Consensus Statement of the Indian Academy of Pediatrics on Diagnosis and Management of Fragile X Syndrome in India

ANUPAM SACHDEVA[1], PRACHI JAIN[1], VINOD GUNASEKARAN[1], SUNITA BIJARNIA MAHAY[1], SHARMILA MUKHERJEE[2], RANDI HAGERMAN[3], SUMA SHANKAR[3], SEEMA KAPOOR[4] AND SHALINI N KEDIA[5]

From [1]Sir Ganga Ram Hospital, [2]Lady Hardinge Medical College, and [4]Maulana Azad Medical College, New Delhi, India; [3]MIND Institute, UC Davis, California, USA; and [5]Fragile X Society, India; for the Indian Academy of Pediatrics Consensus in Diagnosis and Management of Fragile X Syndrome Committee.

Correspondence to: Dr Anupam Sachdeva, Director, Pediatric Hematology Oncology and Bone Marrow Transplantation unit, Institute for Child Health, Sir Ganga Ram Hospital, New Delhi, India. anupamace@yahoo.co.in

Justification: Fragile X Syndrome (FXS) is the most common genetic cause of inherited intellectual disability and autism spectrum disorder (ASD). Early identification results in appropriate management and improvement in functioning. Risk assessment in other family members can lead to prevention of the disorder. This necessitated the formulation of IAP recommendations for the diagnosis and management of FXS in Indian children and adolescents.

Process: The meeting on formulation of national consensus guidelines on Fragile X syndrome was organized by the Indian Academy of Pediatrics in New Delhi on 25th February, 2017. The invited experts included Pediatricians, Developmental Pediatricians, Psychiatrists, Pediatric Neurologists, Gynecologists, Geneticists, Clinical Psychologists and Remedial Educators, and representatives of Parent Organizations. Guidelines were framed after extensive discussions. A writing committee was formed that drafted the manuscript, which was circulated among members for critical appraisal, and finalized.

Recommendations: The committee recommended that early diagnosis of FXS is crucial for early, timely and appropriate management. The interventions including timely occupational therapy, speech therapy and behavioral modifications help to improve the developmental potential and reduce the maladaptive behavior. Pharmacotherapy may be needed to control and improve behavioral symptoms. In addition, the emergence of targeted treatments such as low dose sertraline, metformin and /or minocycline may also be helpful for behavior, and perhaps cognition. Genetic counselling is helpful to communicate the risk for future children with FXS or permutation involvement.

Keywords: *Genetic counselling, Intellectual deficit, Outcome.*

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability and is the second most prevalent genetic cause after Down syndrome. It is also the most common known single gene cause of autism spectrum disorder (ASD) [1]. FXS is estimated to affect 1 in 5,000 men and 1 in 4,000 to 6,000 women worldwide (determined by molecular assay) [2]. Though the exact prevalence in India is not known, it is probably a significant cause of intellectual disability of unknown etiology in our country [3,4].

The objective of these recommendations is to contribute to the dissemination of knowledge on FXS among health professionals, and thus improve the diagnosis and management of these patients.

METHODS

The meeting on formulation of National consensus guidelines on Fragile X syndrome was organized by Indian Academy of Pediatrics in New Delhi on 25th February 2017. The invited experts included Pediatricians, Developmental Pediatricians, Psychiatrists, Pediatric Neurologists, Geneticists, Obstetrician and Gynecologists, Clinical Psychologists, Remedial Educators, and members of Parent Organizations. Guidelines were framed after extensive discussions. A writing committee was formed that drafted the manuscript, circulated these among members for critical appraisal, and finalized the recommendations.

