

Fragile X Syndrome in China

Ranhui Duan, PhD;^{1*} Kathryn Garber, PhD;² Peng Jin, PhD^{2*}

¹State Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan, China

²Department of Human Genetics, Emory University School of Medicine, Atlanta, GA

Fragile X syndrome (FXS) is the most common form of inherited intellectual disability (ID), and the leading monogenic cause of autism spectrum disorders. The FXS cases in China were first reported in 1984, and effort has been made to improve the wellbeing of FXS patients. However, the general Chinese population is unfamiliar with FXS due to the limited public education. Even among those with medical training, there is a lack of awareness. Here our review aims to provide basic information on FXS, introduce the clinical aspects of FXS in China, and outline future research and policy recommendations that may in the future improve FXS genetic testing and counselor training in the Chinese health system.

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INTRODUCTION

Fragile X syndrome (FXS) (MIM#300624) is the most common cause of inherited intellectual disability (ID) and the leading monogenic cause of autism spectrum disorders.¹ Most males with FXS have moderate to severe intellectual disability, post-pubertal macroorchidism, and a variety of maladaptive behaviours that meet the diagnostic criteria for autism. Although they tend to have an elongated face and large, everted ears, the facial features associated with FXS are subtle enough that they may go unrecognized by non-specialists and the general public. The general Chinese population is quite familiar with Down syndrome, but they are unfamiliar with FXS because the facial features are not as striking to the untrained eye and because of limited public education.² Even among those with medical training, there is a lack of awareness; in a recent survey that we conducted among Chinese medical school students, fewer than 30% of the students we contacted knew about or had heard of FXS before attending the Medical Genetics courses.³ To address this lack of awareness, our review aims to provide basic information on FXS, introduce the clinical aspects of FXS in China, and outline future research and policy recommendations that may in the future improve FXS genetic testing and counselor training in the Chinese health system.

MOLECULAR GENETICS OF FXS

The vast majority of FXS cases are caused by a trinucleotide CGG expansion in the 5'-untranslated region of the fragile X

mental retardation gene (*FMRI*), a gene that is located on the X chromosome. This expansion occurs via instability of the repeated element as it is passed from parent to child. There are four allele classes for the *FMRI* CGG repeat, and they are distinguished by the stability of the repeat size during meiosis. Whereas alleles in a general population are stable in size and contain between 6 and 44 CGG repeats, intermediate alleles have 45-54 copies of the repeat and do exhibit some instability as they are passed between generations. This instability is further increased when there are 55-200 copies of the CGG repeat, which is known as the premutation class. During either oogenesis or early post-zygotic events, premutations may, in one generation, undergo further expansion to become full mutations with more than 200 CGG repeats. At this size, the repeat is hypermethylated, and epigenetic silencing of *FMRI* results in the loss of its protein product, fragile X mental retardation protein (FMRP). This loss of FMRP function, in turn, causes FXS.⁴⁻⁶ Although the *FMRI* full mutation accounts for 95%–99% of symptomatic mutations related to FXS¹, deletions or point mutations that disrupt FMRP function can also lead to FXS. Because routine genetic testing for FXS assesses only the size of the CGG repeat and omits sequence analysis of the whole gene, it is unclear exactly what fraction of patients with FXS this represents.

CLINICAL PRESENTATION

There are physical, cognitive and behavioural aspects to the FXS. In addition to the main finding of mild to moderate intellectual disability, these features include macroorchidism in post-pubertal males, a long face, coarse features, large everted ears, and behavioral disturbances. These disturbances may include features of autism, including social withdrawal and repetitive movements - hyperactivity, anxiety and aggression.

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*Corresponding Author:

Dr.Duan: State Key Laboratory of Medical Genetics, Central South University, Changsha, Hunan, China 410078.

(Email: duanranhui@sklmg.edu.cn)

Dr.Jin: Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322. (Email: peng.jin@emory.edu)

Females with the full mutation show greater clinical variability than males.⁷ Up to 50% of females with the full mutation show symptoms of FXS, although they are generally less affected than males because they have a second copy of *FMRI*. Even if she is intellectually normal, a female with the full mutation in *FMRI* may have emotional and disturbances and learning disabilities.^{8,9} These may include depression, shyness, poor eye-contact, and hyperactivity.

