asian populations, thereby supporting recognition and diagnosis of FXS in resource-limited settings.

2. Literature search and study selection

2.1. Study selection process

This study was a systematic review of the physical and behavioral phenotypes of individuals with FXS. The reporting in this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Figure 1) (*22*). However, the review protocol was not preregistered in an international systematic review registry. Four literature databases (PubMed, ScienceDirect, Scopus, and Cochrane/CENTRAL) were systematically searched for relevant studies. The search consisted of main terms "fragile x syndrome", "physical", "behavior", and word variations. When available, both controlled (MeSH) terms and free-text words were used. The full search strategies are detailed in Supplementary Table S1 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=312*). The results were imported and de-duplicated using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org). The final database search was completed on April 2, 2025, yielding 5,830 studies.

We assessed the titles and abstracts prior to selecting papers for inclusion. The inclusion criteria included FXS-specific research studies that identified clinical characteristics of FXS. This study included populations originating from Asia. Initially, we ruled that only studies written in English would be included in the review. However, during the selection process, we identified crucial studies from Asian countries that were not published in English-language journals. After careful consideration, non-English articles were translated using DeepL and independently cross-checked by reviewers familiar with clinical terminology. Studies in the form of case reports, animal studies, and studies that did not emphasize the occurrence of FXS, as well as those that did not specify any physical or behavioral phenotypes, were excluded. Subsequently, studies that reported only premutation occurrences were excluded.

A total of 231 studies remained for full-text review. Our search covered the publication period between 1980-2025. Each article was screened by two reviewers (C.L.M.N. and J.T.), and any disagreements were resolved through discussion with a third reviewer (N.R.B.S., A.U., or T.I.W.). The same procedure was applied to screen full-text reviews.

2.2. Quality assessment

Reviewers assessed the methodological quality of each eligible study using standard criteria commonly applied to primary research in various fields. No established quality appraisal tool specifically addresses phenotype-focused observational studies of rare genetic disorders. Therefore, we adapted elements from the Kmet criteria and previous systematic reviews to develop a pragmatic six-item assessment tool that emphasizes diagnostic confirmation, participant selection, outcome validity, and methodological rigor (*23,24*).

A six-item assessment list in which points were given

to each criterion (high = 2, low = 1, unsure = 0) is shown in Table 1. The points given to each study were divided by the total score of 12 to obtain summary scores for each study, and the quality was classified as high (score > 80%), good (70–80%), adequate (50–70%), or limited (< 50%) (*23,25*). Studies with scores below 50% were excluded. The reviewers resolved disagreements through discussion. If an agreement could not be reached, a third reviewer resolved disagreements. The quality assessment step resulted in 55 included studies.

2.3. Data extraction

Four studies were excluded before data extraction. The reasons for exclusion were as follows: *i*) one study had female PM carriers as the study subjects; *ii*) two studies were part of an included study of a larger cohort; and *iii*) data from one study were deemed inadequate for extraction by the third reviewer. Potentially overlapping cohorts were identified by comparing the study location, recruitment period, investigators, and participant characteristics. In cases of suspected overlap, the study with the most comprehensive dataset was retained. We attempted to conduct a backward reference search and contacted the authors for data clarification. For instance, a backward search of a cohort report (*15*) led to additional data from six different original studies (*26-31*).

Data extraction was performed for the 51 included studies. The first reviewer extracted the data, and the second reviewer confirmed its accuracy. Data were extracted into standardized formats for the following entries: study title, country, research setting, number of