RECOMMENDATIONS

Clinical Suspicion

Clinicians should have a high index of suspicion in any male with intellectual disability (ID) or autistic spectrum disorder (ASD). These children should be examined for the characteristic facial features (long narrow face, prominent jaw, large and protruded ears) and macro-orchidism. Various phenotypic characteristics that can be

observed in FXS patients are detailed in ***Table* I**. Chronic and recurrent otitis media starting early in life is a common observation because of a more collapsible eustachian tube promoting fluid collection and bacterial overgrowth [5]. Seizures have been reported in approximately 13% to 18% with a higher prevalence in male patients. The clinical phenotype of FXS depends on the amount of FMRP produced, which is related to the number of CGG repeats and to the degree of *FMR1* methylation resulting in characteristic phenotype. Therefore, in a prepubertal boy there may only be prominent ears and hyperextensible finger joints with soft skin so that the diagnosis is suggested mainly by behavioral features such as poor eye contact, handflapping, handbiting and anxiety. We recommend that all children with intellectual disability, developmental delay or ASD should have the fragile X DNA test because sometimes the physical features are not obvious or not present, particularly in young children.

The cognitive profile in a child with FXS varies from mild to severe intellectual disability depending upon CGG (cytosine-guanine-guanine) expansion located in the 5' UTR (Untranslated Region) of the *fragile X mental retardation 1* (*FMR1)* gene and the methylation status [2,6]. Average IQ being 40 in males with a completely methylated full mutation. While most females with FXS have a borderline IQ, about 25% of them have an IQ less than 70 and rest 25% have a normal IQ but more learning and emotional problems [7]. Thus, clinicians should have a high index of suspicion for FXS in a boy with developmental delay, language delay and hypotonia in early childhood, and in a female child with low IQ and positive family history.

Features of attention-deficit/ hyperactivity disorder (ADHD), including hyperactivity, inattentiveness, distractibility, restlessness, and impulsivity are cautiously assessed in a child with ID as they are a common behavioral phenotype present in about 80% of boys and 40% of girls with FXS. Anxiety-related symptoms including obsessive-compulsive–like and perseverative behaviors, and emotional lability are also common along with aggressive, self-injurious behavior and frequent temper tantrums. Features of autism are usually present in early childhood, including stereotypies such as hand-flapping, biting, perseverative speech, poor eye contact, and lack of interest in social interaction [8]. However, only 50 to 60% of boys and 20% of girls with FXS meet diagnostic criteria for ASD.

The pattern of FXS inheritance is not a classic Mendelian inheritance pattern due to the dynamic repeat expansion. The expansion from pre-mutation to full-mutation alleles occurs during the transmission of the

TABLE I PHENOTYPIC FEATURES THAT MAY BE SEEN IN FRAGILE X SYNDROME PATIENTS

Characteristics	*Description*
Facial Features	Large and prominent ears (75%) Long face (more common in adulthood) Macrocephaly Mandibular prognathism (80% of adult men) High arched palate Cleft palate (seen in less than 5%) Dental Crowding Malocclusion
Ocular manifestations	Strabismus (8-20%) Refractive errors (20%) Nystagmus (up to 13%) Ptosis (less than 10%)
Ear	Early onset chronic otitis media Recurrent otitis media (45-60%) Deafness due to repeated infections (rare) Large ears
Neurological manifestations	Seizures (16%) Hypotonia (common in infancy) Clonus (adults) Perseverative speech
Behavioural phenotype	Attention deficit hyperactivity disorder (80%) Poor eye contact (90%) Anxiety (70-90%) Repetitive motor behaviour (handflapping) Aggression and tantrums
Development	ASD in 50-60% Developmental delay (90% of boys and 30% of girls) Language delay Cognitive impairment
Orthopedic and connective tissue	Connective tissue dysplasia in form of soft velvet-like skin Pes planus (Flat feet) Hyperextensibility in the meta-carpophalangeal joints Congenital hip dislocation Scoliosis Club foot (rare)
Thorax	Pectus excavatum
Cardiac abnormalities	Mitral valve prolapse (seen by adult age) Aortic dilatation
Genitourinary	Macro-orchidism (95% of adolescent and adult men)
Stature	Obesity (32%) Tall or short stature (final height may be less)
Others	Feeding difficulties Gastroesophageal reflux