Screening checklists to facilitate referrals for *FMRI* mutation test have been developed, and these include assessment of the physical and behavioral features that are frequently observed in FXS, such as increased hyperactivity, shortened attention span, tactile defensiveness, hand-flapping, perseverative speech, joint hyperextensibility, large ears and testes, intellectual disability, delayed attainment of developmental milestones and a positive family history of intellectual disability.⁷⁻⁹ Items related to emotional and behavioral function or biological characteristics of the birth parents, siblings and extended family are supplemented in a screening tool for very young children with FXS.¹⁰ These checklists are designed to indicate which individuals should be referred for diagnostic testing for the *FMRI* gene mutation.¹¹ Among them, a simplified six-item checklist including intellectual disability, family history of intellectual disability, large or prominent ears, elongated face, attention deficit hyperactivity disorder, and autistic-like behavior, has been validated to screen children for FXS, and it has been found to increase the proportion of positive results among samples referred for *FMRI* mutation tests.¹² This simplified checklist is a valid clinical pre-selection tool for use in Chinese populations, as demonstrated by Guo et al in a retrospective analysis of 208 cases (190 males and 18 females) of suspected FXS.¹³

Both male and female carriers of premutation alleles were once considered to be clinically unaffected. Although they don't have features of FXS, it is now known that these individuals may present with a spectrum of clinical findings that is distinct from FXS. This may include Fragile X-associated tremor/ataxia (FXTAS), a progressive neurodegenerative disorder that is characterized by intention tremor, cerebellar ataxia, parkinsonism, and peripheral neuropathy^{14,15} and premature ovarian failure or ovarian insufficiency (POF/POI), accompanied by a decrease in bone density (as observed in many postmenopausal women).^{16,17} Not all premutation carriers are clinically affected; there is age-dependent penetrance of FXTAS, and it is estimated that 40% of male premutation carriers over 50 yrs of age are affected.¹⁴ Fewer female premutation carriers are affected by FXTAS, but approximately 20% of them have POF/POI.¹⁷ Families counselled about FXS must be given information on the premutation-associated phenotypes in order that they may fully understand the implications of an *FMRI* mutation to their family.

PREVALENCE OF THE FRAGILE X FULL MUTATION IN CHINA

Surveys in various populations have documented that the Fragile X full mutation is found in 1 in 4000 to 1 in 6000 males and 1 in 8000 females.^{18,19} A large Canadian

population study of more than 20,000 females indicated a premutation carrier frequency of 1 in 549, whereas intermediate alleles were detected in approximately 1 in 86 individuals tested.¹⁹

Accurate estimates are not available for the prevalence of pre- or full mutation carriers in China at present. In 1002 pregnant women from Southern Taiwan who were screened for *FMRI* repeat size, no carriers of either premutations or full mutations were found.²⁰ We assessed the *FMRI* CGG repeat size in 808 normal Chinese (230 males and 578 females) and found that it ranged from 6 to 87 copies of the repeat. Similar to Caucasian populations, the most common allele sizes were 29 and 30 copies of the CGG repeat, accounting for 45.0% and 30.8% of chromosomes respectively. A single female pre-mutation carrier (29/87 repeats) was detected, whereas 21 women were carriers of intermediate alleles for an allele frequency of 1.5%. In a normal Japanese population (576 males and 370 females), Otsuka et al. found that the allele size ranged from 8 to 50, and the intermediate allele frequency was 0.52% (6/1161) but no pre-mutations were found.²¹ A large-scale screen of CGG repeat size in Asia is needed to obtain accurate allele frequency estimates to compare these populations.

DIAGNOSIS OF FRAGILE X SYNDROME IN CHINA

In China, physicians are quite familiar with Down syndrome, but FXS is less commonly recognized. Physicians who have particular knowledge of FXS or who have seen FXS patients before will refer suspected cases for genetic testing, whereas under-diagnosis may occur. To increase diagnosis, Chinese physicians, especially pediatricians and obstetricians, should be periodically reminded of the features of FXS and updated on the approach to testing.

Affected individuals most often come to the attention of a clinic at the following ages according to the visit records of our clinic: (1) between 1 and 2 years of age, when parents observe developmental delays; (2) between 7-9 years of age, as parents and teachers recognize the mental disabilities of school-aged children; (3) teenage years, when a misdiagnosis or unclear diagnosis is rectified; and (4) age 16 and up, when a family member conceives a baby. Most families find genetic testing centers through physician referrals or through networks of FXS families. A special FXS QQ network has been built to facilitate communication between physicians and families affected by FXS. Furthermore, the national Fragile X Foundation (<http://www.fragilex.org>) provides an international family support network and clinics all around the world, including mainland China.

Patients suspected of having FXS should be referred to a clinical genetics department that facilitates FXS testing. To date, FXS testing in China has been limited to certain hospitals, university medical centers and institutes and is not easily accessible to all patients.