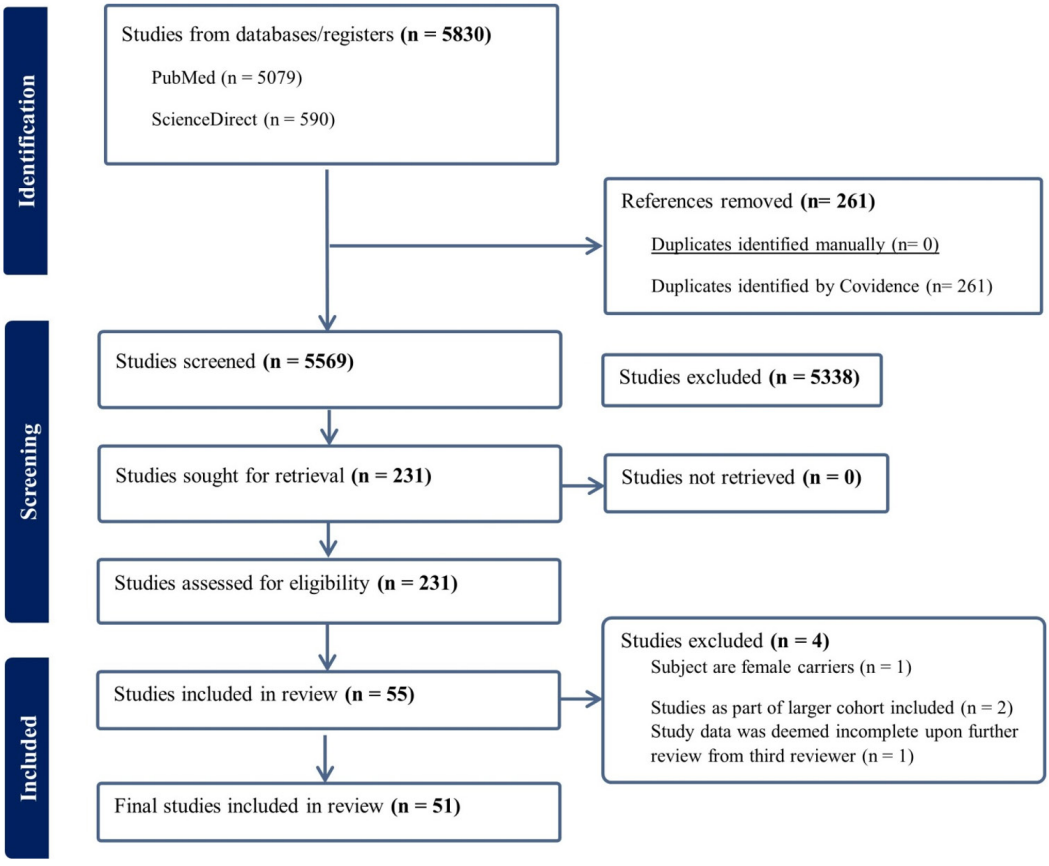

Figure 1. PRISMA flow diagram.

Table 1. Criteria for assessing the quality of the study included

Items	Answer
1. Molecular and cytogenetic diagnosis: Fragile site analysis, PCR, Southern blotting, TP-PCR	High/Low/Unsure
2. Was there a clear statement of the aims of the study?	High/Low/Unsure
3. Was the research design appropriate for addressing the aims of the research?	High/Low/Unsure
4. Was the data analysis sufficiently rigorous?	High/Low/Unsure
5. Patient selection (appropriate and clear inclusion/exclusion criteria)	High/Low/Unsure
6. Objectivity of outcomes/data validity: Physical and behavioral features are evaluated based on reliable references; being examined by experts	High/Low/Unsure

participants, number of individuals with FXS, sex, age, diagnostic testing, and outcomes, including physical and behavioral characteristics.

2.4. Data analysis and interpretation

Physical and behavioral characteristics were reported as percentages based on total number of participants in the included studies. Phenotypic prevalence was calculated using the number of individuals with whom a given characteristic was reported. Characteristics that were not explicitly assessed or reported were treated as missing rather than absent. Related or similar terms were combined into the most appropriate terms for the Fragile-X phenotype, such as the terms "intellectual disability" and "developmental delay" became "developmental delay/intellectual disability", due to a similar condition, only with a different age of diagnosis (*32*). Details of the combined terms are provided in Supplementary Table S2 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=312*).

Behavioral characteristics were categorized based on the Aberrant Behavior Checklist-Community (ABC-C) (*33*), which included five groups of behaviors: hyperactivity, lethargy/social withdrawal, inappropriate speech, irritability, and stereotypic behavior. Physical and behavioral phenotype classification was discussed and decided by a Fragile-X expert (TIW). Two terms, "facial dysmorphism" and "physical signs" were removed because the terms could not be specified.

3. Study and clinical characteristics reported in Asian population

3.1. Included study characteristics

This review summarizes 51 studies conducted between 1984 and 2023. These studies were acquired from different areas, which were classified according to their distinct regions in Asia, including East Asia (China, Hong Kong, Japan, South Korea, and Taiwan), Southeast Asia (Indonesia, Singapore, and Thailand), South Asia (India, Pakistan, and Sri Lanka), and Western Asia/ Middle East (Kuwait, Iran, Israel, Saudi Arabia, and Türkiye), as shown in Figure 2. The inclusion criterion for the methodological quality assessment was set at 50%. Included studies had quality ratings of strong in 44 studies, good in two studies, and adequate in five studies.