maternal X chromosome carrying pre-mutation, to her children and depends on the mother's pre-mutation CGG repeat size; the higher the repeat size, greater is the risk of expansion to a full-mutation allele [9-11]. Various allele groups with their respective clinical manifestations in FXS are shown in ***Table* II**. The final phenotype also depends upon the on the Activation Ratio (AR) which expresses the percentage or ratio of cells with the normal allele present on active X chromosome, so that higher AR correspond to higher FMRP expression levels produced by the normal *FMR1* allele [6]. Hence, females have a wider range of phenotype varying from typical physical features with intellectual impairment to mild learning disability with absent physical characteristics. [12]. So, it is recommended to keep a low threshold for testing for FXS in female with a positive family history.

There are other *FMR1* gene-related disorders in which the carriers of a pre-mutation typically have normal IQ and little or no features of FXS. However, they are at risk for developing the Fragile X-associated tremor/ataxia syndrome (FXTAS) [13], and the Fragile X-associated primary ovarian insufficiency (FXPOI) [14]. In addition, they may be at risk for other medical conditions like depression, anxiety, migraine headaches, hypertension, insomnia, sleep apnea, immune mediated diseases including hypothyroidism and fibromyalgia, chronic fatigue and chronic pain syndrome, but the prevalence of these problems varies from 10%-50% and the symptoms depend on the age and sex of the individual [13,15]. These manifest later in adulthood and we recommend that they be explained to parents as a part of prognosis.

Laboratory Diagnosis

Conventional cytogenetic techniques using the light microscope (which allowed the observation of the distal narrowing of the long arm of the X chromosome at the band 27.3) were previously used for the diagnosis of FXS. These narrowed segments were known as the fragile sites. Nowadays, more sensitive and specific molecular tests are available which allow diagnosis of full-mutation and pre-mutation carriers, by determining the number of repeats and the methylation status of the regulatory region. The gold standard DNA testing for the diagnosis of FXS is a combination of Polymerase chain reaction (PCR) and Southern blot analysis and are the recommended methods for FXS laboratory confirmation. PCR uses specific primers for the *FMR1* gene and can identify patients with an expanded *FMR1* allele in both the full-mutation and pre-mutation range [16]. Southern blot analysis identifies alleles throughout the mutation ranges and allows the determination of the methylation status. The consensus committee recommends that all children presenting with intellectual disability and/ or developmental delay and/or ASD with no known diagnosis should have *FMR1* DNA testing. We also believe that if there are typical facial features, a positive family history of intellectual disability, or macro-orchidism then there is an increased chance of obtaining a positive result. If the genetic test supports the diagnosis of FXS in the proband, family screening should be offered with special attention to family members with tremor, ataxia, neurological symptoms or early ovarian insufficiency. The clinician or genetic counselor should be careful about identifying the mother as the carrier as there is a risk of stigmatizing. The consensus committee recommends that the same molecular tests can be used for diagnosis of a fragile X mutation in the fetus of pregnant carrier mother on chorionic villus or amniotic fluid sampling. For developmental delays and intellectual disability in children with phenotype not strongly suspicious of FXS, chromosomal microarray is recommended as first tier test (screening test) and will identify a number of chromosomal disorders such as DiGeorge (22q11.2 deletion) syndrome [17]. If chromosomal microarray is not conclusive, such children should have the fragile X DNA test because sometimes the physical features are not obvious or not present, particularly in young children. Hence we recommend that in all children with developmental delays and intellectual disability having phenotype not strongly suspicious of FXS, chromosomal microarray is recommended as first tier test (screening test) followed by fragile X DNA test (if microarray remains inconclusive).

Approach to FXS diagnosis is shown in ***Fig.* 1** and the differential diagnosis of FXS is listed in ***Table* III**.