Nationwide insurance programs cover the general health care expenses for 95% of the Chinese people. As part of this,

general screening for Down syndrome is conducted as part of routine prenatal tests. In most regions of China, newborns are screened free of cost for metabolic disorders such as congenital hypothyroidism (CH) and phenylketonuria (PKU), and the coverage rates achieved in cities such as Beijing, Shanghai, and Guangzhou has reached 95%. Additionally, tests for specific genetic disorders on newborns can be conducted in certain hospitals or laboratories upon request. However, to date, the major healthcare insurance plans in China have not covered the cost of genetic testing for FXS, and the fees for this testing are unaffordable for some families, particularly those residing in less developed areas.

MOLECULAR TESTING

The Fragile X Mental Retardation (*FMRI*) gene is located on chromosome Xq27.3. The diagnosis of FXS requires the detection of an alteration in the *FMRI* gene at Xq27.3.²² Mutations resulting in an expanded CGG trinucleotide repeat are detected by a combination of CG-rich polymerase chain reaction (PCR) and Southern blot analysis.⁹

Due to difficulties amplifying CG-rich DNA sequences, only a few genetic testing laboratories in China perform comprehensive FXS testing, including both high CG-content PCR and Southern blot analysis in parallel. Some commercial FXS testing trial packs or kits have been introduced in China, such as the AmplideX™ *FMRI* PCR Kit from Asuragen, the Fragile X PCR test from Abbott, and a trial pack from PE (Perkins Elmer).^{23,24} However, the lack of appropriate instruments, well-trained technicians and limitations of the kit designs impede the widespread use of the kits for genetic testing and prenatal diagnosis of FXS in China.

Cytogenetic methods were the first developed for the diagnosis of FXS. In this approach, cells are cultured in a folate-deficient medium so that fragile sites can be assessed. Compared with molecular methods, this technique is unreliable with low sensitivity and an elevated false positive rate. Physicians should review lab reports from patients previously tested for FXS and order molecular testing if the cytogenetic method was used. If standard molecular testing shows a normal CGG repeat tract length, *FMRI* sequencing for pathogenic deletions and point mutations can be carried out upon the family's request.²⁵

PRENATAL DIAGNOSIS

There are few certified prenatal diagnosis centers in China that offer FXS testing. Prenatal testing for FXS can be performed using either chorionic villus samples (CVS) or amniocytes. It is recommended that parental samples be used to demonstrate appropriate inheritance of the maternal and paternal alleles, which may aid the analysis. CVS should be interpreted carefully, as the methylation pattern observed in placental (CVS) tissue at 10-12 weeks gestation is incomplete and does not reflect that observed in the livebirth. Even though methylation status cannot be determined, prenatal diagnosis by CVS has proven reliable when based on CGG repeat size, although it can be difficult to distinguish between large premutation and small full mutation alleles.²⁶ Under such circumstances, amniocentesis may be used to

confirm the fetal status because the methylation pattern observed in amniocytes reflects that of the liveborn baby. With either type of sample, caution is needed to interpret the allele size and methylation status in mosaic cases.

GENETIC COUNSELING

When a diagnosis of FXS is suspected or has been made, it may require several sessions over a period of time to provide comprehensive genetic counseling for the family. Guidelines in the United States suggest that genetic counselors prepare families for possible test outcomes and explain the outcomes to them, educate them about the *FMRI*-associated disorders, and facilitate communication among family members.⁸ The counseling protocols in China are different from those in Western countries. In China, the physicians who meet the patients explain the diagnostic and clinical aspects of the disease according to the genetic diagnosis, analyze the inheritance patterns and recurrence risks, and review available testing options and management measures with families. However, the physicians do not often show emotional support to their clients in decision-making.²⁷ In an attempt to standardize the training process for genetic counselors overall, the Chinese government initiated a training program based on the guidelines of the American Board of Genetic Counseling.²⁸ Considering the differences in the economies, cultures, and healthcare systems between the United States and China, it is essential that genetic counseling guidelines be adapted for use in China.^{27,29} A specialized FXS clinical and research consortium in China should be organized to provide the most up-to-date knowledge and recommendations for Chinese physicians and to provide optimal assistance to affected individuals and their families.

One of the differences between Chinese and Western culture that most complicates genetic counseling is the attitude towards confidentiality. In the modern Chinese family, the hierarchical relationship between parent and child is no longer exactly as it was in the past, but the influence and authority of parents still exists.³⁰ For example, some parents live with their sons or daughters even after they are married. Parents also commonly provide financial support for housing and care for grandchildren until they are at least at two years old. Thus, parents may play a role in decision-making surrounding genetic diagnoses. Because of this parental influence, it can be challenging to determine how to inform family members of genetic diagnoses and to identify the individuals who possess the power to make final decisions within a family. An understanding of the patient's family background and status would help counselors offer better services to patients.