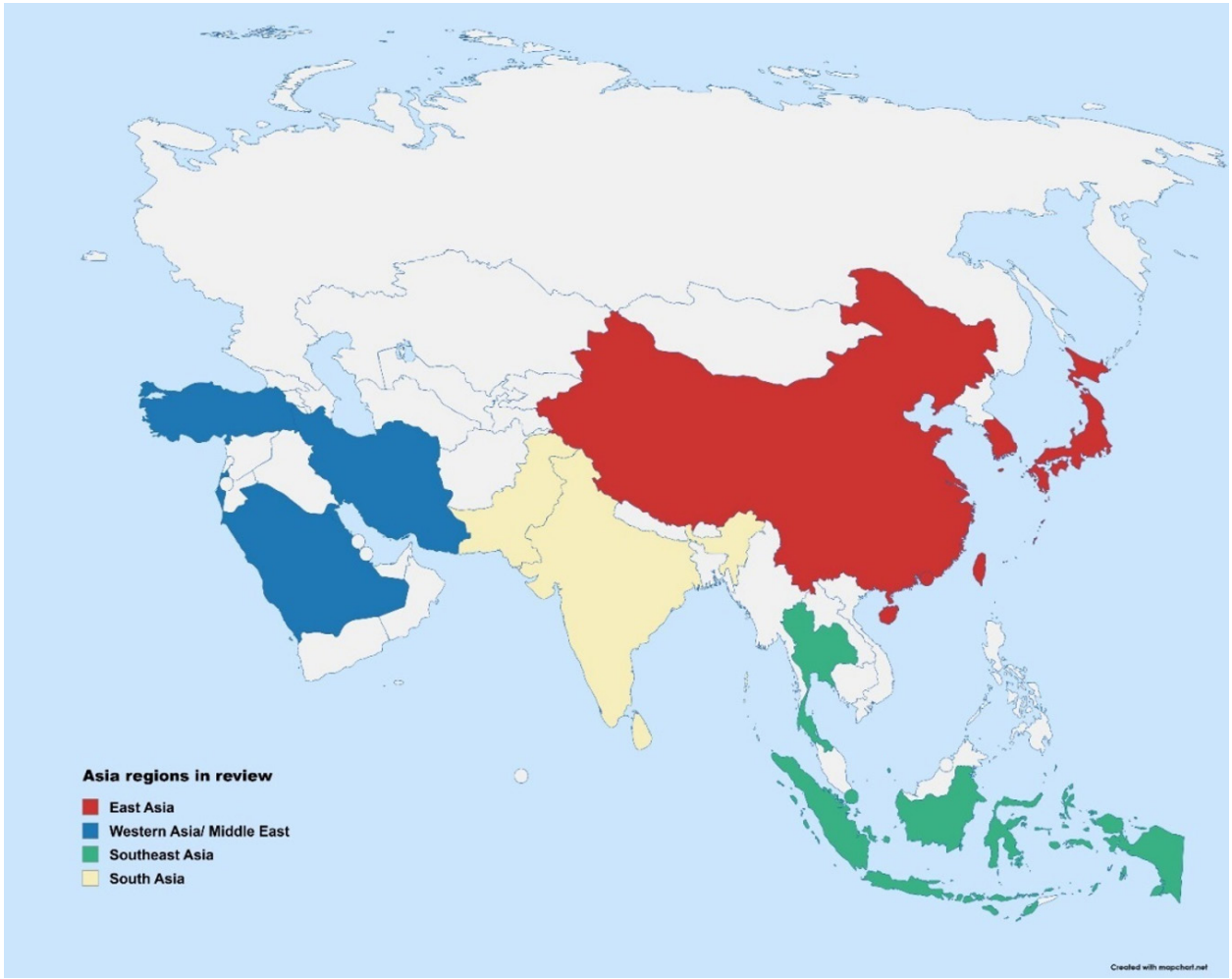

Figure 2. Included regions and countries in this review, showing 4 Asia regions and 16 countries.

The majority of the study population came from tertiary healthcare centers (70.6%), followed by those who underwent institutional screening (21.6%). Meanwhile, three studies combined both settings, and one study was based on province-wide population screening (*34*). Some studies described only a single characteristic, either a physical or behavioral trait. Details of included studies are shown in Table 2 (*7,15,34-82*).

3.2. Demographic and overall characteristics

Of the 24,173 participants identified across all included studies, 1,097 were diagnosed with FXS (4.54%). All diagnosed individuals were assessed for behavioral characteristics. Since not all studies described the individual's sex, the known numbers of male and female individuals with FXS were 700 and 87, respectively. 24 of the 51 articles mentioned the age of diagnosis/detection, with the majority (n = 15) diagnosed in childhood. Irrespective of physical or behavioral characteristics, the most observed feature was developmental delay/intellectual disability (98.04%). Some characteristics were reported infrequently (less than 1%). Table 3 highlights main findings of the included studies.

3.3. Physical characteristics

Physical features were described in 34 of the 51 articles (66.67%; Table 4). A total of 403 individuals were counted for physical characteristics, of which 380 were male, and 23 were female. The three most prevalent physical characteristics were large and prominent ears (72.63%), elongated face (57.49%), hyperextensible metacarpophalangeal (MCP) joint (48.06%), and macroorchidism (45.21%). Other features, such as a broad forehead, prognathism, and a high-arched palate, were reported less frequently. The "eye and periorbital problems" group included long palpebral fissure, strabismus, periorbital puffiness, hypertelorism, and other ophthalmological findings (see Supplementary Table S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=312*).

3.4. Behavioral characteristics

All studies described at least one behavioral characteristic (Table 5). Intellectual disability (ID) was reported in 98.04% of all cases, the most prevalent finding in FXS, followed by hyperactivity (77.61%) and lethargy/social withdrawal (55.37%). ADHD became a distinct list, which included terms such as "attention deficit", "unspecified ADHD", "inattentive", "hyperactive-impulsive", and "combined ADHD", and was described in 12 studies, yielding a prevalence of 54.32%. There were 19 studies exploring autism spectrum disorders, with a prevalence of 38.00%.