TABLE II ALLELE GROUPS WITH THEIR RESPECTIVE CLINICAL MANIFESTATIONS IN FRAGILE X SYNDROME (FXS)

Allele group	*Number of CGG repeats*	*Clinical presentation*
Normal alleles	Up to 44	Normal unless partial deletion of *fragile X* gene occurs
Grey zone or intermediate alleles	Between 45 and 54	Precursor for PM alleles
Pre-mutation (PM) alleles	Between 55 and 200	Not classic FXS phenotype, but may have other medical, endocrinologic, psychiatric and neurological problems
Full mutation (FM) alleles	Greater than 200	Classic FXS phenotype

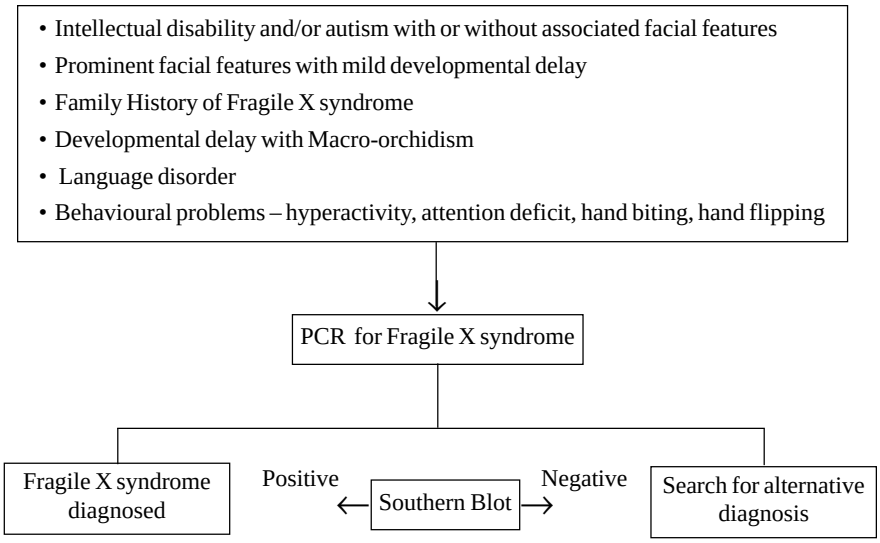

FIG. 1 *Algorithm for diagnosis of Fragile X syndrome.*

TABLE III MAIN DIFFERENTIALS OF FREIGILE X SYNDROME IN VIEW OF INTELLECTUAL DISABILITY

Syndromes	*Intellectual disability*	*Dysmorphic features*	*Stature*	*Head size*	*Testicular size*	*Weight*	*Diagnostic tests*
Fragile X syndrome	Mild to moderate	May be typical or subtle	+++	++	+++	++/+++	PCR, Triplet primer PCR, Southern Blot
Sotos syndrome	Mild to moderate learning problems	Macrocephaly, Frontal bossing, long face, hypertelorism, prominent chin, large hand and feet, advanced bone age	+++	+++	++	++	Sequencing gene and FISH for chromosomal region *NSD*1, for microdeletion
Prader-Willi syndrome	Mild to moderate	Obesity, small facial feature, almond shaped eyes, small hands and feet, hypotonia, LBW, feeding difficulties in infancy	+	++	+	+++	DNA methylation studies for chr 15q11 region
Klinefelter syndrome	Absent or mild	Tall stature, Hypotonia, behavioural problems poor development of secondary sexual characters, gynecomastia	+++	++	+	++/+++	Karyotype

LBW: Low birth weight; PCR: Polymerase chain reaction; FISH: Flourescent in-situ hybridization.

Utility of Molecular Confirmation of Fragile X Syndrome

The diagnostic test for FXS is highly accurate. Diagnosing FXS establishes the reason of cognitive deficits and/ or behavioral problems in a child. It allows the parents and/or caregivers to gain an understanding of the disorder and how it affects the child's development and behavior. This would assist in focused management to maximize their child's potential. Diagnosing FXS would help at-risk families to decide on their appropriate management of family planning and future pregnancies. They could benefit from options of prenatal diagnosis if appropriate for them.