SCREENING

Reliable testing methods now allow for large-scale population-based screening for conditions associated with *FMRI*. There is debate over the value of this testing and over which groups should be tested, but potential approaches could include preconception carrier testing in reproductive-age women, prenatal carrier testing of mothers, or full mutation testing as part of newborn screening.³¹ In China,

several groups have conducted fragile X screening in groups of people with mental retardation and/or autism of unknown cause.³²⁻³⁶ Zhao et al screened more than 1,000 families with mental retardation and/or epilepsy using the cytogenetic method for fragile X testing and detected 98 cases of FXS.³⁷ Liu et al used molecular testing to size the *FMRI* CGG repeat in 466 children of Han nationality with autism spectrum disorder and the frequency of the *FMRI* mutation at 0.43%.³⁸

Our survey of 749 Chinese medical students indicated strong support for general population carrier screening of all women of reproductive age (60.5%).³ This support was shared by 284 Chinese women who had never before heard of FXS. These women were randomly recruited so that their attitudes towards prenatal carrier screening for FXS could be assessed. After they were provided with basic knowledge of FXS, 73.9% of them indicated that they preferred to take the test.³⁹ An analysis in US dollars indicates that widespread prenatal screening for FXS would be cost-effective when examined relative to quality adjusted life years.⁴⁰ In China, a prenatal cytogenetic test for Down syndrome generally costs about 500 RMB,⁴¹ so the fragile X carrier screening among prenatal women would be acceptable with a similar cost. This cost-benefit analysis does not address the ethical issues surrounding screening, such as the lack of effective treatments for FXS and the difficulty predicting the severity of the FXS phenotype before a child is born.

SPECIAL EDUCATION AND TREATMENTS

In China, children with mild (IQ 50-69) or borderline (IQ 70-84) intellectual disability are permitted nine-years of compulsory education, but children with moderate to severe intellectual disability have to pursue special mental health services. The aims of these specialized schools are: to assess the child, improve their mental health, teach basic self-care skills, make referrals to mental health specialists, make specific diagnoses, and provide opportunities for interactions between parents of the children.⁴² Services dedicated to Autism are accessible in China. If similar services dedicated to FXS could be developed, the parents of recently-identified patients could receive information and emotional support from specially trained physicians and support staff and from other experienced parents.

Individuals with FXS are commonly prescribed medications using a symptom-based approach. This may include medications for attention deficits, hyperactivity, mood disturbances, aggression, and anxiety.⁴³ Although this may improve certain aspects of the behavioral disturbances, responses are incomplete, and patients may be on several medications at one time.^{44,45} As in Western countries, Chinese physicians generally prescribe medications according to the clinical presentation of the patients, and the diagnosis of FXS does not influence this approach. Because the underlying mutation is known and the certain aspects of the FXS phenotype have been successfully modeled in animals, the development of targeted medications based on the biochemical mechanism of FXS is promising.⁴⁶ Treatment approaches target the regulation of the mGluR

pathway through drugs that mimic the effect of FMRP. Targeted drug development for FXS is still in the research phase, and several clinical trials are in progress.^{47,48} In our experience with Chinese families affected by FXS, many are interested in enrollment in drug trials, provided they are relatively safe and have a solid research study design.

CONCLUSION

Immediate improvements are needed in the diagnosis and management of FXS patients in China. We believe this should include targeted education of healthcare professionals, better information for the general population, and the development of guidelines for the diagnosis of FXS in China. FXS is one of the most common causes of intellectual disability and the lack of a diagnosis means that families do not receive proper information on the implications of this diagnosis for other family members. We recommend that literature should be immediately composed by experts in Chinese to describe the features, inheritance, genetic testing and counseling strategies, and management of FXS, and this should be distributed widely to pediatricians and gynecologists. A website dedicated to FXS in the Chinese format should be built to provide basic information on FXS to the Chinese population. A strong network should be built between Obstetrics and Gynecology hospitals, OG departments in large hospitals and prenatal diagnosis centers, so that patients suspected of having FXS could be referred to appropriate facilities for genetic counseling and testing according to their geographic location. Most importantly, guidelines must be developed that standardize FXS testing and genetic counseling in China to ensure that all patients receive appropriate information.

CONFLICT OF INTEREST

None.

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