3.5. Associated medical findings

Some reported comorbidities included sleep problems (26.87%), which were reported in 11 studies, and epilepsy/seizures (21.18%), which were described in three studies. Meanwhile, a few reports mentioned gastrointestinal problems (*48,65*), connective tissue disorders (*15*), and other conditions with few individuals (only reported in one or two patients), such as schizophrenia (*47*), tetralogy of Fallot, Sotos syndrome-like, medulloblastoma, hypothyroidism, conductive hearing loss, precocious puberty, primary amenorrhea, and rectal cancer in one study (*7*).

4. Phenotypic variability and clinical implications

4.1. Comparison to non-Asian population

This review revealed that DD/ID and behavioral abnormalities (*i.e.*, hyperactivity and lethargy/social withdrawal) as the main features of FXS described across all studies. Meanwhile, physical characteristics were reported more heterogeneously. The most commonly described physical feature was large prominent ears, and the other features were reported in less than half of the studies. We compared our findings with those of other populations, such as the Caucasian/North American cohort of Lachiewicz *et al.* (*83*) and Brazilian/South American populations from Romero's study (*84*). Figure 3 shows a comparison heatmap between the three populations.

Large prominent ears and an elongated face were the most commonly identified craniofacial characteristics, with different findings. Across the three populations, large prominent ears were reported consistently, suggesting this feature as a global physical finding in individuals with FXS. Meanwhile, an elongated face was significantly more prevalent in the Caucasian cohort than in the Asian and Brazilian cohorts. A broad forehead was less commonly found in the Asian population. Other physical features commonly described were hyperextensible joints and flat feet. Notably, all Caucasian patients presented with hyperextensible joints, compared with approximately half of the Asian and Brazilian populations. The physical phenotype of children with FXS evolves with age and becomes comparable to the classic phenotype in the final stage of adolescence (*85*). Heulens *et al.* (2013) confirmed that typical facial characteristics of FXS include a long, narrow face and prominent ears. The remarkably narrow midface may explain the apparent prominence of the ears. A long face develops earlier than previously assumed and becomes increasingly apparent with age (*86*). Various findings on craniofacial features suggest that reliance on facial dysmorphology alone is insufficient for clinical

Table 2. Included studies in this review

Author, Year (*Ref.*)	Country	Quality assessment results (%)	Research settings	No. of FXS Individuals	No. of FXS Male	No. of FXS Female	Age of diagnosis
Alanay, 2007 (*35*)	Turkey	91.67	Tertiary healthcare service	24	24	0	2-17 y (mean 8.5 y)
Anvari, 2022 (*36*)	Iran	100.00	Tertiary healthcare service	12	9	3	25–80 y
Aoi, 1989 (*37*)	Japan	91.67	Institutional screening	1	1	0	43 y
Arinami, 1986 (*38*)	Japan	91.67	Institutional screening	13	13	0	19–69 y (38 y)
Arinami, 1987 (*39*)	Japan	91.67	Institutional screening	2	0	2	31 and 33 y
Bastaki, 2004 (*40*)	Kuwait	100.00	Tertiary healthcare service	20	20	0	NA
Chandrasekara, 2017 (*41*)	Sri Lanka	100.00	Institutional screening	11	11	0	5–18 y (mean 10.4 y)
Charalsawadi, 2017 (*7*)	Thailand	100.00	Tertiary healthcare service	56	56	0	2–16 y
Chaudhary, 2014 (*42*)	Saudi Arabia	91.67	Tertiary healthcare service	9	9	0	3–27 y
Chen, 2015 (*43*)	China	100.00	Tertiary healthcare service	5	5	0	NA
Dean, 2019 (*44*)	India	100.00	Tertiary healthcare service	18	18	0	1–26 y (mean 9.6 y)
Demirhan, 2003 (*45*)	Turkey	100.00	Tertiary healthcare service	14	9	5	6 m–12 y
Fazeli, 2022 (*46*)	Iran	83.33	Tertiary healthcare service	2	0	2	NA
Gabis, 2011 (*47*)	Israel	83.33	Tertiary healthcare service	28	23	5	Mean 14.2 y
Gabis, 2018 (*48*)	Israel	83.33	Tertiary healthcare service	117	92	25	2–52 y (mean 17 y)
Gu, 2006 (*49*)	China	91.67	Tertiary healthcare service	5	5	0	18–60 y
Guruju, 2009 (*50*)	India	91.67	Institutional screening	25	25	0	Female (>16 y; *n* = 4); Male (> 16 y; *n* = 17; 12–17 y; *n* = 3; < 12 y; *n* = 5)
Hong, 1999 (*51*)	South Korea	91.67	Tertiary healthcare service	5	5	0	Mean 3.8 y
Horiguchi, 2003 (*52*)	Japan	58.33	Institutional screening	56	NA	NA	NA
Horiguchi, 2005 (*53*)	Japan	58.33	Tertiary healthcare service	9	9	0	< 3 y (*n* = 3); 4–6 y (*n* = 3); > 20 y (*n* = 3)
Hou, 1998 (*54*)	Taiwan	100.00	Combined (both tertiary healthcare center and institutional screening)	233	NA	NA	NA
Hou, 2023 (*55*)	China	100.00	Tertiary healthcare service	3	3	0	2–62 y
Iqbal, 2000 (*56*)	Saudi Arabia	66.67	Tertiary healthcare service	26	24	2	NA
Jain, 1998 (*57*)	India	83.33	Tertiary healthcare service	29	29	0	3–28 y (mean 10.28 y)
Kabakus, 2006 (*58*)	Turkey	100.00	Tertiary healthcare service	8	8	0	5–18 y (mean 8.8 y)
Kanwal, 2015 (*59*)	Pakistan	100.00	Combined (both tertiary healthcare center and institutional screening)	13	10	3	NA
Ke, 2005 (*60*)	Taiwan	91.67	Tertiary healthcare service	12	10	2	2–7 y (mean 4.3 y)
Limprasert, 2000 (*61*)	Thailand	91.67	Tertiary healthcare service	27	27	0	8 m–13.6 y (mean 7.9 y)