Indications for molecular genetic tests/confirmatory tests for FXS: The consensus committee recommends to perform molecular genetic tests in following conditions:

- Children with Intellectual disability with phenotypic feature/ facial characteristics as described above;
- Prominent facial features with mild developmental delay;
- Developmental delay associated with macroorchidism, language delay and behavioral problems;
- All children with autistic spectrum disorder **(**ASD);
- Family history suggestive of FXS – with consult and at risk of intellectual disability in self or offspring;
- Family history suggestive of intellectual disability of undiagnosed nature - for accurate reproductive counseling.

The committee also feels that tests for FXS may be considered and should be performed in situations mentioned below:

- Intellectual disability of undiagnosed etiology;
- Children with seizure disorder with or without developmental delay, with no obvious cause of seizures identified;
- Children with developmental delay with repeated ear infections and/ or ocular symptoms as described above;
- Children with behavioral problems without an obvious cause;
- Females with primary ovarian failure or infertility of undiagnosed etiology;
- Adults with neurodegenerative disorder with progressive intention tremors, cerebellar ataxia and/ or autonomic instability.

Management of Child With FXS

Supportive strategies including speech therapy, occupational therapy, special educational services and behavioral interventions are key to managing children with FXS and the consensus committee strongly recommend for the same.

Recommendations for age appropriate health supervision and interventions and mentioned in ***Table* IV**.

Pharmacological interventions

Medications play a role to control symptoms of ADHD, aggressive episodes, self-injurious behavior and anxiety-related issues as shown in ***Table* V**. Modifying these symptoms with medications significantly improves an affected child's ability to participate more successfully in activities in home and school settings. The consensus committee recommends the judicious use of medications for symptom-control under the care of a specialist health care provider. New targeted treatments that have the potential to reverse the neurochemical abnormalities in FXS have been developed and a few are available by prescription currently. The early use of low dose sertraline (2.5 to 5.0 mg/day) in young children with FXS between the ages of 2 to 6 years has demonstrated efficacy in improving aspects of development on the Mullen Scales of Early Learning compared to placebo [18]. For those on sertraline, significant improvements in visual perception, fine motor and composite T scores were seen compared to placebo and in a *post hoc* analysis, those with FXS and ASD on sertraline demonstrated a significant improvement in expressive language compared to those on placebo. Generally this treatment is well tolerated without significant side-effects, except that approximately 20% of children with FXS treated with sertraline can develop a significant increase in hyperarousal such that the dose must be lowered or discontinued.

Minocycline is also a targeted treatment for FXS because it can lower the increased levels of MMP9, which interfere with appropriate synaptic connections. A controlled trial of minocycline in children with FXS demonstrated improvements in behavior for those aged 3.5 to 16 years [19]. However, minocycline given in a dose of 25 to 100 mg a day depending on age can sometimes lead to darkening of the permanent teeth if started before 8 years. In addition, darkening of the nail beds, gums or skin may occasionally occur with prolonged treatment. Minocycline can rarely lead to a lupus like syndrome with a rash and/or swollen joints and this corresponds to significant elevation of the antinuclear antibody (ANA). If these symptoms occur, then minocycline should be discontinued; the symptoms usually resolve [19]. More

TABLE IV RECOMMENDATIONS FOR AGE-APPROPRIATE HEALTH SUPERVISION IN FRAGILE X SYNDROME

Birth to 1 month of age

- Examine for orthopedic abnormalities – congenital dysplasia of hip, club foot
- Record and monitor increase in head circumference, length and weight at regular intervals
- Watch for any feeding difficulties or gastro esophageal reflux

1 month to 1 year

- Keep a close watch on development milestones. Hypotonia is commonly encountered causing mild developmental delay
- Appropriate occupational and speech therapy should be initiated early
- Feeding difficulties to be addressed
- Growth parameters need to be strictly monitored

1 year to 5 years

- Ophthalmologic evaluation for refractive errors, astigmatism and strabismus, and corrective measures as appropriate
- Orthotics treatment for orthopedic problems like flat foot, hyper mobile joints and gait disturbances
- Appropriate management of inguinal hernia
- Watch for seizures and institute appropriate evaluation and anti-epileptic medications
- Chronic or recurrent otitis media may be encountered and may require insertion of PE tubes
- Receptive and expressive communication should be monitored closely as language delay may become evident by 2 years of age
- Complete psychological evaluation including IQ testing is an essential part of the developmental evaluation
- Tantrums and hyperactivity frequently develop in the second year of life
- Behavioral intervention techniques emphasizing the importance of decreasing excessive sensory stimuli and using positive behavioral reinforcement and the use of behavioral charting are beneficial
- Pharmacological interventions may be required if symptom control does not occur with behavioral therapy and psychological interventions.