Note: m = month(s); NA = not available; y = year(s).

Table 2. Included studies in this review (continued)

Author, Year (*Ref.*)	Country	Quality assessment results (%)	Research settings	No. of FXS Individuals	No. of FXS Male	No. of FXS Female	Age of diagnosis
Luo, 2009 (*62*)	China	83.33	Tertiary healthcare service	4	4	0	NA
Madokoro, 1989 (*63*)	Japan	75.00	Combined (both tertiary healthcare center and institutional screening)	2	2	0	31 m, 7 y
Matsuishi, 1987 (*64*)	Japan	83.33	Tertiary healthcare service	2	2	0	2.5 y, 3.5 y
Mei, 2023 (*65*)	China	100.00	Tertiary healthcare service	42	39	3	1 y 9 m–13 y 6 m
Moon, 1993 (*66*)	South Korea	100.00	Tertiary healthcare service	10	10	0	2–10.2 y
Nagarathinam, 2021 (*67*)	India	91.67	Tertiary healthcare service	3	3	0	22 y, 15 y, 11 y
Nanba, 1995 (*68*)	Japan	91.67	Tertiary healthcare service	2	2	0	6 m–49 y (mean 10.7 y)
Okazaki, 2021 (*69*)	Japan	91.67	Tertiary healthcare service	7	7	0	6–20 y
Pandey, 2002 (*70*)	India	100.00	Tertiary healthcare service	3	3	0	16 y, 18 y, 27 y
Ruangdaraganon, 2000 (*71*)	Thailand	91.67	Tertiary healthcare service	9	9	0	NA
Saha, 2001 (*72*)	India	100.00	Institutional screening	7	6	1	16–18 y
Seki, 1994 (*73*)	Japan	58.33	Tertiary healthcare service	3	3	0	NA
Sharma, 2003 (*74*)	India	58.33	Institutional screening	65	57	8	2–51 y
Shen, 1997 (*34*)	China	1997.00	Regional screening	7	4	3	NA
Sihombing, 2021 (*15*)	Indonesia	100.00	Institutional screening	43 (22 for physical characteristics)	17*	5*	3–25
Tan, 2000 (*75*)	Singapore	100.00	Institutional screening	6	6	0	5.6–15.5 y (mean 10.5 y)
Tirosh, 1992 (*76*)	Israel	100.00	Tertiary healthcare service	7	7	0	6–21 y (mean 10 y)
Tuncbilek, 1999 (*77*)	Turkey	100.00	Tertiary healthcare service	5	5	0	2–13 y (mean 7.5 y)
Verma, 1994 (*78*)	India	100.00	Tertiary healthcare service	20	20	0	< 10 y (n = 13); > 10 y (n = 7)
Winarni, 2022 (*79*)	Indonesia	100.00	Institutional screening	49	32	17	Mean: 32.9 ± 14.62 y (M); 33.4 ± 13.98 y (F)
Wong, 1992 (*80*)	Hong Kong	100.00	Tertiary healthcare service	2	2	0	NA
Xu, 1984 (*81*)	China	83.33	Tertiary healthcare service	3	3	0	NA
Zhang, 2022 (*82*)	China	91.67	Tertiary healthcare service	13	12	1	age of FXS positive mostly 6-18 y (53.8%; n = 7); followed by 1-6 y (46.2%; n = 6)

Note: m = month(s); NA = not available; y = year(s).

recognition of FXS, particularly in younger children and Asian populations. However, the presence of large, prominent ears alongside other hallmarks of FXS may prompt initial suspicion for further evaluation.

Males with FXS often present with macroorchidism, which is also associated with age (*87*). Macroorchidism becomes more prominent after puberty, and as a result, it is underdiagnosed in younger or prepubertal individuals and might not be found in early screening. In our study, this feature was identified only in 45.21% of males,

Table 3. Most commonly described characteristics across all included studies

Characteristics	No. of individuals	Prevalence (%)
Physical characteristics*		
Large, prominent ears	284/391	72.63%
Elongated face	188/327	57.49%
Hyperextensible metacarpo-phalangeal joint	124/258	48.06%
Broad and/or prominent forehead	80/161	49.69%
Macroorchidism	137/303	45.21%
Flat feet	33/148	22.30%
Behavioral Characteristics**		
DD/ID	1,050/1,071	98.04%
Hyperactivity	312/402	77.61%
Lethargy/social withdrawal	227/410	55.37%
ADHD	88/162	54.32%
Inappropriate speech	105/197	53.30%
Other medical conditions		
Sleep problems	18/67	26.87%
Epilepsy/seizure	36/170	21.18%

*from 403 individuals with described physical features. **from 1,097 individuals with described behavioral features.