5 years to 12 years

- Keep a watch for development of macro-orchidism which usually develops by 9 years of age in affected boys
- Precocious puberty may occur in females with FXS
- Watch for seizures and institute appropriate evaluation and anti-epileptic medications
- Behavioral and occupational therapy should be continues as per individuals requirement

13 years to early adulthood

- Mitral valve prolapse occurs in approximately 50% of affected adults, so a cardiac evaluation and follow up with cardiologist is recommended if any abnormality is detected
- Marital and reproductive counseling for patients with FXS in reproductive age group needs to be considered

TABLE V DRUGS USED IN FRAGILE X SYNDROME

Drugs	*Symptom control*
Methylphenidate	Hyperactivity, inattention, and impulsivity
Alpha-2-adrenergic agonists clonidine and Guanfacine	Hyperactivity, hyperarousal to sensory stimuli, impulsivity and aggressive behaviours; also helps in regulating sleep
Melatonin	Regulating sleep pattern
Selective serotonin-reuptake inhibitors	Mood disorders, anxiety, obsessive-compulsive behaviors, tantrums

recently, the use of metformin has been identified as a targeted treatment for FXS because it lowers the MEK-ERK pathway and in animal models for FXS it rescues many of the features of FXS. A recent report of seven patients treated with metformin clinically demonstrated improvement in behavior and language [20]. A controlled trial of metformin is underway for children and adults with FXS to better understand the benefits for behavior and cognition. Metformin is currently FDA approved for treatment of obesity and type 2 diabetes, so it may be considered if these problems are present in a patient with FXS.

Managing co-morbidities

Recurrent otitis media may lead to conductive hearing loss and additional language and articulation problems, and therefore there should be a low threshold for early placement of pressure equalizing tubes in children with FXS and recurrent otitis media [5]. Tonsillectomy or adenoidectomy may be considered if chronically infected tonsils or adenoids are present or the child has sleep apnea. The consensus committee recommends a consultation with ENT specialist once diagnosis of FXS is established for early care of hearing and speech.

Genetic counseling

Genetic counseling is recommended for all family members who are affected or at risk of having a pre-mutation (PM) or an offspring with a full-mutation (FM). It is important to highlight the variability of the clinical phenotype and offer molecular diagnosis. Females who are PM carriers have a risk of transmitting the FM to their offspring. That risk depends on the mother's CGG repeat size and she can be counseled using that information [9-11]. Males with PM will pass their expanded allele to all daughters but none to their sons. The father's PM can expand and sometimes contract, but it stays within the PM range. Adults with a PM should be counseled about their risk of developing ataxia (FXTAS), ovarian insufficiency (FXPOI), anxiety, depression or other medical problems that can occur in PM carriers [13,14]. Males with FM transmit only PM size alleles to their daughters. The current understanding is that the large repeat size of a FM cannot be maintained during spermatogenesis. The consensus committee recommends genetic counseling for all family members who are affected or at risk of having a PM or an offspring with a FM.

CONCLUSION

Fragile X syndrome is an important cause of intellectual disability and ASD, with a broad spectrum of clinical phenotypes. Early diagnosis and timely intervention, genetic and reproductive counseling, access to behavioral and pharmacological treatment, and to services are key to attain optimal outcomes. Behavioral modifications and management of co-morbidities could help these children to lead a more productive life. The consensus committee recommends that all children presenting with intellectual disability and/or developmental delay and/or ASD with no known diagnosis should have *FMR1* DNA testing. The same molecular tests should be used for diagnosis of a fragile X mutation in the fetus of pregnant carrier mother on chorionic villus or amniotic fluid sampling. We recommend that in all children with developmental delay and intellectual disability having phenotype not strongly suspicious of FXS, chromosomal microarray is recommended as first tier test (screening test) followed by fragile X DNA test (if microarray remains inconclusive). Early use of supportive strategies including speech therapy, occupational therapy, special educational services and behavioral interventions are key measures to manage children with FXS. Medications should be used judiciously for control of symptoms under the care of a specialist health care provider. We recommend genetic counseling for all family members who are affected or at risk of having a pre-mutation or an offspring with a full-mutation.

Contributors: PJ, AS: prepared the manuscript; AS, VG, SBM, SM, RH, SS, SK, SNK: analyzed and critically reviewed the manuscript. All authors approved the manuscript.
Funding: None; *Competing interests*: Shalini N Kedia is the Chairperson and founder member of Fragile X society, which promotes public and professional awareness of Fragile X syndrome, and hold workshops and conferences towards this cause.

REFERENCES

1. Hunter J, Rivero-Arias O, Angelov A, Kim E, Fotheringham I, Leal J. Epidemiology of fragile X syndrome: A systematic review and meta-analysis. Am J Med Genet A. 2014;164:1648-58.
2. Saldarriaga W, Tassone F, Gonzalez-Teshima LY, Forero-Forero JV, Ayala-Zapata S, Hagerman R. Fragile X syndrome. Colomb Med. 2014;45:190-8.
3. Pandey UB, Phadke S, Mittal B. Molecular screening of FRAXA and FRAXE in Indian patients with unexplained mental retardation. Genet Test. 2002;6:335-9.
4. Katikala L, Guruju MR, Madireddi S, Vallamkonda O, Vallamkonda N, Persha A, *et al*. Distribution of CGG/GCC repeats at the FMR1 and FMR2 genes in an Indian population with mental retardation of unknown etiology. Genet Test Mol Biomarkers.2011;15:281-4.
5. Kidd SA, Lachiewicz A, Barbouth D, Blitz RK, Delahunty C, McBrien D, *et al*. Fragile X syndrome: A review of associated medical problems. Pediatrics. 2014;134: 995-1005.
6. Godler DE, Tassone F, Loesch DZ, Taylor AK, Gehling F, Hagerman RJ, *et al*. Methylation of novel markers of fragile X alleles is inversely correlated with FMRP expression and FMR1 activation ratio. Hum Mol Genet. 2010;19:1618-32.
7. Prouty LA, Rogers RC, Stevenson RE, Dean JH, Palmer KK, Simensen RJ, *et al*. Fragile X syndrome: growth, development and intellectual function. Am J Med Genet. 1988;30:123-42.
8. Farzin F, Perry H, Hessl D, Loesch D, Cohen J, Bacalman S, *et al*. Autism spectrum disorders and attention-deficit/ hyperactivity disorder in boys with the fragile X premutation. J Dev Behav Pediatr. 2006;27:S137-44.
9. Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: Human genome epidemiology review. Genet Med. 2001;3:359-71.

Box I SUMMARY OF RECOMMENDATIONS FOR EARLY DIAGNOSIS AND MANAGEMENT OF FRAGILE X SYNDROME (FXS)

- All children with intellectual disability and/ or developmental delay and / or autistic spectrum disorder with no known diagnosis should undergo fragile X DNA test.
- The gold standard DNA testing for the diagnosis of FXS is a combination of PCR and Southern blot analysis.
- Early diagnosis and timely intervention in form of behavioral modifications and management of co-morbidities could help these children lead a more productive life.
- Supportive strategies including speech therapy, occupational therapy, special educational services and behavioral interventions as key measures to manage children with FXS.
- Medications may be used judiciously by a specialist health care provider to control aggressive episodes, self-injurious behavior and anxiety related issues and new targeted therapy may improve learning and development.