Table 4. Physical characteristics

Physical Characteristics*	No. of individuals	Prevalence	No. of studies describing the features
Large, prominent ears	284/391	72.63%	30/51
Elongated face	188/327	57.49%	22/51
Macroorchidism	137/303	45.21%	21/51
Hyperextensible metacarpo-phalangeal joint	124/258	48.06%	12/51
Large Hands and Feet (including macrocephaly, increased growth)	65/110	59.09%	10/51
Broad and/or prominent forehead	80/161	49.69%	9/51
Prognathism	79/122	64.75%	9/51
High arched/cleft palate	51/145	35.17%	8/51
Eye and periorbital problems	44/139	31.65%	7/51
Flat feet	33/148	22.30%	6/51
Single transverse palmar crease	16/65	24.62%	5/51
Slender/tall stature	36/52	69.23%	3/51
Short stature	15/15	100.00%	2/51
Hypotonia	4/30	13.33%	2/51
Dry skin	15/20	75.00%	1/51
Prader-Willi like symptoms	4/29	13.79%	1/51
Low set ears	7/20	35.00%	1/51
Gynecomastia	5/20	25.00%	1/51

*from 403 individuals with described physical features.

Table 5. Behavioral characteristics and other medical conditions

Characteristics	No. of individuals	Prevalence	No. of studies describing the features
Behavioral characteristics*			
Developmental delay/intellectual disability	1,050/1,071	98.04%	48/51
Hyperactivity	312/402	77.61%	24/51
Lethargy/social withdrawal	227/410	55.37%	23/51
Autism spectrum disorders	95/250	38.00%	19/51
ADHD (attention deficit, unspecified, inattentive, hyperactive-impulsive, combined)	88/162	54.32%	12/51
Irritability	99/209	47.37%	12/51
Stereotypic behavior	93/226	41.15%	12/51
Inappropriate speech	105/197	53.30%	11/51
Depression or anxiety (including specific phobia, grimace & giggling, post-traumatic stress disorder)	26/53	49.06%	4/51
Other medical conditions			
Sleep problems	18/67	26.87%	11/51
Epilepsy/seizure	36/170	21.18%	3/51

*from 1,097 individuals with described behavioral features.

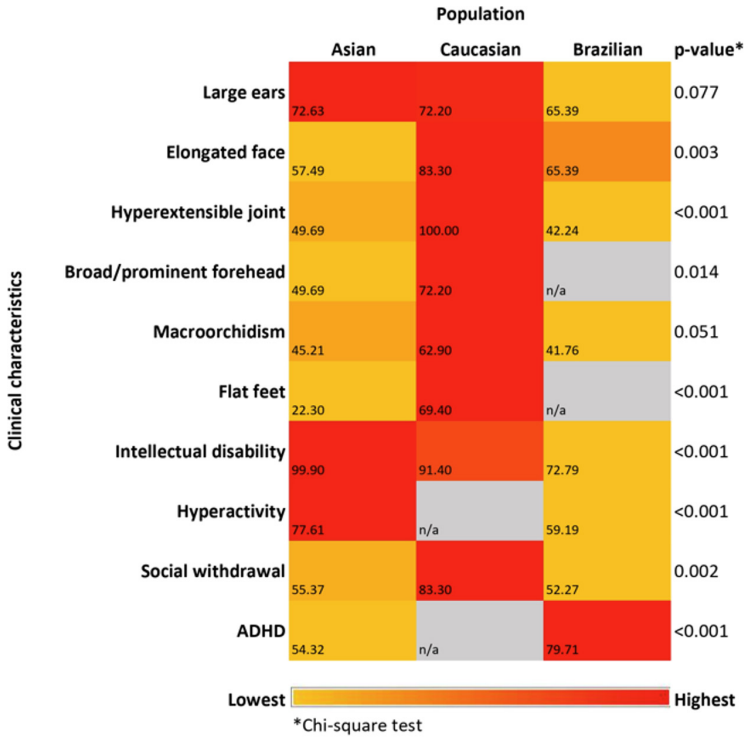

Figure 3. Heatmap comparison of the main clinical characteristics of FXS individuals between the Asian, Caucasian, and Brazilian populations.

which is less than that observed in the Caucasian cohort and another study by Merenstein *et al*., which revealed more than 80% in the post-pubertal group of FXS males (*88*). This proportion may not represent the true number, since this study did not specify male individuals who have reached puberty.

Almost all FXS cases had ID/DD in our study, which was comparable to the Caucasian cohort and more commonly reported than in the Brazilian population. Most studies included in this review applied the Hagerman checklist when examining FXS clinical features. Notably, a review by Hagerman *et al.* stated that physicians generally rely on behavioral characteristics to recognize FXS (*89*). This finding suggests that the Asian dataset found more severe clinical features on the checklist or that milder cases are less frequently referred for genetic evaluation.