10. Yrigollen CM, Martorell L, Durbin-Johnson B, Naudo M, Genoves J, Murgia A, *et al*. AGG interruptions and maternal age affect FMR1 CGG repeats allele stability during transmission. J Neurodev Disord. 2014;6:24.
11. Nolin SL, Sah S, Glicksman A, Sherman SL, Allen E, Berry-Kravis E, *et al*. Fragile X AGG analysis provides new risk predictions for 45-69 repeat alleles. Am J Med Genet A. 2013;161:771-8.
12. Berry-Kravis E, Potanos K, Weinberg D, Zhou L, Goetz CG. Fragile X-associated tremor/ataxia syndrome in sisters related to X-inactivation. Ann Neurol. 2005;57:144-7.
13. Hagerman R, Hagerman P. Advances in clinical and molecular understanding of FMR1 premutation and fragile X-associated tremor/ataxia syndrome. Lancet Neurol. 2013;12:786-98.
14. Wheeler AC, Bailey DB, Berry-Kravis E, Greenberg J, Losh M, Mailick M, *et al*. Associated features in females with an FMR1 premutation. J Neurodev Disord. 2014; 6:30.
15. Hagerman RJ, Hagerman P. Fragile X-associated tremor ataxia syndrome-features, mechanisms and management. Nat Rev Neurol. 2016;12:403-12.
16. Filipovic-Sadic S, Sah S, Chen L, Krosting J, Sekinger E, Zhang W, *et al*. A novel FMR1 PCR method for the routine detection of low abundance expanded alleles and full mutations in fragile X syndrome. Clin Chem. 2010;56: 399-408.
17. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, *et al*. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86:749-64.
18. Hess LG, Fitzpatrick SE, Nguyen DV, Chen Y, Gaul KN, Schneider A, *et al*. A randomized, double blind, placebo-controlled trial of low dose sertraline in young children with fragile X syndrome. J Dev Behav Pediatr. 2016;37:619-28.
19. Leigh MJ, Nguyen DV, Mu Y, Winarni T, Schneider A, Chechi T, *et al*. A randomized double-blind placebo controlled trial of minocycline in children and adolescents with fragile X syndrome. J Dev Behav Pediatr. 2013;34:147-55.
20. Dy ABC, Tassone F, Eldeeb M, Salcedo-Arellano MJ, Tartaglia N, Hagerman R. Metformin as a targeted treatment in fragile X syndrome. ClinGenet. 2018;93:216-22.

ANNEXURE I: PARTICIPANTS OF THE CONSULTATIVE MEETING

Chairperson and Convener: Anupam Sachdeva (Delhi)

Experts (In alphabetical order): Ajay Gambhir (Delhi), Ami R. Kothari (Mumbai), Anisha Ghosal (Delhi), Anjana Thadani (Mumbai), Anju Aggarwal (Delhi), Anne Skomorowsky (New York), Arun Singh Danewa (Delhi), Ashish Sahani (Delhi), Atish Bakane (Delhi), Bakul Parekh (Mumbai), Divya Aggarwal (Delhi), Flora Tassone (California), Harish Pemde (Delhi), IC Verma (Delhi), Imran Noorani (Delhi), Madhulika Kabra (Delhi), Meenakshi Sauhta (Delhi), Monica Juneja (Delhi), MP Jain (Delhi), Nandini Mundkur (Bengaluru), Neerja Gupta (Delhi), Prachi Jain (Delhi), Praveen Kumar (Delhi), Praveen Suman (Delhi), Randi Hagerman (California), Ratna D Puri (Delhi), Renu Saxena (Delhi), Robert Miller (California), Roma Kumar (Delhi), Samir Dalwai (Mumbai), Seema Kapoor (Delhi), Shalini N Kedia (Mumbai), Shambhavi Seth (Delhi), Sharmila Mukherjee (Delhi), Suma Shankar (California), Sunita Bijarnia Mahay (Delhi), Suvasini Sharma (Delhi), Stephanie Sherman (Atlanta), Vinod Gunasekaran (Delhi).