In this study, hyperactivity was more frequently reported as a distinctive behavioral phenotype in the Asian population with FXS, than in the Brazilian population. Conversely, attention deficit was more prevalent in the Brazilian cohort. These two features are often termed ADHD; however, in both populations, hyperactivity and attention deficit (ADHD) were described distinctly. A previous study showed that hyperactivity and attention problems are frequent behavioral signs of FXS (*90*). Based on the ABC-C criteria, hyperactivity and social withdrawal were the most common groups of behavioral characteristics in our study, followed by inappropriate speech, irritability, and stereotypic behavior. Our study revealed that 38% of individuals with ASD were Asian, comparable to the known prevalence of FXS with ASD from a study in the Caucasian population (*91*). Approximately 60% to 90% of people with FXS exhibit symptoms related to autism, including avoidant eye gazing, hand flapping, repetitive activities, and verbal perseverations (*92*). Hatton *et al.* showed that autistic behavior in children with FXS develops slowly but significantly and periodically (*93*), while Hernandez *et al*. reported that it remained consistent (*94*).

4.2. Factors associated with the variability in clinical characteristics

4.2.1. Genetic factors

Various studies have been conducted to determine the genetic factors, specifically the correlation between protein levels and patient phenotypic characteristics. Insufficient or low levels of FMRP are essential in the pathogenesis of FXS (*95*). Size and methylation mosaicism are common in FXS. A previous study found that 82% of FXS, especially in males, carry mosaic FM/PM alleles (*96*). Some individuals have both "size" and "methylation" mosaicism, where some cells carry methylated alleles and others carry unmethylated alleles (with a CGG repeat number that spans from the premutation to full mutation range). Unmethylated alleles can be transcriptionally involved and overexpressed,

possibly leading to the production of FMRP (*97*). Therefore, patients with FXS in the mosaic may exhibit a milder phenotype (*98*). These mechanisms show that the resulting neurodevelopmental features are present globally across all ethnicities (*7*).

4.2.2. Variability in females with FXS

The phenotypic features of FXS are determined by biological sex and exhibit incomplete penetrance and variable expressivity (*95*). Consequently, females with FXS are often underdiagnosed. Our data consisted of 16 (31.38%) studies with female participants, half of whom reported physical characteristics. Some observed shyness and social withdrawal/lethargy in their studies (*39,79*), while another study reported hyperactivity in females with FXS (*45*). This finding shows a remarkable underrepresentation of females with FXS. This might be due to the fact that females with the full mutation also show the physical and behavioral characteristics the same as males with FXS, but with less severity. The clinical presentation of X-linked neurodevelopmental disorder genes in females is influenced by various factors, including the gene's escape from X Chromosome Inactivation (XCI) or skewing, variation type, and inheritance pattern (*99*). A preliminary cohort study in females with FXS showed that the overall cognitive profile was within the borderline or low-average range, and the cognitive score, specifically nonverbal abilities, correlated with overall adaptive behavior (*100*).

4.2.3. Variation in age and developmental trajectories

The age at diagnosis is a critical factor in identifying clinical characteristics of FXS (*82*). Our cohort consisted of patients of various age ranges, the youngest being 6 months (*45*) and oldest 51 years (*74*). When reporting phenotypes, some studies might observe more features than others, as seen in the various degrees of clinical feature descriptions. For example, macroorchidism was only described in less than half of all studies, although all studies described male patients. Similarly, hyperactivity, as one of the hallmarks of behavioral features in FXS, was reported in approximately half of the cohort data. Both features are associated with age, sex, and life course. A study showed that males exhibit hyperactivity more frequently than females, and irritability, stereotypic behavior, and hyperactivity were mildly improved in FXS males and females, lethargy slightly increased in males, and inappropriate speech remained consistent in males (*79*). According to a study by Bailey, Jr *et al.* (2009), the average age of FXS diagnosis was 35–37 months for boys and 41.6 months for females in the US (*101*). In Australia, the mean age of FM FXS searching for a diagnosis was 4.3 years (males) and 9.4 years (females) (*102*). Because early physical signs of FXS are often subtle, clinicians should consider genetic testing for any children aged two to three presenting with ID/DD or speech delay (*89*).

4.2.4. Social factor and healthcare accessibility

Aside from biological factors, home environment factors were revealed to contribute to the general cognitive outcomes, specifically to language and attention capability in females with FXS (*103*). Environmental variables significantly influenced the autistic behavior. Variations in the environment, such as family, home, and educational settings, may improve or worsen behavioral and psychiatric issues associated with FXS, in addition to FMRP impacts (*104*).

Research indicates that families with FXS tend to be more positive, with fewer instances of behavioral problems in children and adults and less criticism (*105*). In boys with FXS, the quality of the family environment predicted adaptive behavior. Families with a boy with FXS are more inclined to improve the environment with appropriate stimuli and implement early treatments to adjust their home life to their needs (*106*). Although genetic factors may have played a role, the initial phenotypic involvement of FXS and subsequent improvement followed by combination therapy is noteworthy in young children with FXS. Early therapy for FXS can result in significant improvements (*107*).

4.2.5. Diagnostic pathway and differences in study settings

The variations between our cohorts need to be contextualized within the accessibility of healthcare services and the diagnostic approach. A definitive diagnosis may be delayed in young children due to the lack of a distinct phenotype, which can cause families to undergo a diagnostic odyssey and defer application of particular treatments (*43*). Our cohort revealed differences in the diagnostic pathway, ranging from screening for intellectually disabled individuals in institutions to studies from referral genetic centers. Social determinants of health, such as referral infrastructure, insurance coverage, and availability of social support, influence the diagnostic odyssey in individuals with DD/ID. In regions with limited resources, unavailability of first-tier genetic testing resulted in only that individuals with more pronounced clinical features would be reported (*108*). Even in the United States, up to 40% of families with females affected by FXS and 25% of those with affected males had another child before the first child received a diagnosis (*101*). Furthermore, significant variations in behavioral features were observed, such as the high prevalence of hyperactivity in our cohort compared to the Brazilian cohort, which may reflect provider-level diagnostic biases or differing center's capacities for comprehensive evaluation, rather than true biological factors (*109*).

We also explored the diagnostic testing methods used for the detection of FXS. Nevertheless, not all studies explained how the full mutation alleles were detected or the size of CGG repeats. Chromosomal analysis was utilized in some studies to diagnose FXS, especially in earlier publications. Historically, the molecular diagnosis of FXS relied on a combination of PCR and Southern blotting analysis to characterize full mutations (*110*). Triplet-primed PCR combined with high-resolution melting (HRM) and capillary electrophoresis analysis has become an alternative to the gold standard (*111*). More recently, long-read sequencing and optical genome mapping (OGM) have been introduced for molecular diagnosis of FXS (*98*). The availability of straightforward and precise testing will significantly improve diagnosis and management of individuals and families with FXS.

4.3. Study limitations

Common limitations acknowledged across the included studies were the diverse study populations and incomplete outcome data on clinical characteristics. A modified quality assessment tool may introduce the potential for subjective assessment and reduced reproducibility. The classification of each reported feature based on its associated traits is challenging because of the significant heterogeneity among studies. During data extraction, we realized a lack of systematic phenotypic assessment; thus, the prevalence estimates for behavioral features may be affected by reporting bias. To address these limitations, we listed all the phenotypes from the included studies and applied the appropriate denominator for each feature to provide a comprehensive overview of the Asian population.

We compared our cohort with the Caucasian/North American and Brazilian/South American populations to explore possible variations in FXS phenotypes. The primary limitation of this analysis is the difference in cohort sizes, particularly in the Caucasian cohort. The relatively small size of the Caucasian cohort limits the statistical power to explore subtle phenotypic differences and increases risk of errors. Furthermore, the prevalence of hyperextensible joints in the Caucasian study must be interpreted cautiously due to possible selection bias. Future studies with more balanced sampling might be beneficial to validate clinical feature variations between populations.

5. Conclusion and future directions

The challenges in the early clinical assessment of FXS are strongly correlated with age at diagnosis. The distinctive behavioral and physical characteristics of FXS typically appear gradually and become prominent as development progresses, especially in late childhood and adolescence, enhancing clinical recognition. However, delayed clinical detection poses an important issue, as it can limit the possibility of early intervention. Early initiation of treatment increases likelihood of behavioral improvement in children with FXS. Some studies have explored the clinical suspicion framework for individuals with ID/DD in various global settings, all emphasizing need for FXS testing in (particularly) males with ID/DD, with presence of family history and clinical history related to FXS (*112-114*). The differences lie in the level of diagnostic testing, with more recent studies suggesting FXS testing as a second-tier test due to its low diagnostic yield (*114*). Our study in an Asian cohort suggests that clinicians may continue to work cautiously towards familial ID/DD with ASD and mild, age-related phenotypes (*i.e.*, large ears and elongated face, macroorchidism, hyperactivity, and social withdrawal).

Future research should prioritize a shift from ID-based detection to earlier, developmentally focused screening, particularly in children with unexplained developmental delays, autism, or ADHD. Age- and sex-stratified analyses are essential for clarifying developmental trajectories and better characterizing female phenotypes, which remain underrepresented. We emphasize that understanding clinical characteristics is critical for healthcare providers and individuals who may encounter these findings while suspecting an FXS diagnosis. Clinicians should be aware that individuals with FXS are prone to a variety of medical issues, not just typical disorders such as ID, ADHD, and ASD (*4*). Furthermore, increasing parental and caregiver knowledge of the clinical hallmarks of FXS starting in newborns may allow for earlier identification of possible consequences. This is especially important for children who exhibit developmental delays that fall outside the expected milestones. Several regions have limited access to advanced testing services, typically due to affordability and access constraints. In such cases, molecular testing may be more effective and efficient when prioritized for patients with indicative clinical symptoms.

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